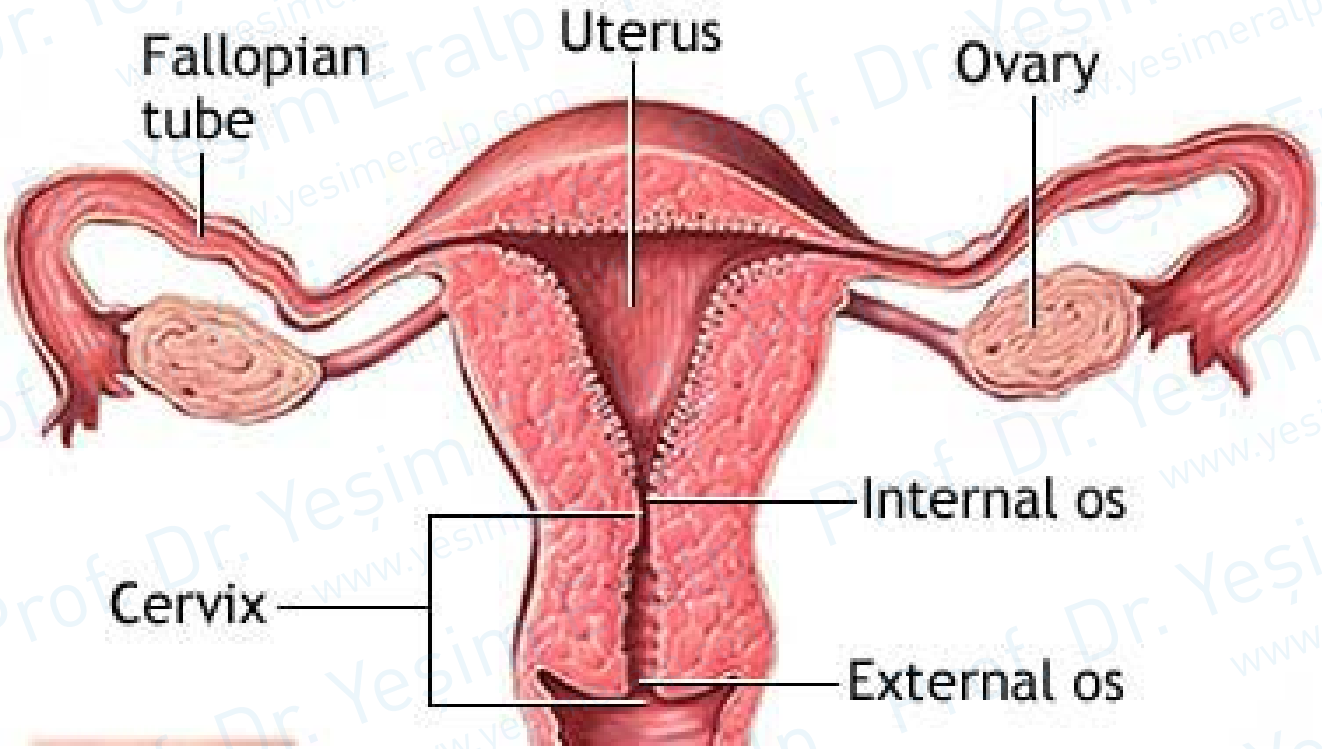
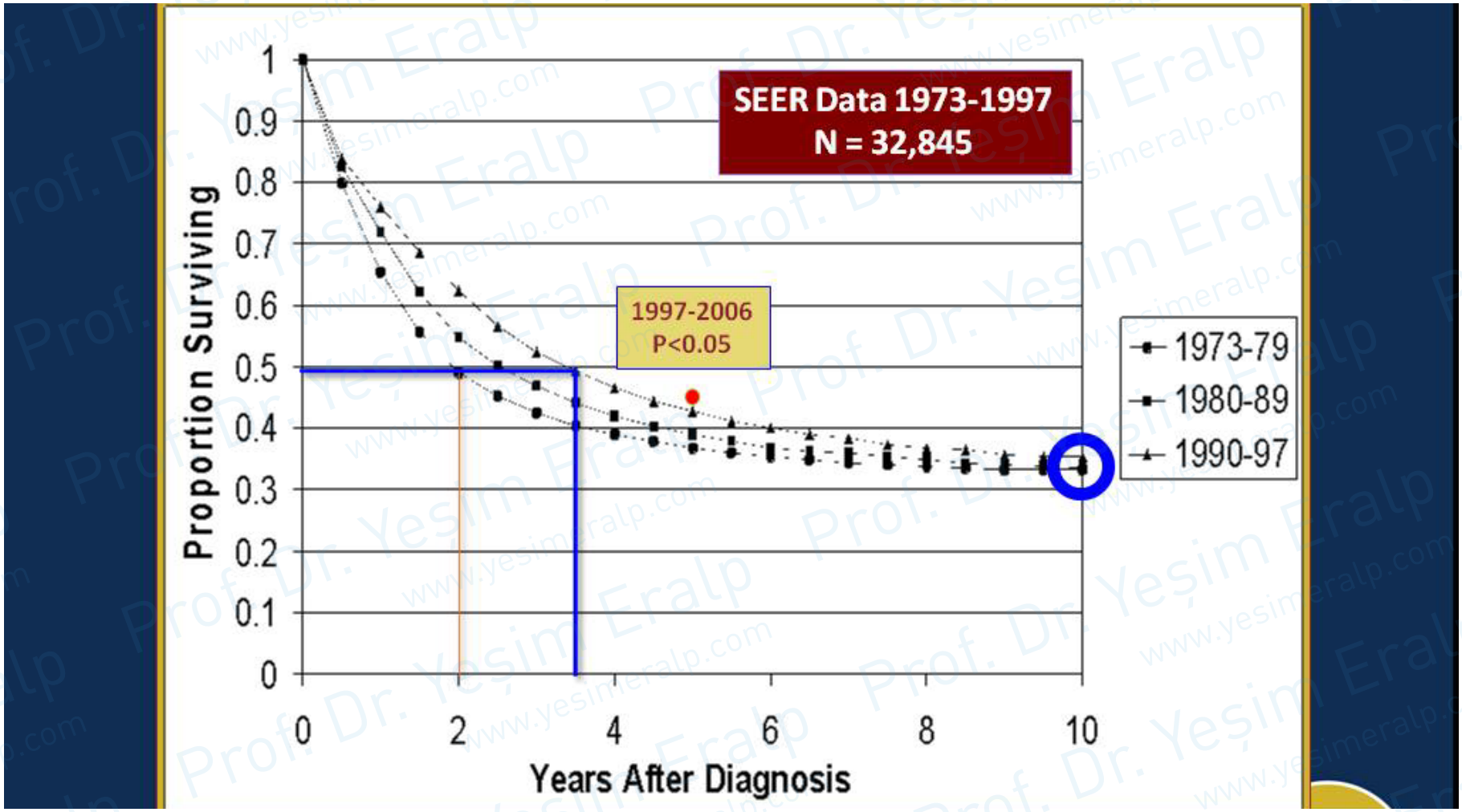
JİNEKOLOJİK KANSERLERDE HEDEFE YÖNELİK TEDAVİLER

Dr. Yeşim ERALP
İÜ Onkoloji Enstitüsü

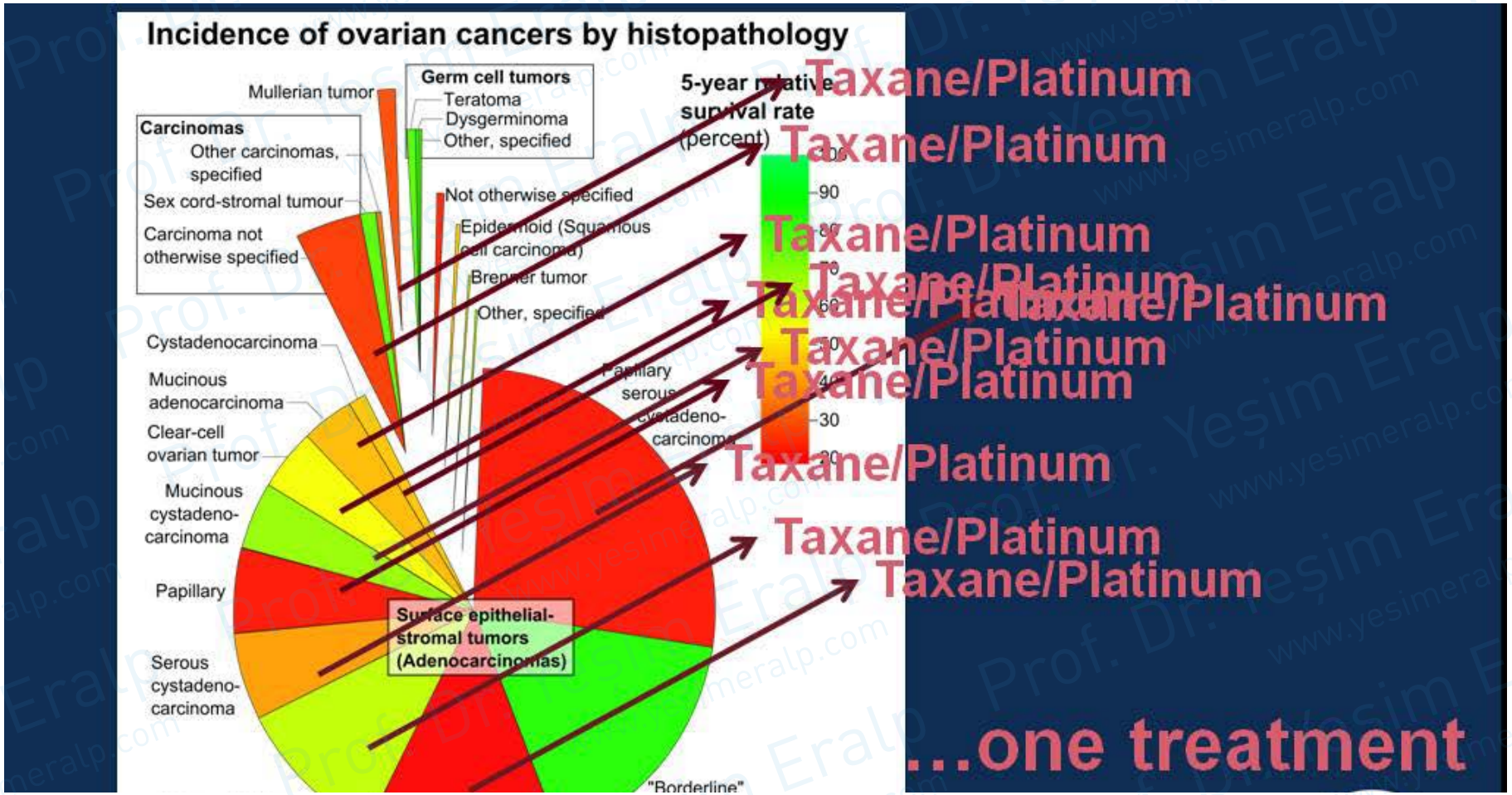

Fallopian tube
Uterus
Ovary
Internal os
Cervix
External os

OVER KANSERİ

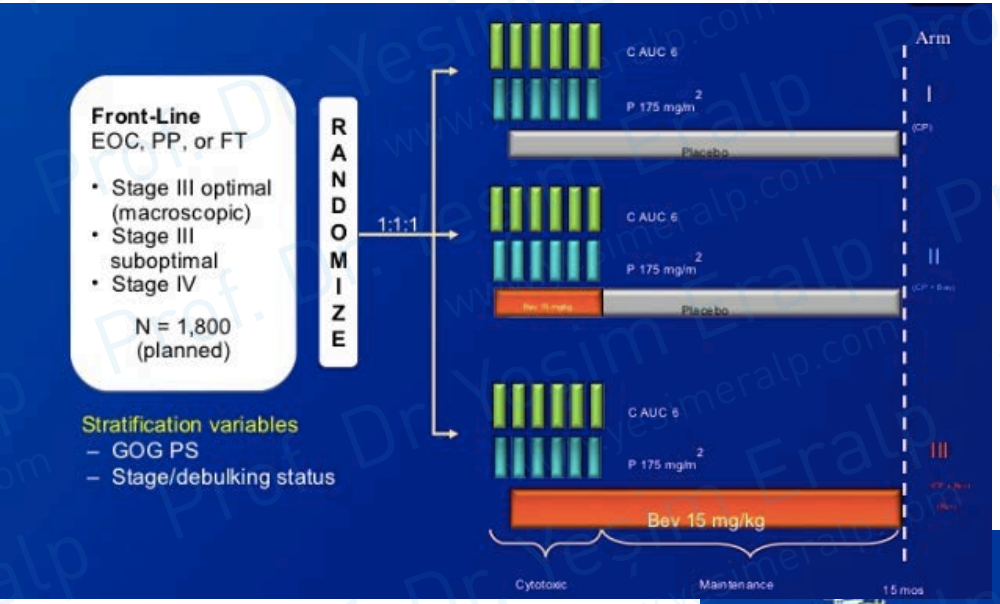
Over Kanseri & Sağkalım



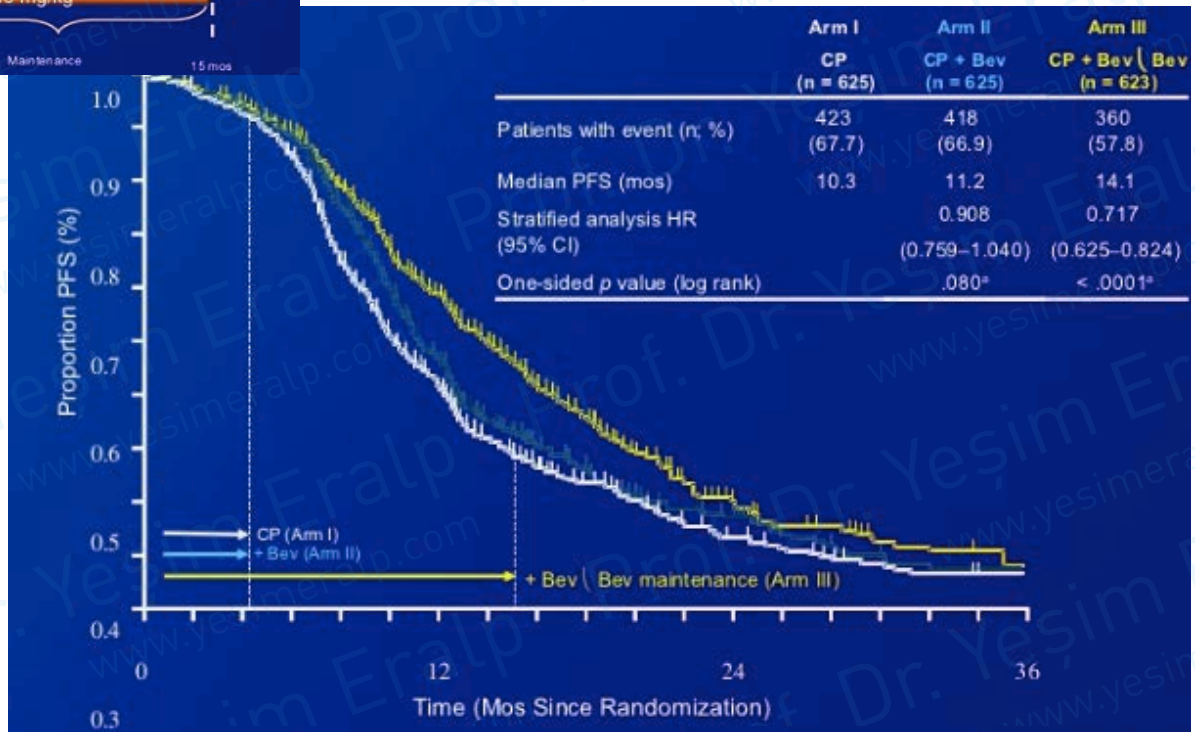
OVER Kanseri: Çok alt-tip & Tek tedavi



GOG 218

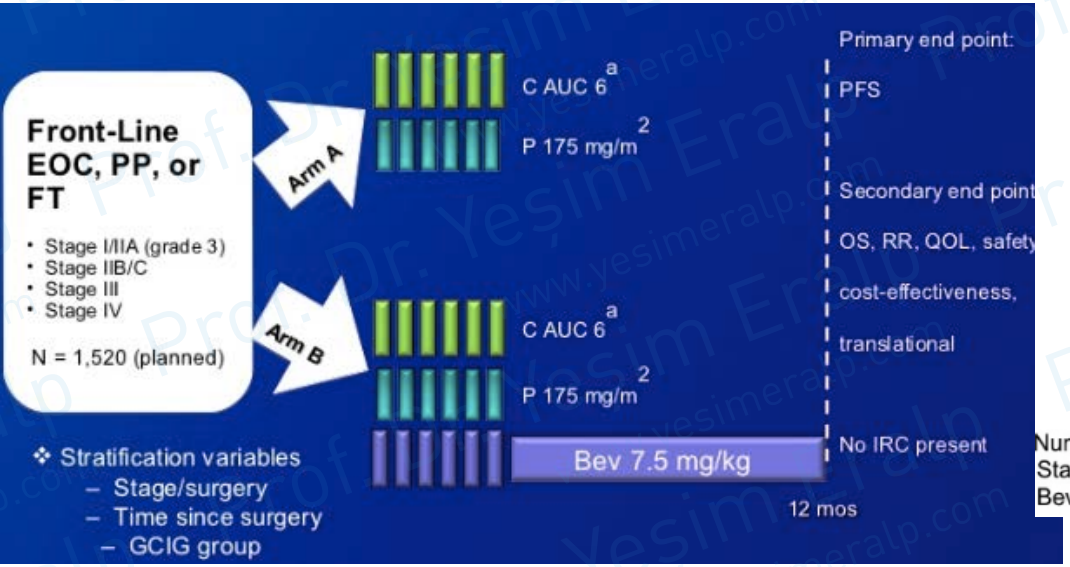


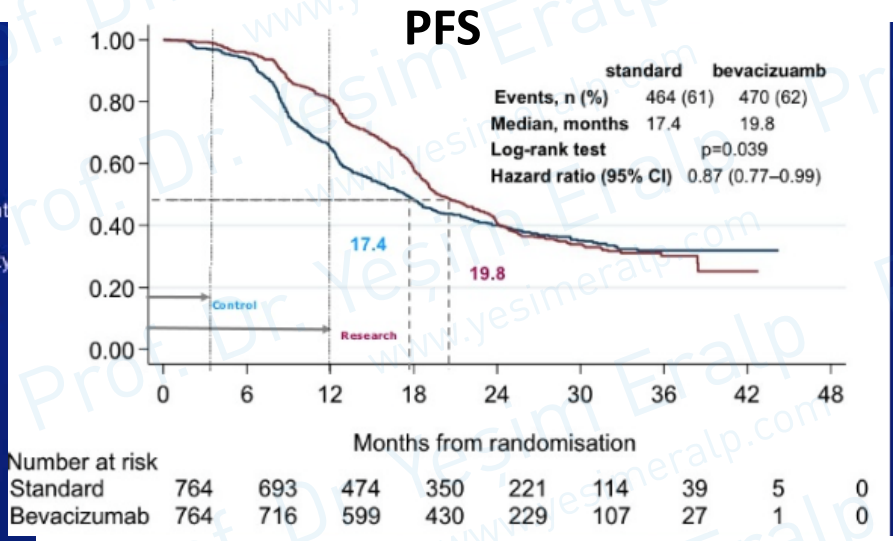
Bev: 15 mg/kg
Idame Bev: x 16 kür



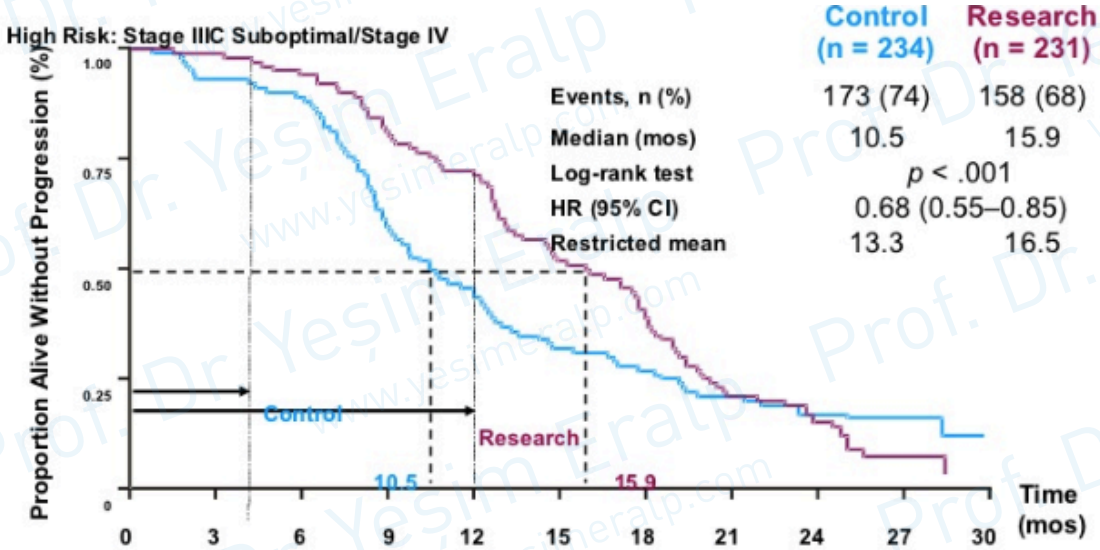
Robert A. Burger
N Engl J Med 2011;365:2473-83

ICON 7



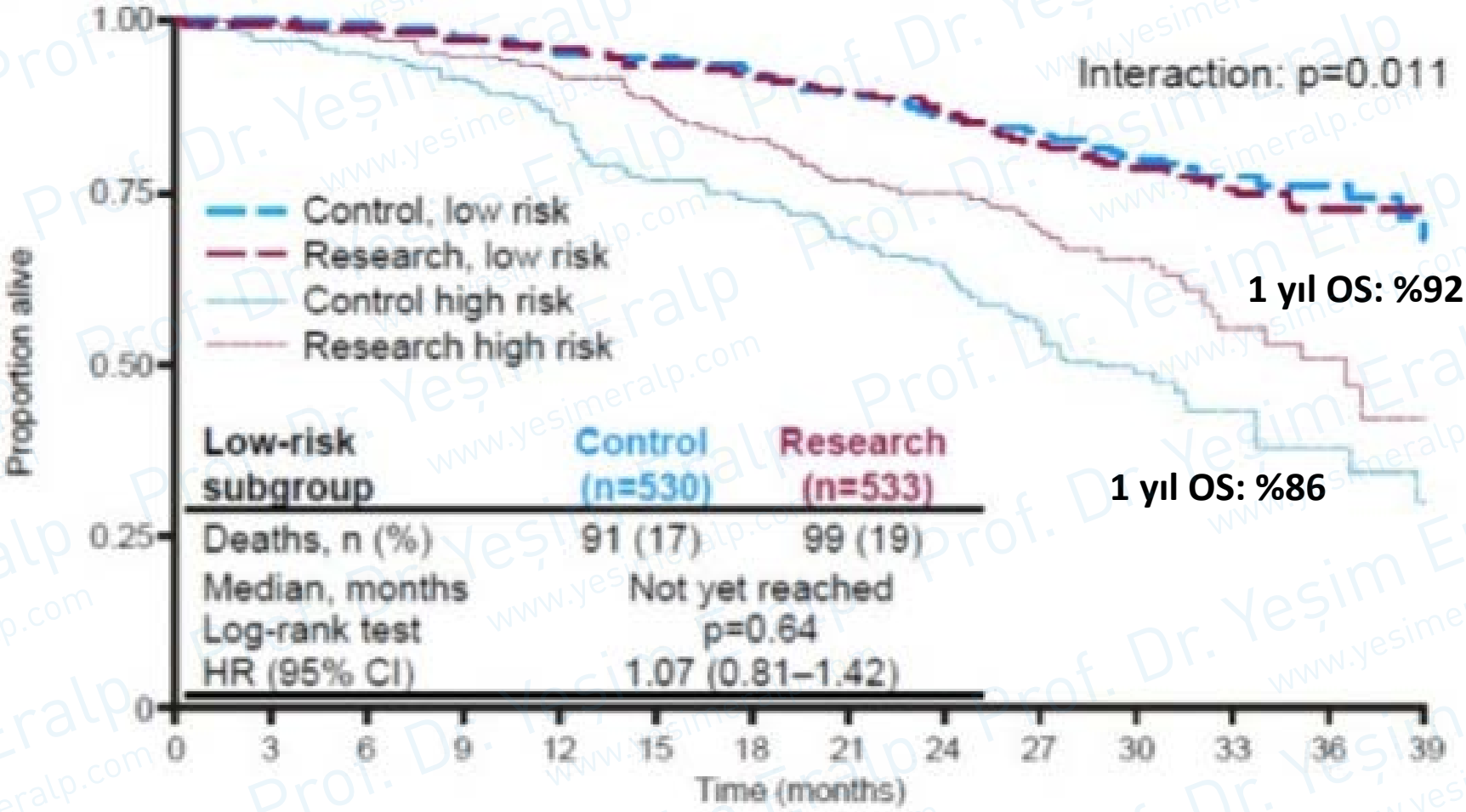


Bev: 7.5 mg/kg
Idame Bev: x 12 kür



Timothy J. Perren
N Engl J Med 2011;365:2484-96

ICON 7: Genel Sağkalım



Timothy J. Perren

N Engl J Med 2011;365:2484-96

OVER KANSERİNDE TEDAVİ ALGORİTMALARI: 2012

PRİMER TEDAVİ

Carboplatin + Paklitaksel

+ Bevacizumab

GOG 218
ICON 7

1. NÜKS

Platin Duyarlı

Platin Dirençli

+ Bevacizumab

OCEANS

Carboplatin + Gemsitabin

Haftalık Paklitaksel

+ Bevacizumab

AURELIA

Lipozomal Doksorubisin

(+/- Trabektedin)

+ Bevacizumab

2. & sonraki NÜKSLER

+ Bevacizumab

Carboplatin + Lip Doksorubisin

Carboplatin + Dosetaksel

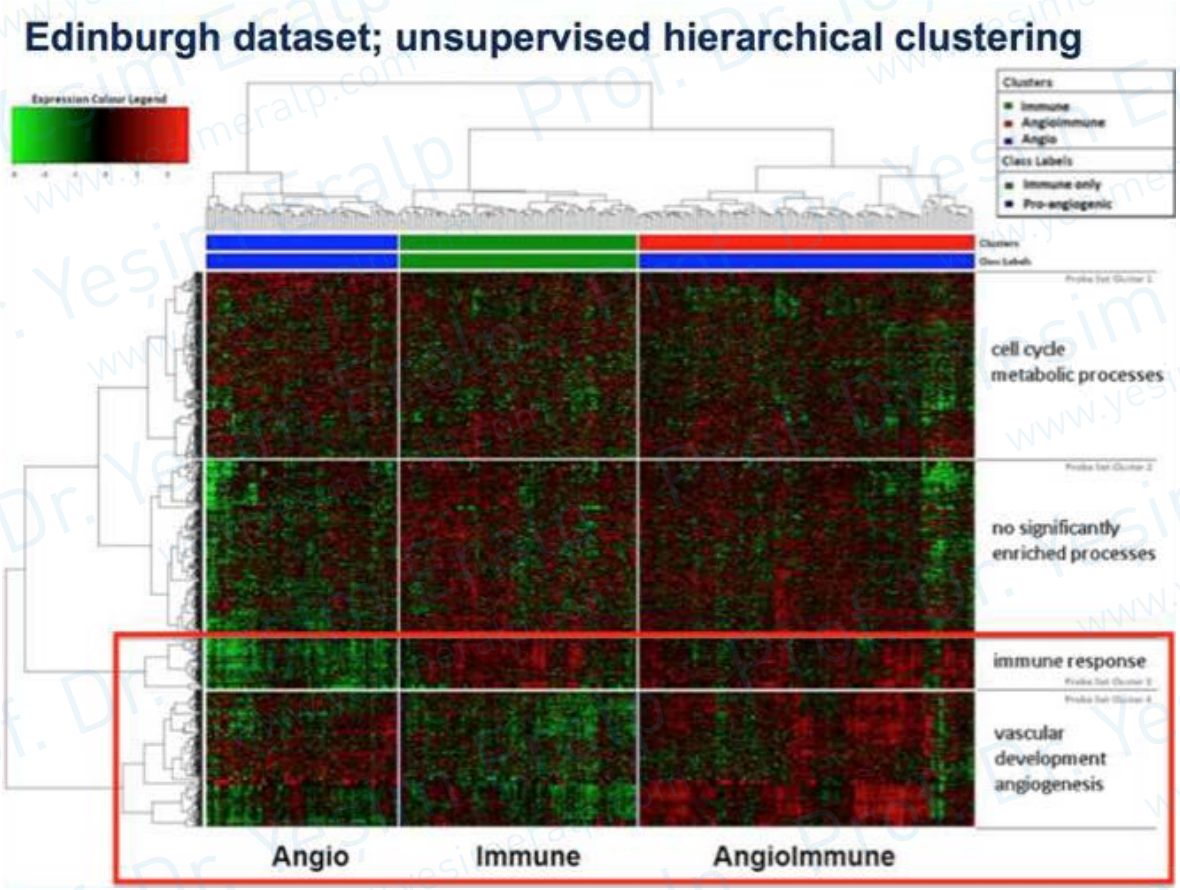
Gemsitabin

Vinorelbin

Etoposid

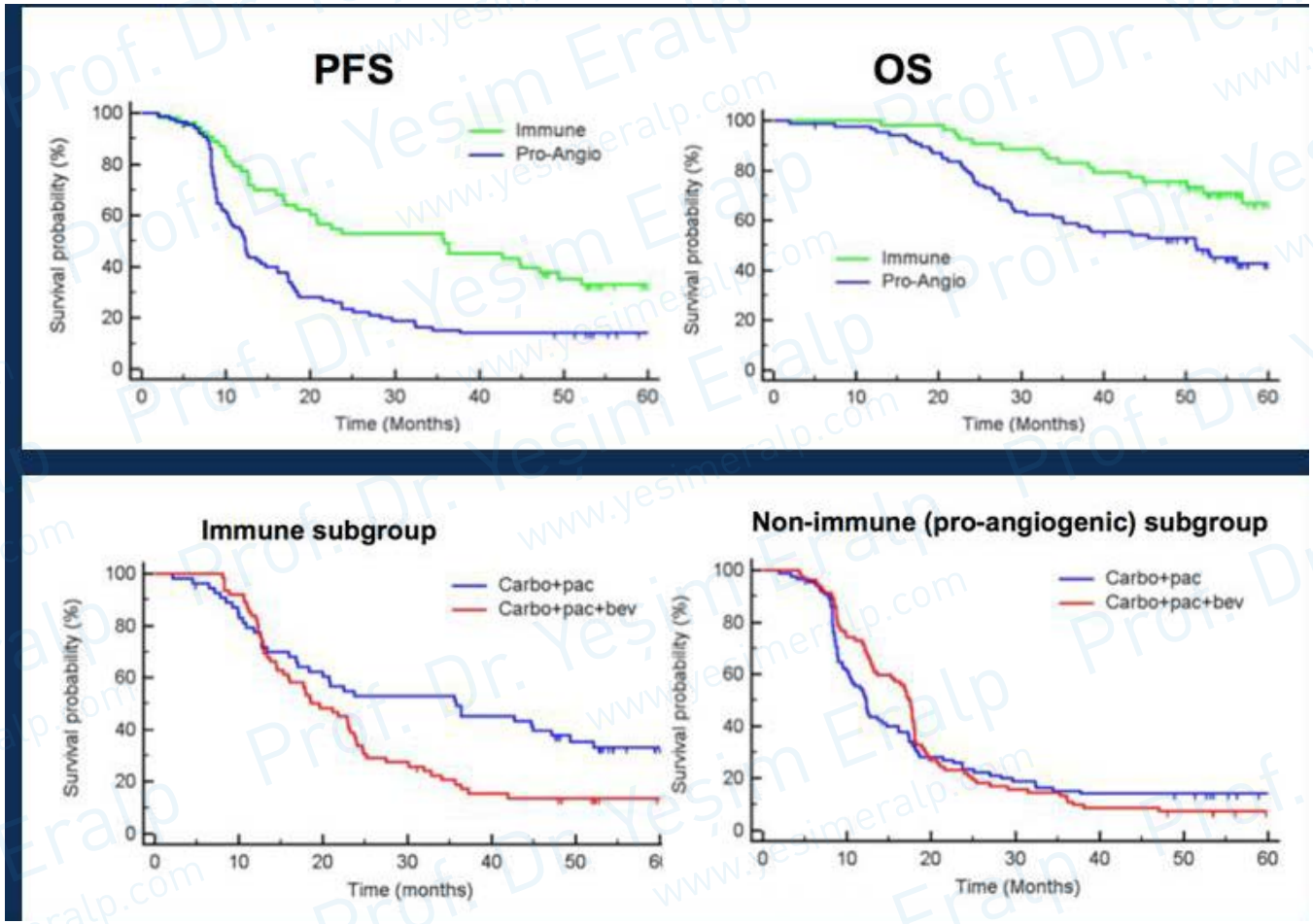
Anjiogenez direnci ??

Moleküler Alt-tip Analizi: ICON-7



Presented By Jonathan Ledermann at 2014 ASCO Annual Meeting

ICON 7:
Moleküler alt-grup etkinliği



Kontrol kolu:

Immun vs Pro-anjiojenik

BEV kolu:

Immun vs Pro-anjiojenik

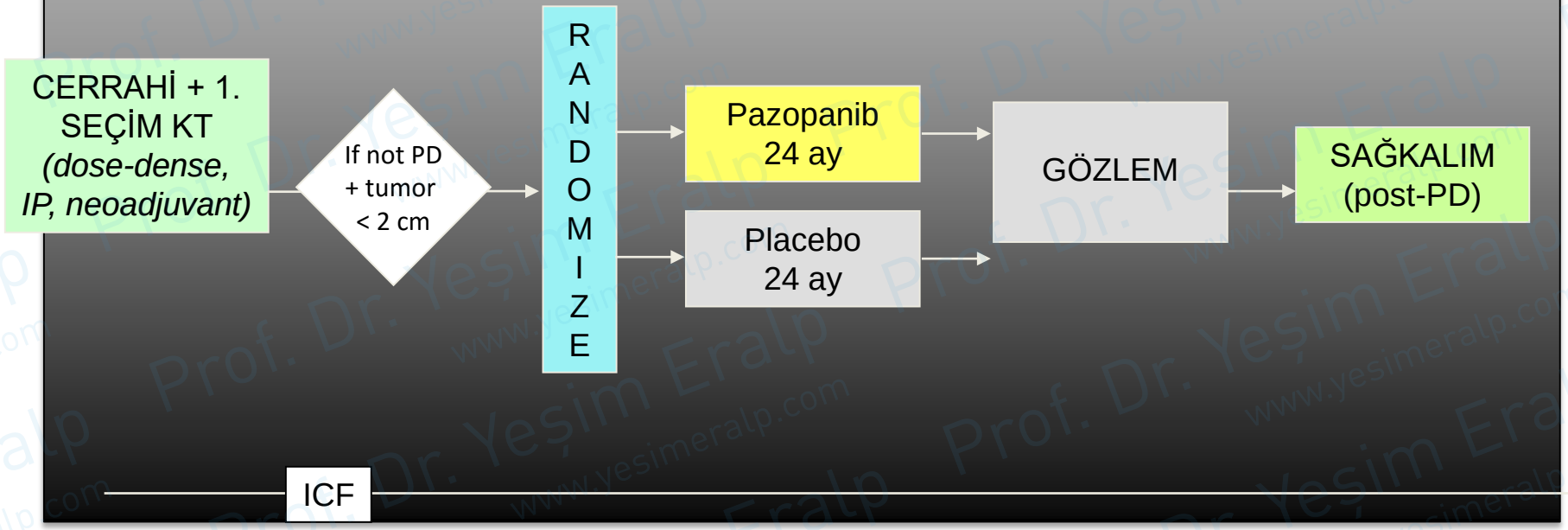
Immun kolda olumsuz etki !!

Presented By Jonathan Ledermann at 2014 ASCO Annual Meeting

REMİSYONDA İDAME

AGO-OVAR 16

- Faz III randomize, çiftkör, multicenter
- N=940 (1:1) 2009-2010
- Pazopanib: 800 mg/gün 24 ay*



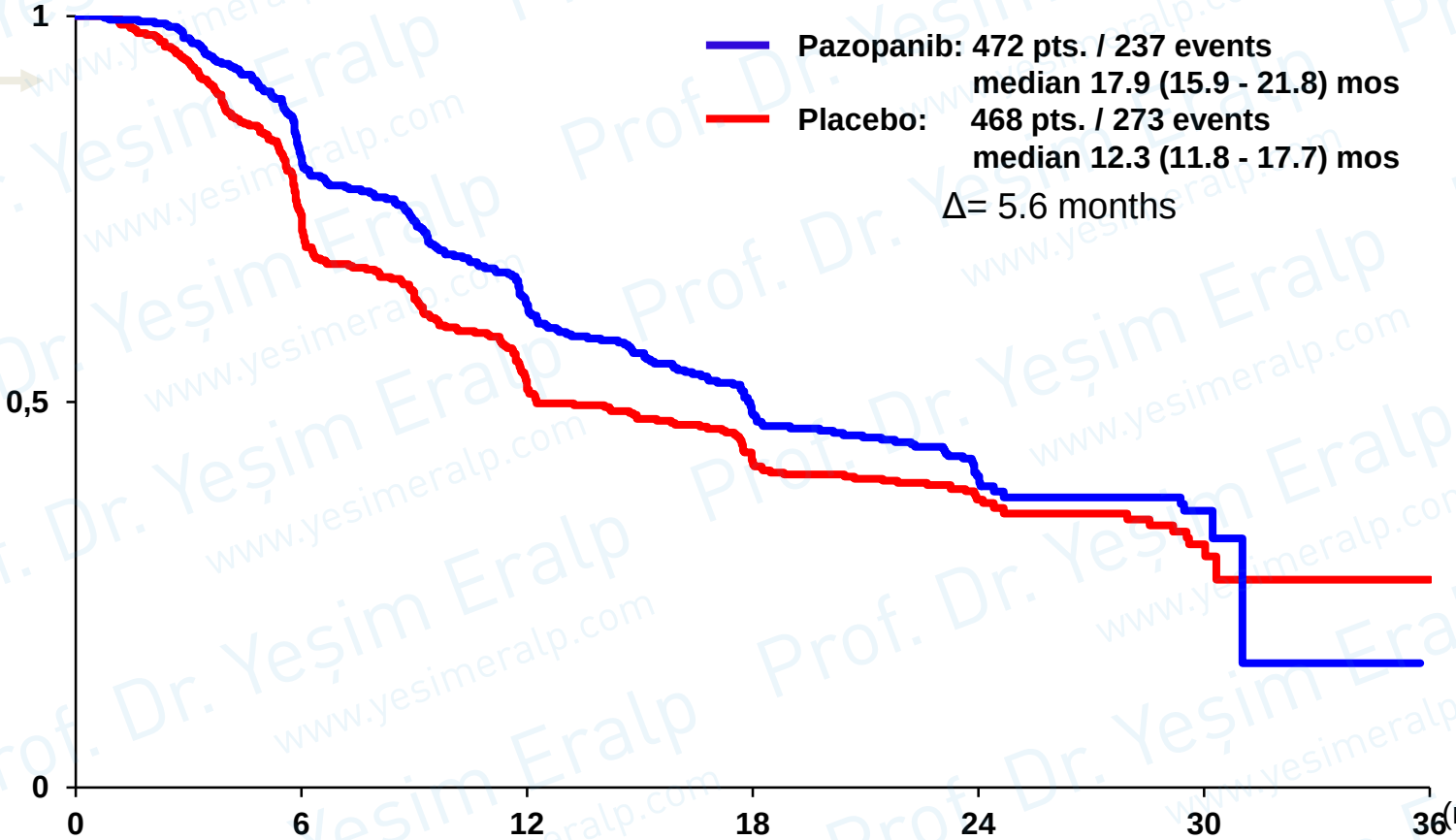
*Original design was for 12 months and later amended to 24 months

Du Bois A et al J Clin Oncol 31, 2013 (suppl; abstr LBA5503)

AGO-OVAR 16

Primary Endpoint: Progression-free Survival (RECIST)

Median time from Diagnosis: 7 months



Patients at risk							
	472	332	234	171	91	19	
	468	318	208	164	88	20	1

Du Bois A et al J Clin Oncol 31, 2013 (suppl; abstr LBA5503)

AGO-OVAR 16

Grad 3-4 Yan Etkiler

	Placebo (N=461)	Pazopanib (N=477)	Δ
Hipertansiyon	**26 (6%)**	**147 (31%)**	**121 (25%)**
KC toksisite	**3 (<1%)**	**45 (9%)**	**42 (9%)**
Nötropeni	**7 (2%)**	**47 (10%)**	**40 (8%)**
Diare	**5 (1%)**	**39 (8%)**	**34 (7%)**
Asthenia / Fatigue	1 (<1%)	13 (3%)	12 (3%)
Thrombocytopenia	3 (<1%)	12 (3%)	9 (2%)
Palmar-plantar erythrodysesthesia	1 (<1%)	9 (2%)	8 (2%)
Headache	3 (<1%)	8 (2%)	5 (1%)
Abdominal pain	5 (1%)	8 (2%)	3 (<1%)
Proteinuria	2 (<1%)	6 (1%)	4 (<1%)
Arthralgia	3 (<1%)	5 (1%)	2 (<1%)

İdame Olaparib: Study 19

Hastalar:

- Platinum-duyarlı HG serous over ca
- ≥2 platin-bazlı rejim
- yanıt: CR/PR

Olaparib 400mg bid, PO (n=136)

Randomized 1:1

Plasebo (n=129)

Primary endpoint

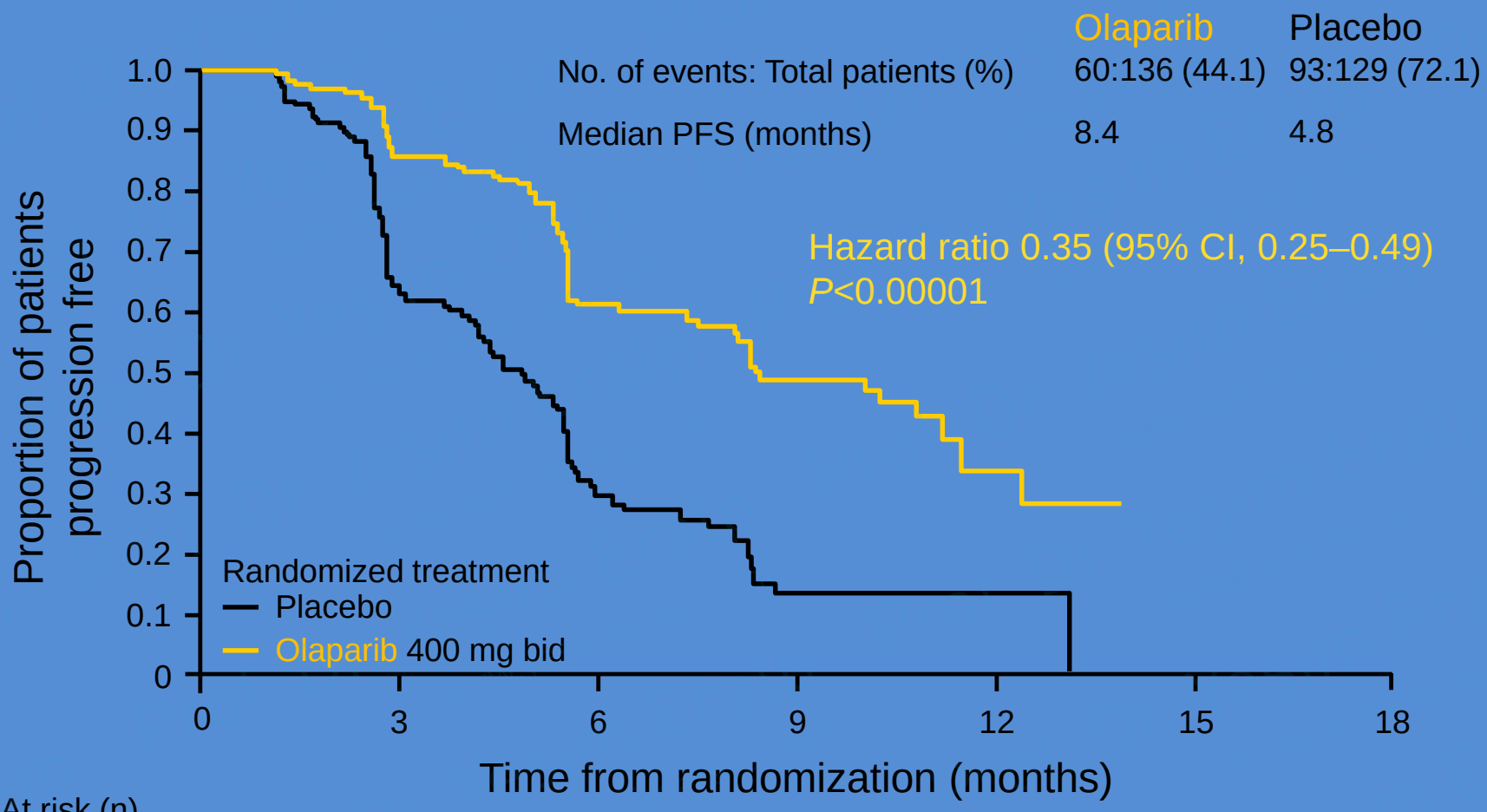
PFS by RECIST

Secondary endpoints

TTP by CA-125 (GCIG criteria) or RECIST, OS, safety

Ledermann et al. J Clin Oncol 2011;29 (suppl; abstr 5003); N Engl J Med. 2012 Apr 12;366(15):1382-92.

Study 19: PFS



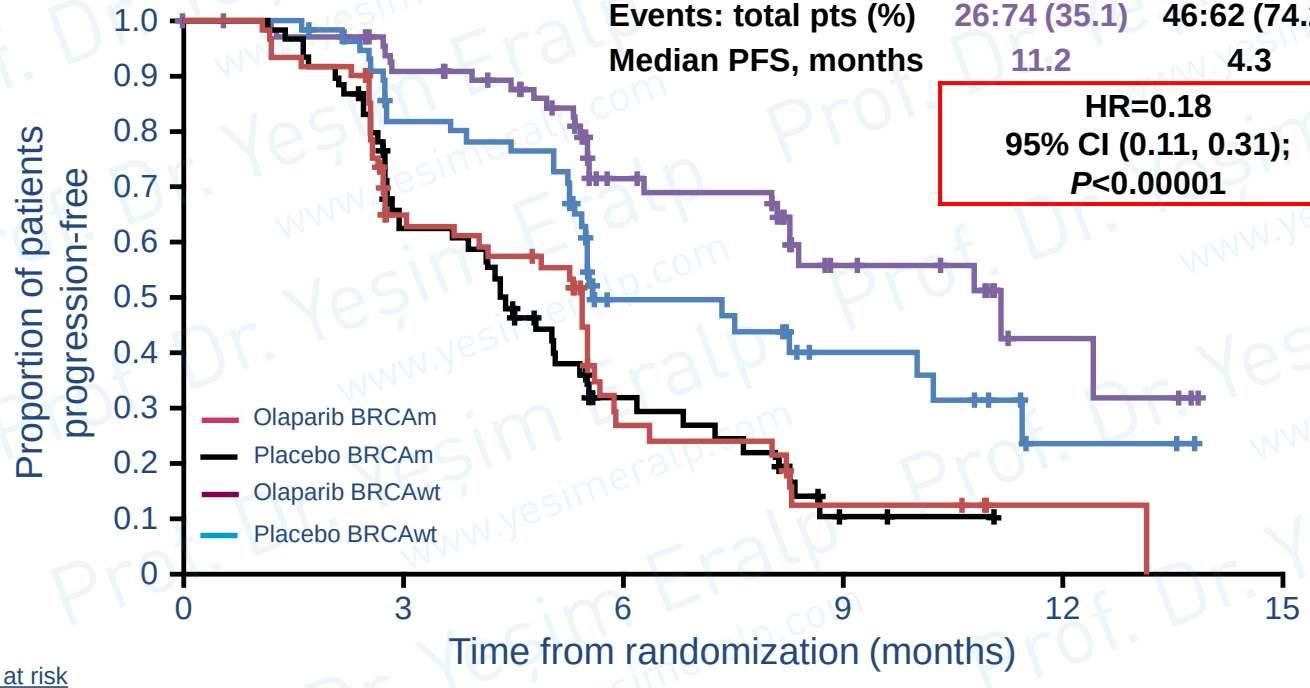
At risk (n)

Olaparib	136	104	51	23	6	0	0
Placebo	129	72	23	7	1	0	0

Ledermann et al. J Clin Oncol 2011;29 (suppl; abstr 5003); N Engl J Med. 2012 Apr 12;366(15):1382-92.

Study 19: PFS & BRCAm status

	BRCAm (n=136)		BRCAwt (n=118)	
	Olaparib	Placebo	Olaparib	Placebo
Events: total pts (%)	26:74 (35.1)	46:62 (74.2)	32:57 (56.1)	44:61 (72.1)
Median PFS, months	11.2	4.3	5.6	5.5
	HR=0.18 95% CI (0.11, 0.31); *P*<0.00001		HR=0.53 95% CI (0.33, 0.84); *P*=0.007	



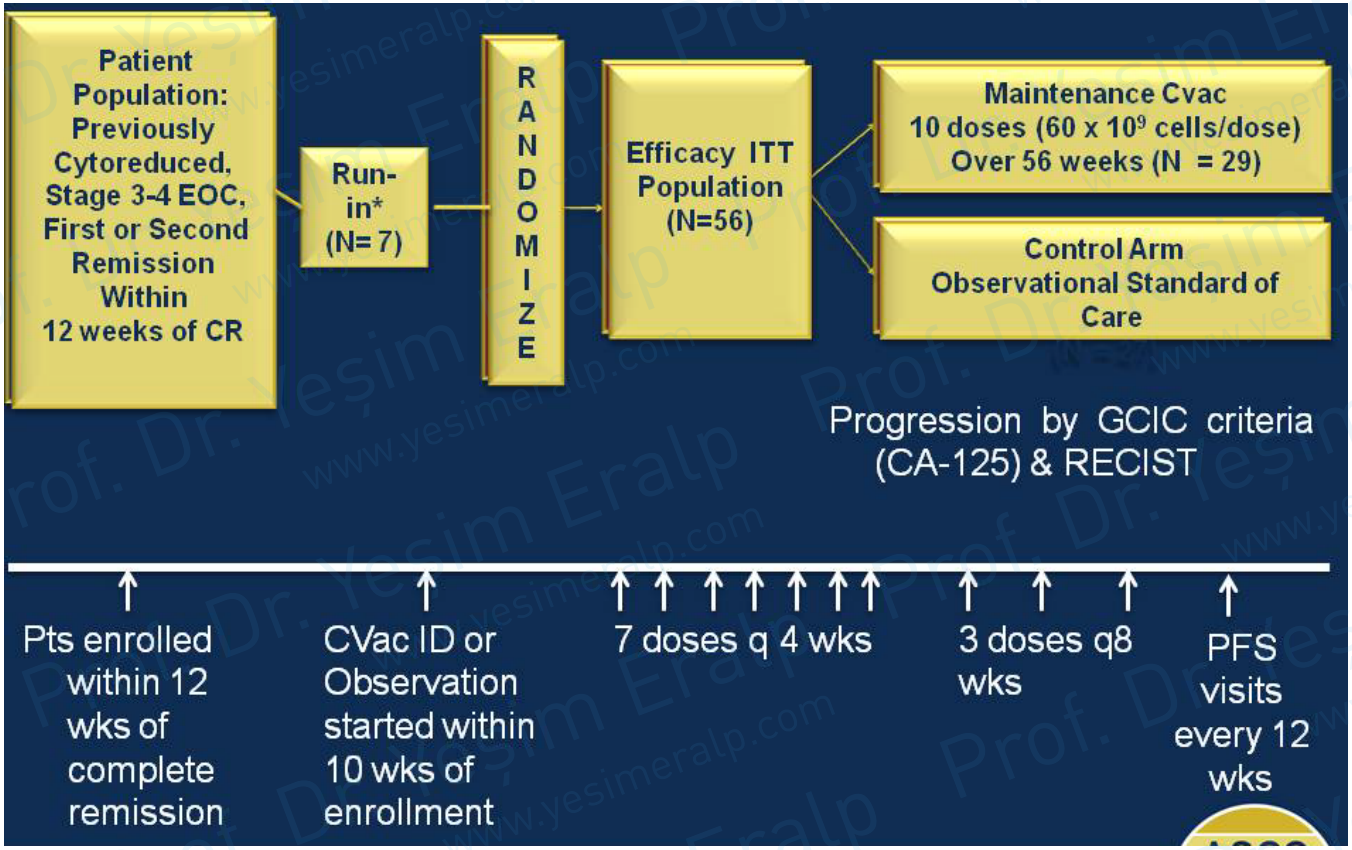
Number at risk

Olaparib BRCAm	74	59	33	14	4	0
Placebo BRCAm	62	35	13	2	0	0
Olaparib BRCAwt	57	44	17	9	2	0
Placebo BRCAwt	61	35	10	4	1	0

BRCAwt, wild type (includes patients with no known BRCAm or a mutation of unknown significance)

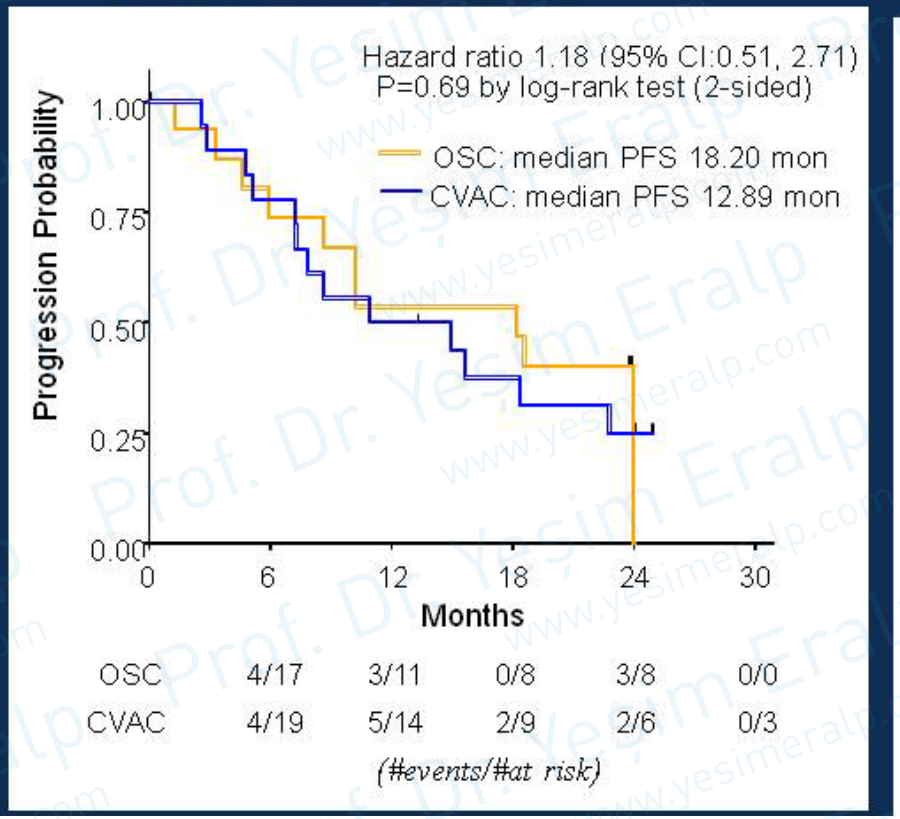
C-VAC & CAN-003

- MUC-1 proteini taşıyan dendritik kanser aşısı
- Over kanserinde ve bazı ca tiplerinde aberran ekspresyon

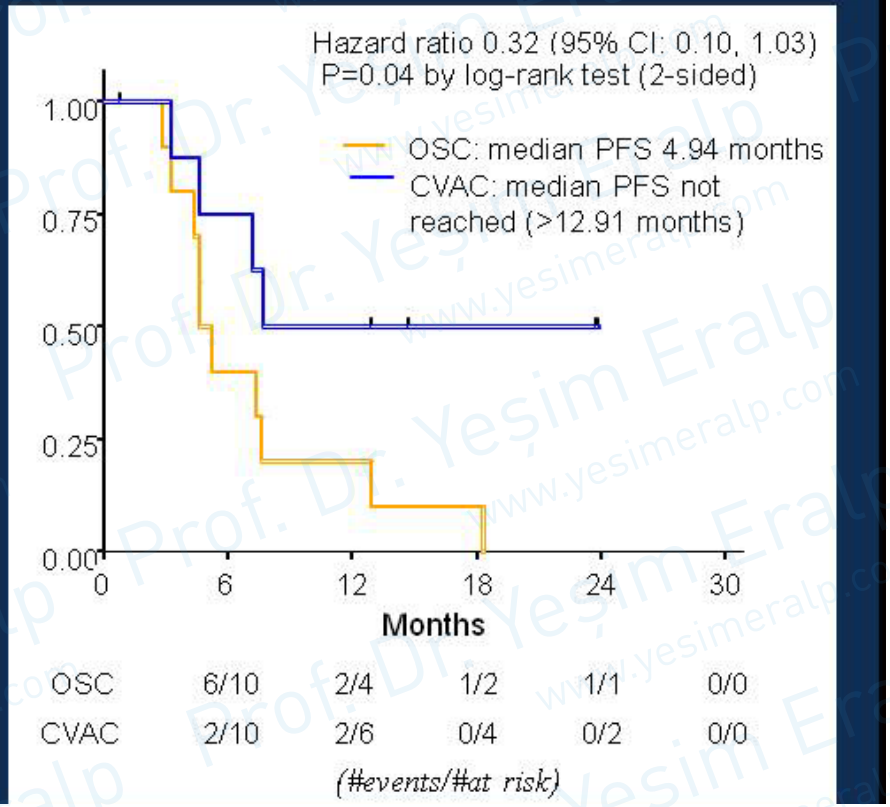


CAN-003 PFS Results

- First Remission CR1



- Second Remission CR2



- Sadece 2. remisyonda PFS avantajı
  - KT ile MUC ekspresyon farkı ?
  - Daha iyi prognozlu grupta etkinlik farkı yok ?
- Doku ve immun yanıt analizleri devam ediyor

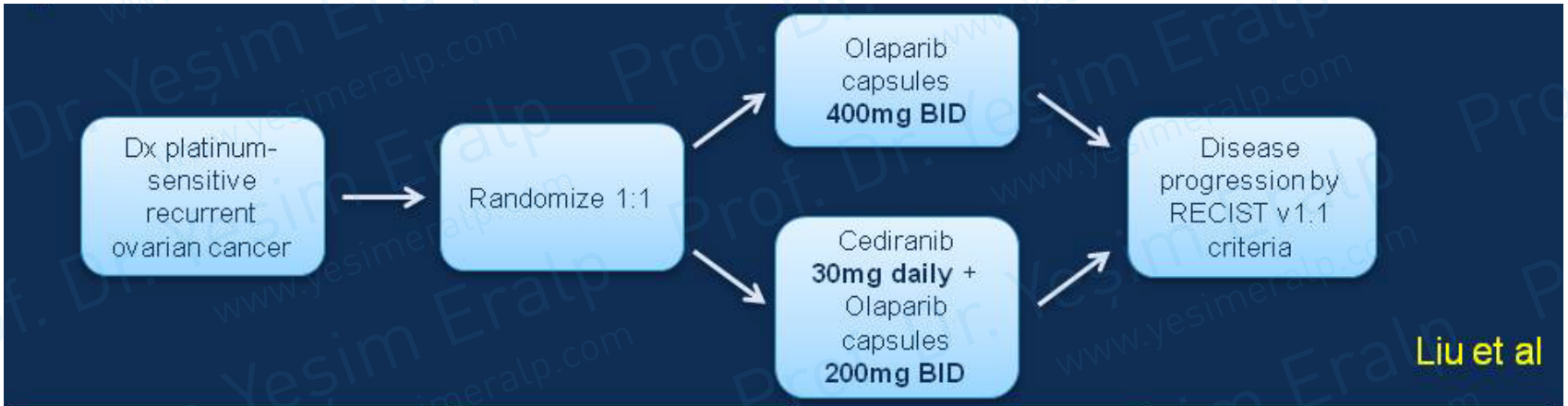
PLATİN DUYARLI NÜKS

Platin-duyarlı Nükste Etkinlik

	PFS (med months)	% 1st relapse	% 6-12 m PFI
OCEANS C/Gem	8.4	100	42
OCEANS + bev	**12.4**	*100*	*41*
CALYPSO C/Pax	9.4	83	36
CALYPSO C/PLD	11.3	83	36
ICON 4 C/Pax	12.0	90	25
OVAR 2.5 C/Gem	8.6	100	40
ICON 6 Plat-based	8.7	100	36
ICON 6 +cediranib	**11.1**	*100*	*30*
TRINOVA-1 wk PAC *	**5.4**	**NA**	**NA**
TRINOVA-1 wk PAC + Trebananib	**7.2**	**NA**	

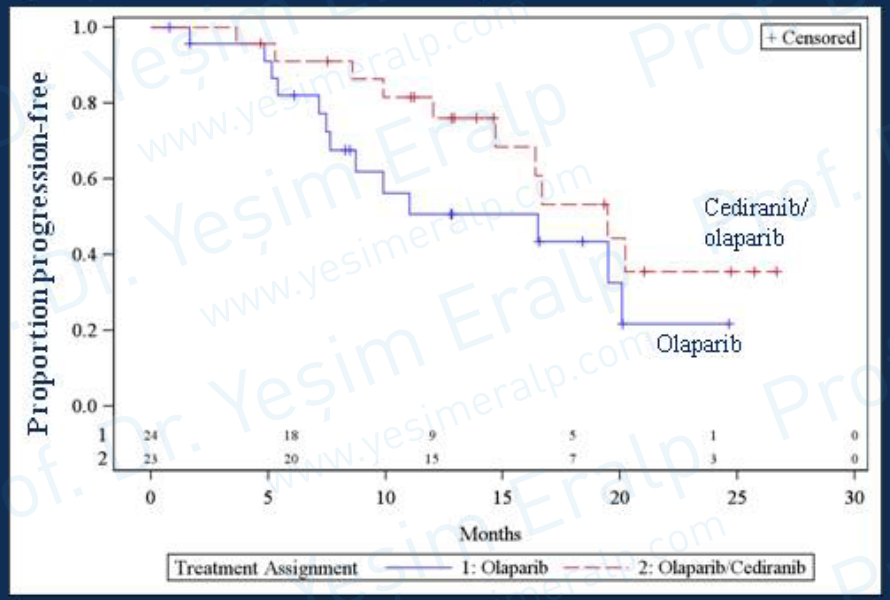
*: GS avantajı

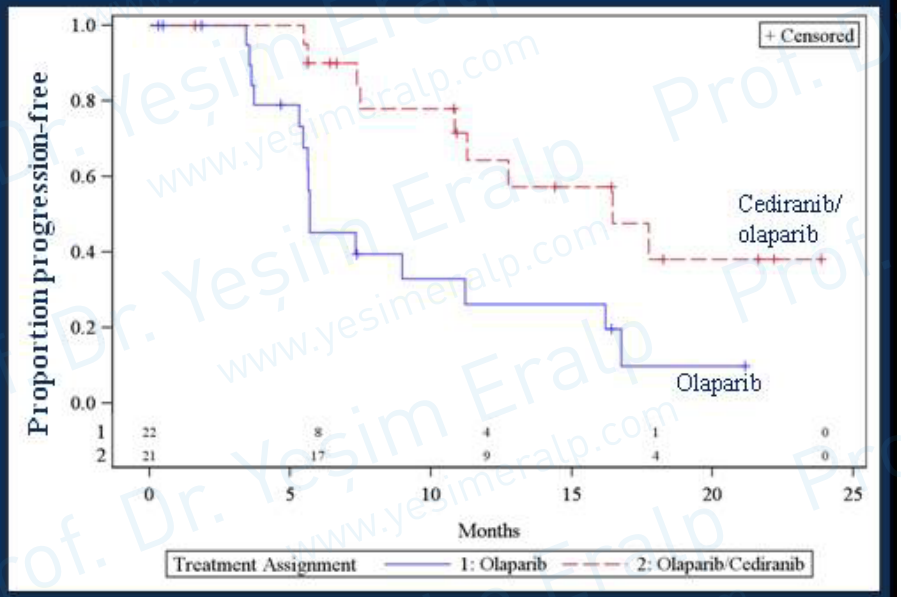
Platin-duyarlı Nükste Olaparib +/- Cediranib



	Olaparib (N = 46)	Cediranib/olaparib (N = 44)	P-value
BRCA mutation status			
Carrier	24 (52.2%)	23 (52.3%)	0.92
Non-carrier	11 (23.9%)	12 (27.3%)	
Unknown	11 (23.9%)	9 (20.5%)	
Prior platinum-free interval			
6-12 months	26 (56.5%)	23 (52.3%)	0.83
>12 months	20 (43.5%)	21 (47.7%)	
Number of prior lines			
1	17 (37.0%)	26 (59.1%)	0.11
2	18 (39.1%)	10 (22.7%)	
3+	11 (23.9%)	8 (18.2%)	

Cediranib + Olaparib: BRCA nMut grupta PFS avantajı





	BRCA Mutation Carrier		BRCA Non-carrier/Unknown	
	Olaparib	Ced/Olap	Olaparib	Ced/Olap
PFS events	13	10	15	9
Median PFS	16.5 mo	19.4 mo	5.7 mo	16.5 mo
	p=0.16		p=0.008	
	HR 0.55 (95% CI: 0.24-1.27)		HR 0.32 (95% CI: 0.14-0.74)	

Rebecca Kristeleit 2014 ASCO Annual Meeting

Platin duyarlı Over Kanserinde Olaparib + Cediranib

- BRCA nMut PFS: 5.7 vs 16.5 ay: KT siz seçenek !!
- HT, diare, yorgunluk: çoğu cediranib ile ilgili
  - Kombine kolda %77; olaparib %24 doz azaltması gerekmiş
- Gelecek hedefler:
  - Platin bazlı KT vs Olaparib + Cediranib (BRCAnMut)
  - Platin bazlı KT+ Cediranib vs Olaparib + Cediranib idame (BRCAnMut)

Response to platinum-based chemotherapy in Platinum-sensitive relapsed ovarian cancer

	PFS (med months)	% 1st relapse	% 6-12 m PFI
OCEANS C/Gem	8.4	100	42
OCEANS + bev	**12.4**	*100*	*41*
CALYPSO C/Pax	9.4	83	36
CALYPSO C/PLD	11.3	83	36
ICON 4 C/Pax	12.0	90	25
OVAR 2.5 C/Gem	8.6	100	40
ICON 6 Plat-based	8.7	100	36
ICON 6 +cediranib	**11.1**	*100*	*30*
OLAPARIB	**9.0**	**37**	**57**
OLAPARIB + CEDIRANIB	**17.7**	**59**	**52**

Presented by: JA Ledermann

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Jonathan Ledermann at 2014 ASCO Annual Meeting

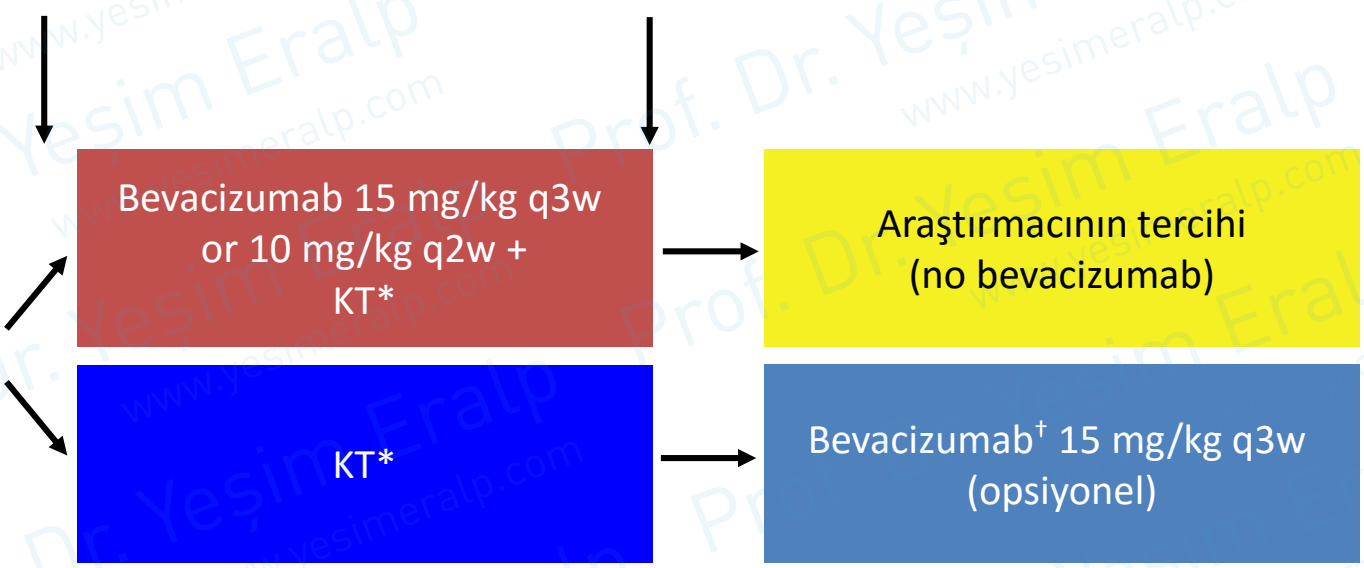
PLATİN DİRENÇLİ NÜKS

AURELIA:
Platin-dirençli Over ca Bevacizumab + KT

- Randomize, faz III

KT, önceki antiangiogenic ted, tedavisiz aralık(< 3 vs 3-6 ay)göre stratifiye

PD/toksisite



*KT seçimi: paclitaxel 80 mg/m^2 Days 1, 8, 15, and 22 q4w; topotecan 4 mg/m^2 Days 1, 8, and 15 q4w (or 1.25 mg/m^2 Days 1-5 q3w); PLD 40 mg/m^2 Day 1 q4w.
†Permitted on clear evidence of PD.

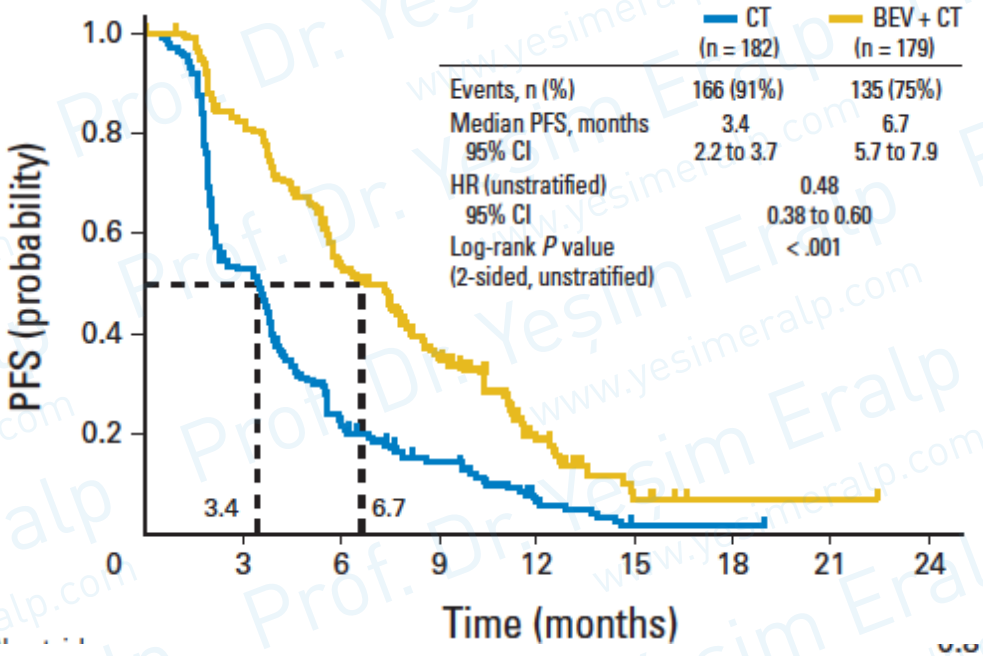
Eric Pujade-Laura J Clin Oncol 32:1302-1308. © 2014

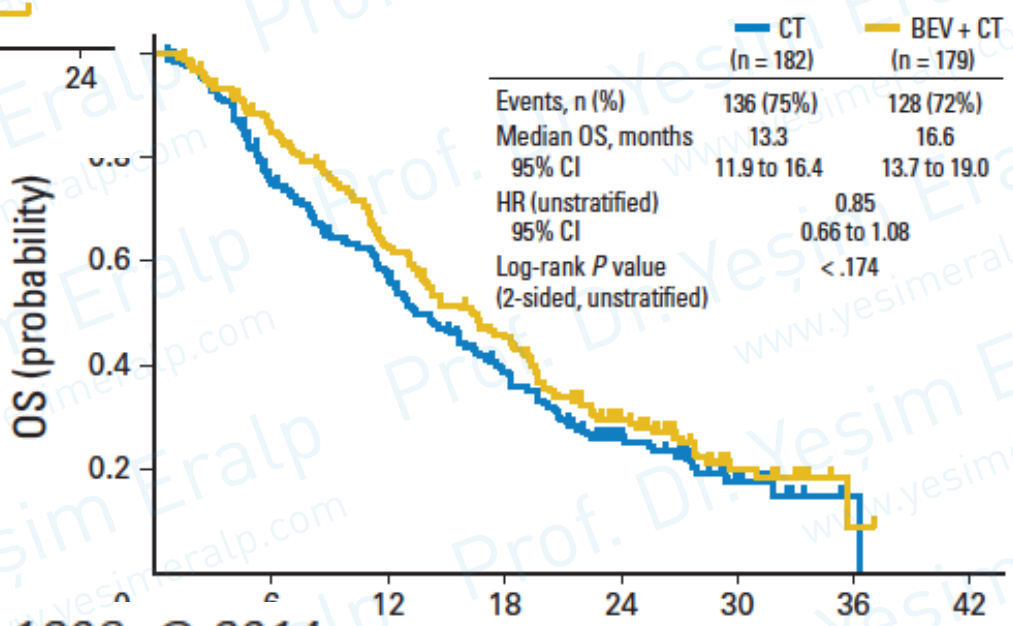
AURELIA: Hasta Özellikleri

	Bevacizumab + CT (n = 179)	CT (n = 182)
Median age, yrs (range)	62 (25-80)	61 (25-84)
ECOG PS 0, %	60	54
Primary ovarian cancer, %	93	86
Serous/adenocarcinoma at diagnosis, %	87	84
Grade 2/3 histology at diagnosis, %	82	84
Previous antiangiogenic therapy, %	7	8
PFI < 3 mos, %	28	25
Measurable disease, %	80	79
Ascites, %	34	30

Pujade-Lauraine E, et al. ASCO 2012. Abstract LBA5002. Reproduced with permission.

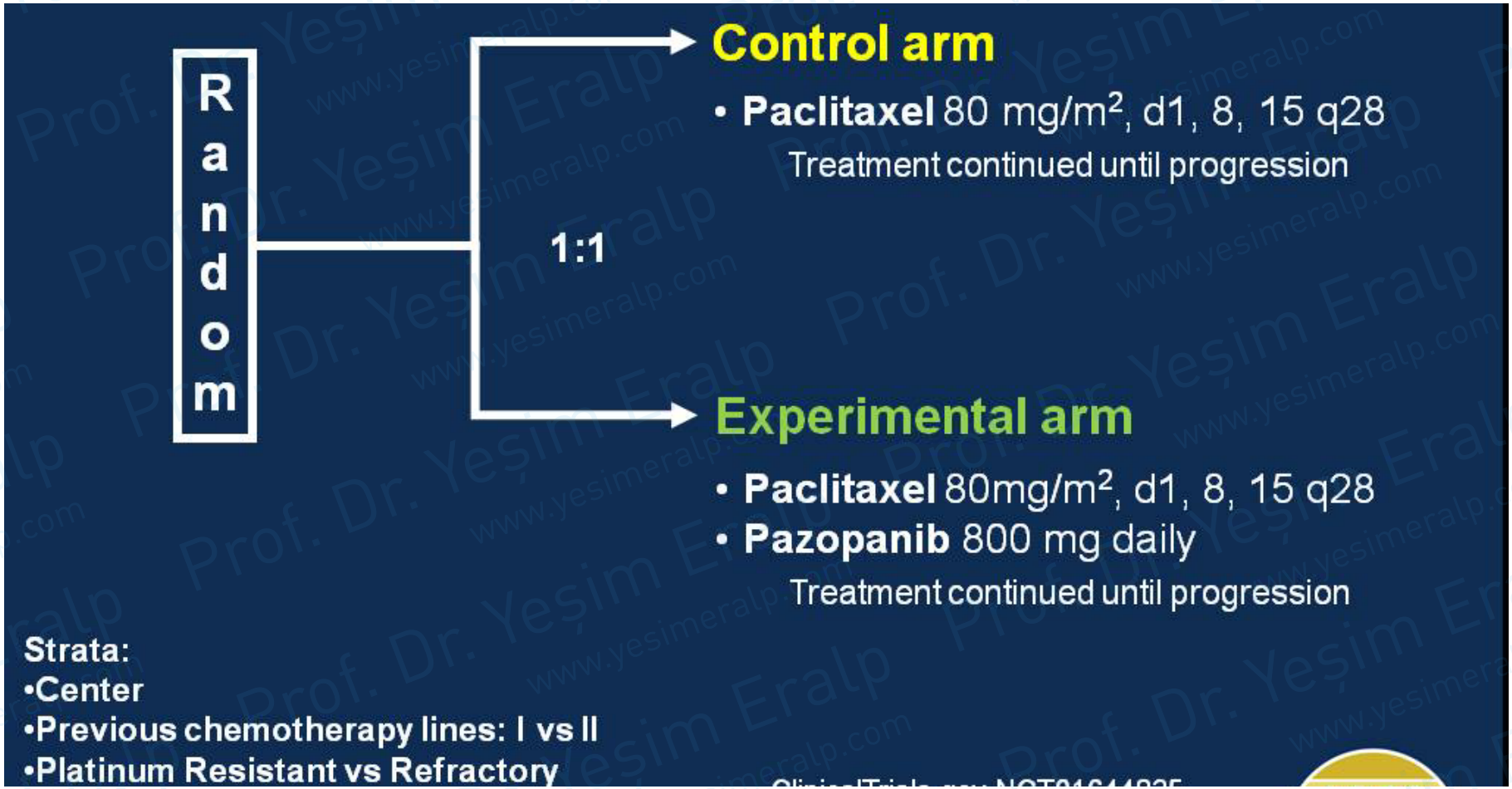
AURELIA: PFS & OS





Eric Pujade-Laura J Clin Oncol 32:1302-1308. © 2014

MITO-11:
Platin-dirençli Nükste PAC + Pazopanib



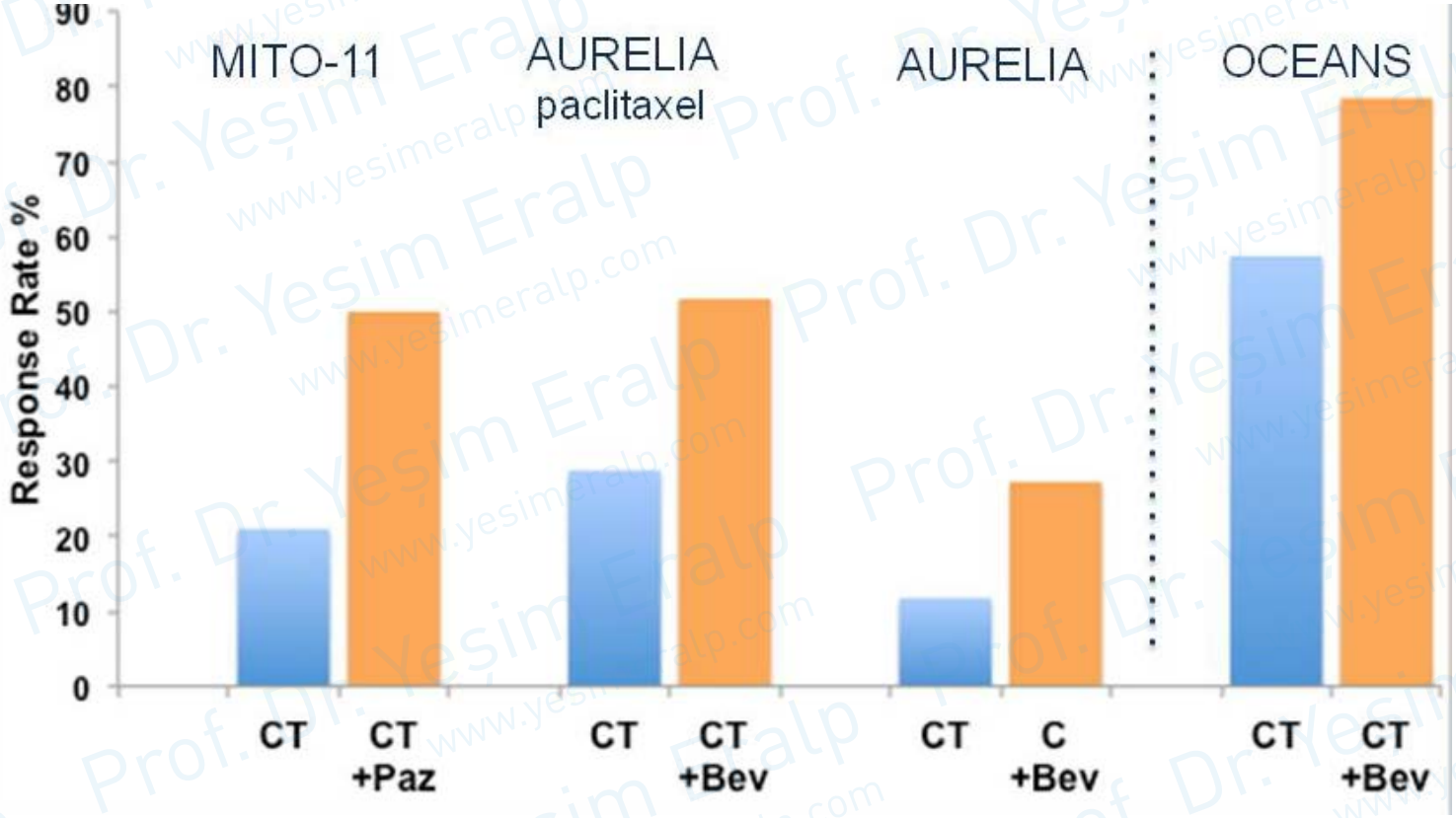
Hasta Özellikleri

	Paclitaxel (n = 36)	Paclitaxel + pazopanib (n = 37)	Total (n = 74)
Median age (range)	58 (27-74)	56 (43-74)	57 (27-74)
Platinum-free-interval			
Resistant	27 (76%)	28 (76%)	56 (76%)
Refractory	8 (22%)	9 (24%)	17 (23%)
Sensitive*	1(2%)	0(0%)	1(1%)
Previous chemo lines			
1	15 (41%)	17 (46%)	32 (43%)
2	18 (51%)	17(46%)	36(49%)
3**	3 (8%)	3 (8%)	6 (8%)

* Ineligible according to protocol, included into ITT analysis.
** Having received 2 platinum-containing regimens, one non-platinum for resistant disease

Presented By Sandro Pignata at 2014 ASCO Annual Meeting

Pt-dirençli Hastalık: KT Yanıt Oranları



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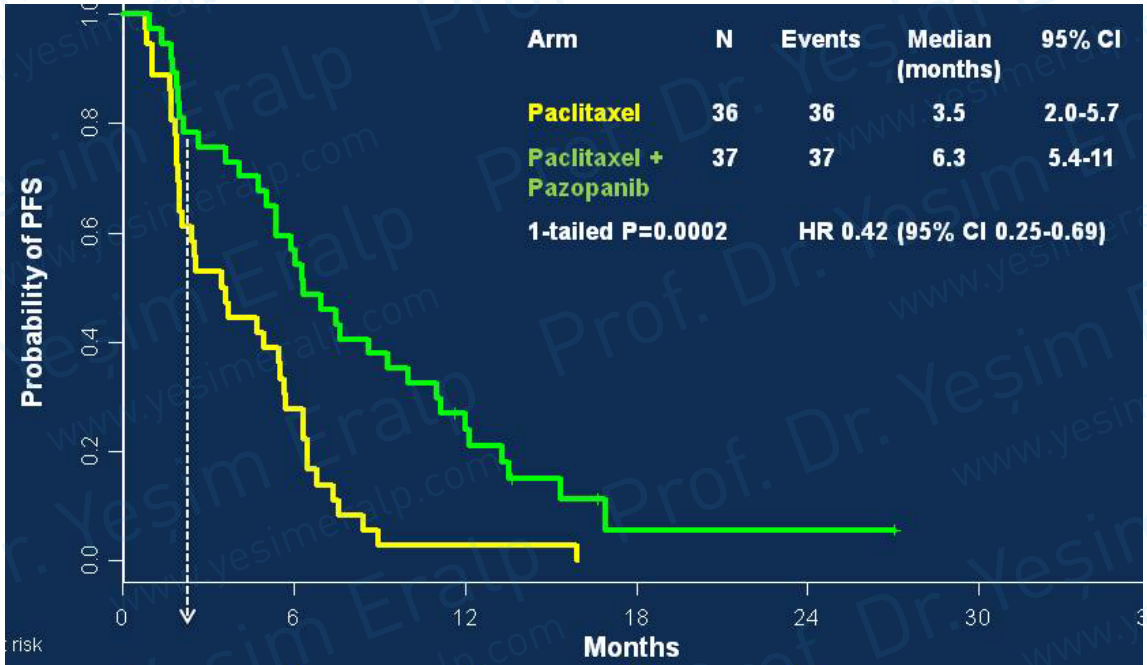
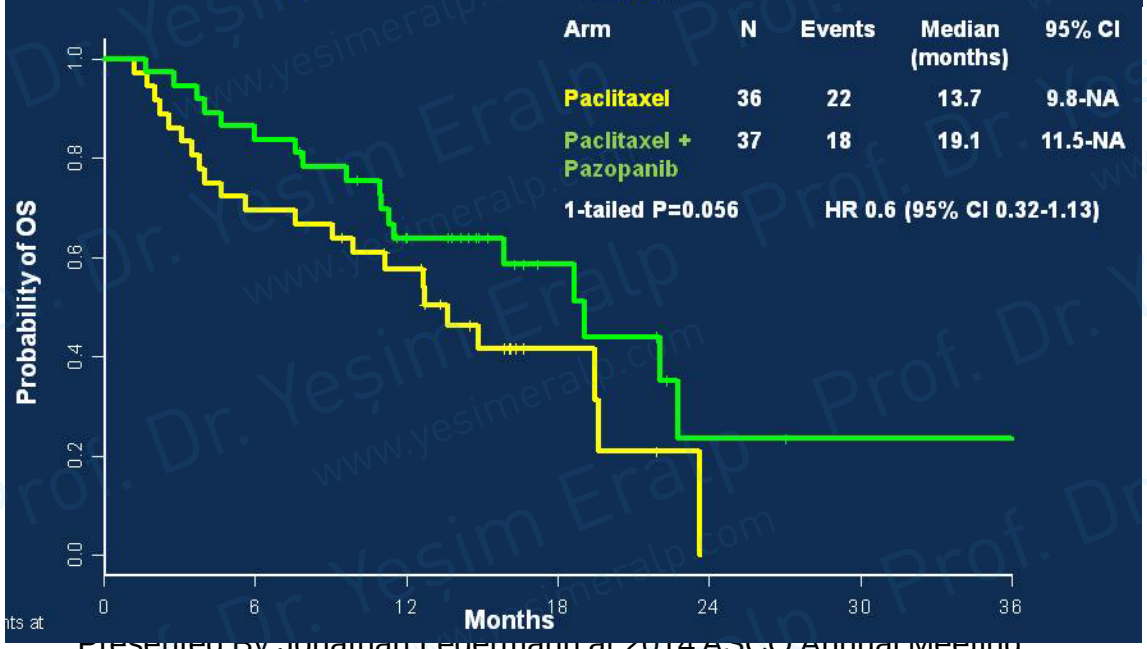
PFS



OS



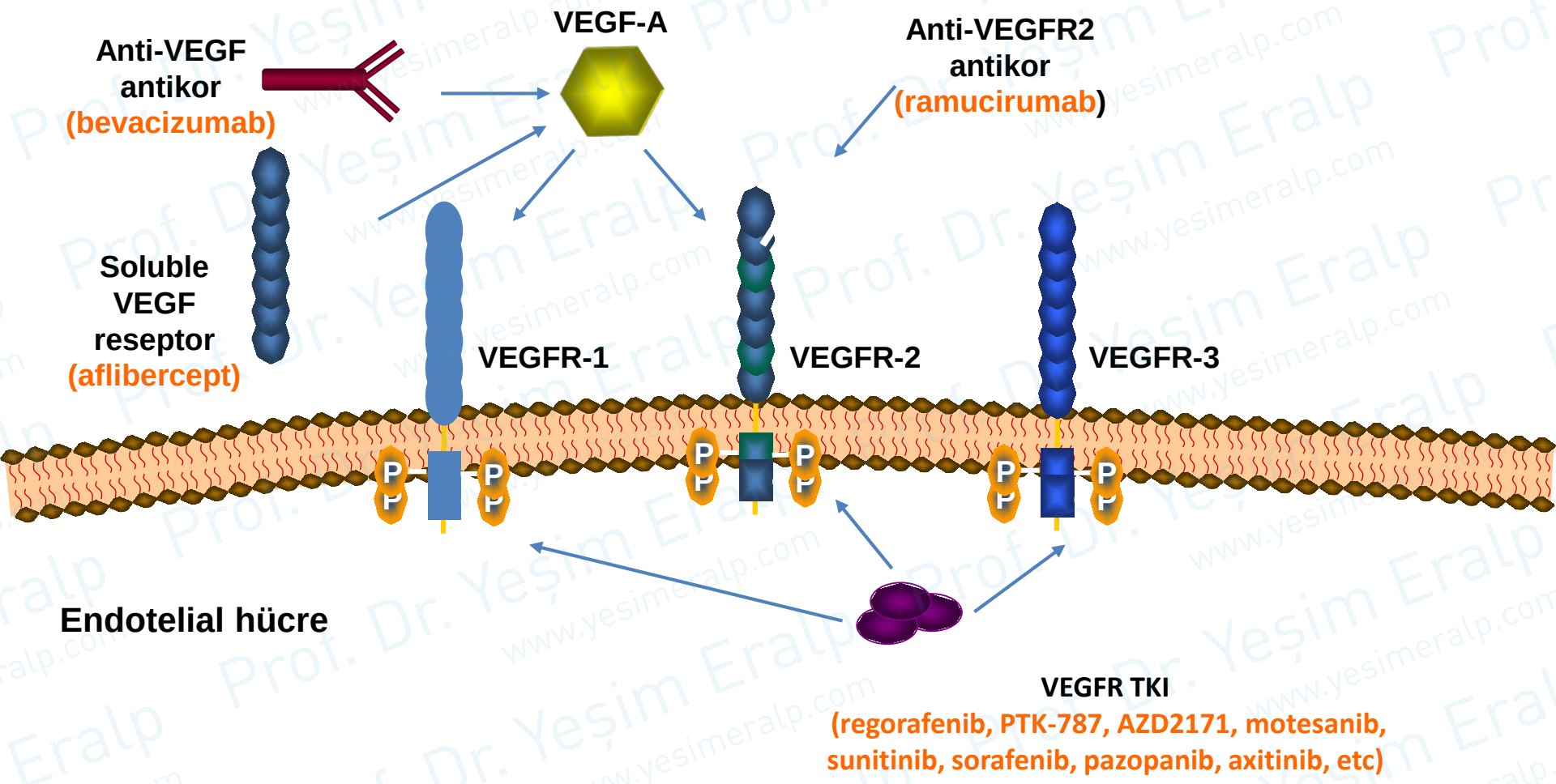
Presented By Jonathan Lederman at 2014 ASCO Annual Meeting

MİTO-11: sonuç

- Grad 3-4 Yan etkiler:
  - HT: %8 vs 0
  - Yorgunluk: %11 vs %6
  - Diare: %5 vs %3
  - Perf: %3 vs 0

- Umut verici PFS değeri
- QoL ??
- Yarar gören alt-grup: Biyobelirteç analizi ?

VEGF Yolağını Hedefleyen Ajanlar



Angiopoietin Axis

Ang1 and Ang2 Interact With Tie2 Receptor to Mediate Vascular Remodeling

Ang1 stabilizes endothelial junctions and increases pericyte coverage[1,2]

"Vessel quality"

Ang2 promotes endothelial sprouting and increases blood vessel density[1,2,3]

"Vessel quantity"

Ang1 and Ang2 levels are elevated in patients with ovarian carcinoma[4]

Trebananib (AMG 386)

Peptibody That Binds and Neutralizes Ang1 and Ang2

- Trebananib is an investigational recombinant peptide-Fc fusion protein ("peptibody")

TRINOVA-1: Study Design

Stratification Factors

- Platinum-free interval (≤ 6 vs 6 to 12 months)
- Measurable disease (Yes/No)
- Region (North America, Western Europe/Australia, rest of world)

ClinicalTrials.gov Identifier: NCT01204749

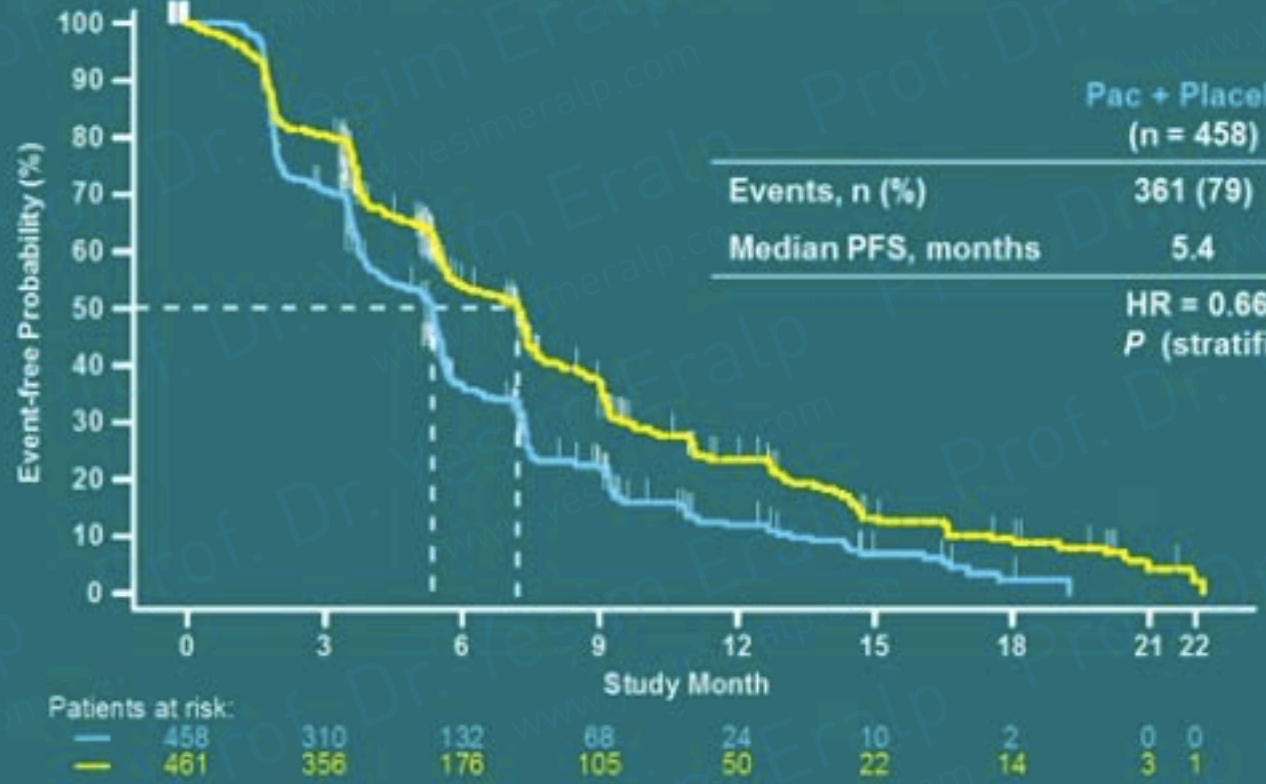
Primary endpoint – PFS

- Planned at ≥ 510 PFS events
- Sample size = 900
- 90% power to detect a 33% difference (median of 6 vs 8 months)

Key secondary endpoint – overall survival (OS)

Prior lines of therapy, n (%)*		
1	172 (38)	190 (41)
2	172 (38)	174 (38)
3	114 (25)	95 (21)
Platinum-free interval, n (%)†		
≤ 6 months	245 (53)	235 (51)
6 to 12 months	212 (46)	223 (48)

PFS Primary Analysis (March 2013*)

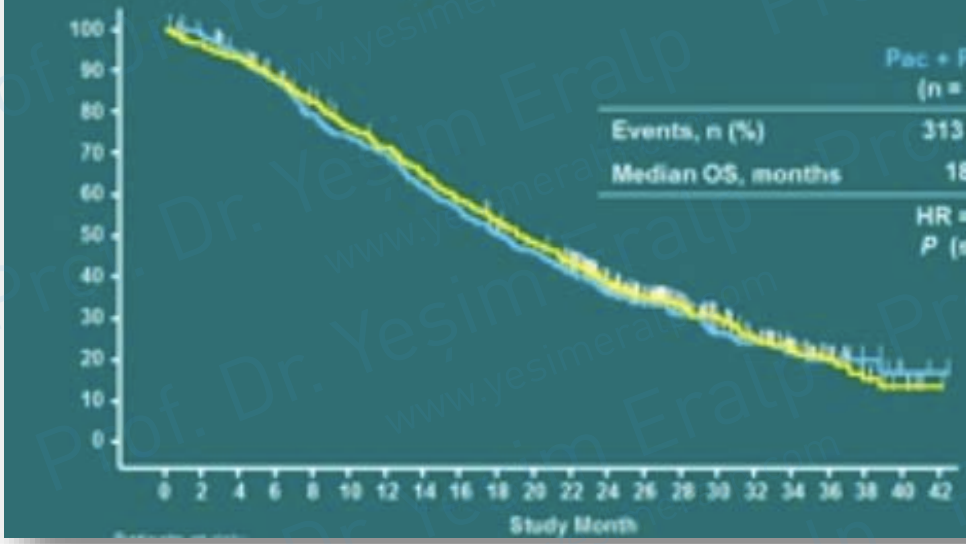


	Pac + Placebo (n = 458)	Pac + Trebananib (n = 461)
Events, n (%)	361 (79)	310 (67)
Median PFS, months	5.4	7.2

HR = 0.66 (95% CI, 0.57–0.77)
P (stratified log-rank) < 0.001

*Monk BJ et al. *Lancet Oncol* 2014;15:799–808.

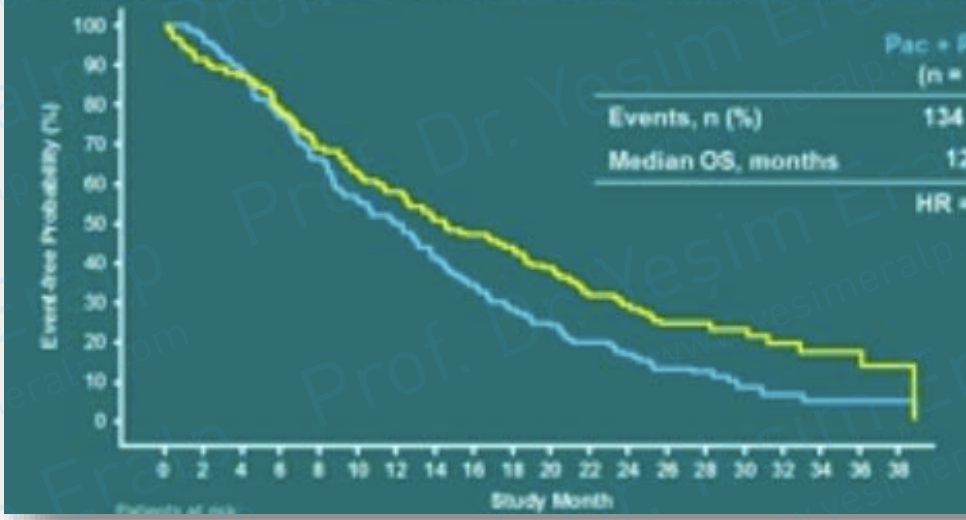
OS in ITT Population



	Pac + Placebo (n = 458)	Pac + Trebananib (n = 461)
Events, n (%)	313 (68)	315 (68)
Median OS, months	18.3	19.3

HR = 0.95 (95% CI, 0.81–1.11)
P (stratified log-rank) = 0.52

Preplanned OS Subgroup Analysis of Patients With Ascites at Baseline



	Pac + Placebo (n = 154)	Pac + Trebananib (n = 141)
Events, n (%)	134 (87)	107 (76)
Median OS, months	12.3	14.5

HR = 0.72 (95% CI, 0.55–0.93)
= 0.011

Sonuç: Trebananib & Over Ca

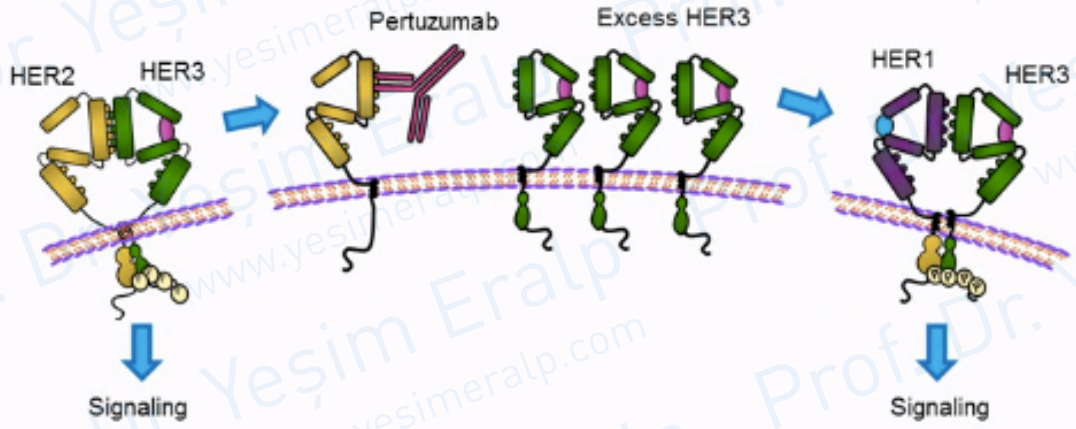
- Anjiopoietin over kanseri için değerli bir hedeftir
- Trebananib (+ Paklitaksel) genel çalışma grubu içinde
  - ORR & PFS avantajı
  - Başta ascitesli hastada OS avantajı (protokol öncesi stratifikasyon)

Efficacy and safety of chemotherapy ± pertuzumab for platinum-resistant ovarian cancer: AGO-OVAR 2.20/ENGOT-ov14/PENELOPE double-blind placebo-controlled randomized phase 3 trial

C Kurzeder[1]; I Bover[2]; F Marmé[3]; J Rau[4]; P Pautier[5]; N Colombo[6]; D Lorusso[7]; P Ottevanger[8]; M Bjurberg[9]; C Marth[10]; P Barretina-Ginesta[11]; I Vergote[12]; A Floquet[13]; JM del Campo[14]; S Mahner[15]; L Bastiere-Truchot[16]; L Mitchell[16]; S Polleis[17]; A du Bois[1]; A Gonzalez-Martin[18]

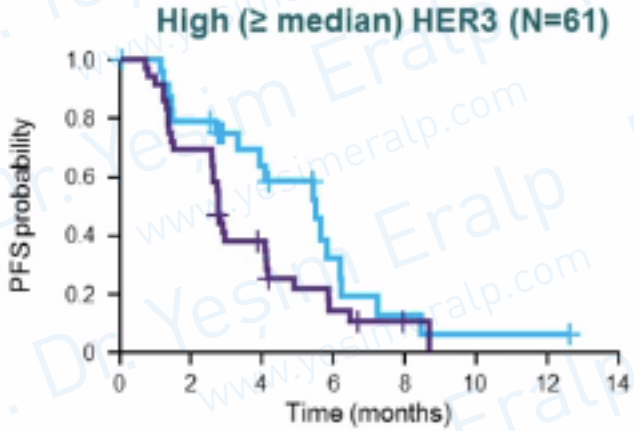
[1]AGO and Kliniken Essen Mitte, Essen, Germany; [2]GEICO and Hospital Son Llàtzer, Palma de Mallorca, Spain; [3]AGO and

Hypothesized mechanism of action of pertuzumab in OC

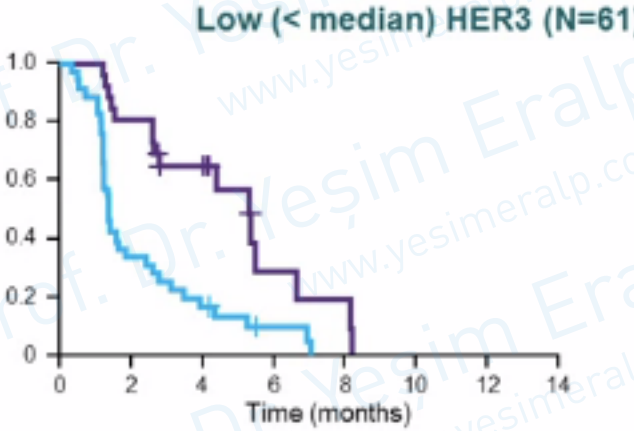


- When pertuzumab inhibits HER2 dimerization in patients with high HER3 mRNA expression, HER3 forms heterodimers with other HER family receptors, such as HER1
- The resulting complexes initiate signaling, driving proliferation and survival of the tumor despite pertuzumab treatment, allowing tumors to escape the effect of pertuzumab
- This escape mechanism would not be available in tumors with low HER3 mRNA expression, leading to better response to pertuzumab

TOC3258g: PFS & HER3
platin-dirençli hastalıkta retrospektif analiz

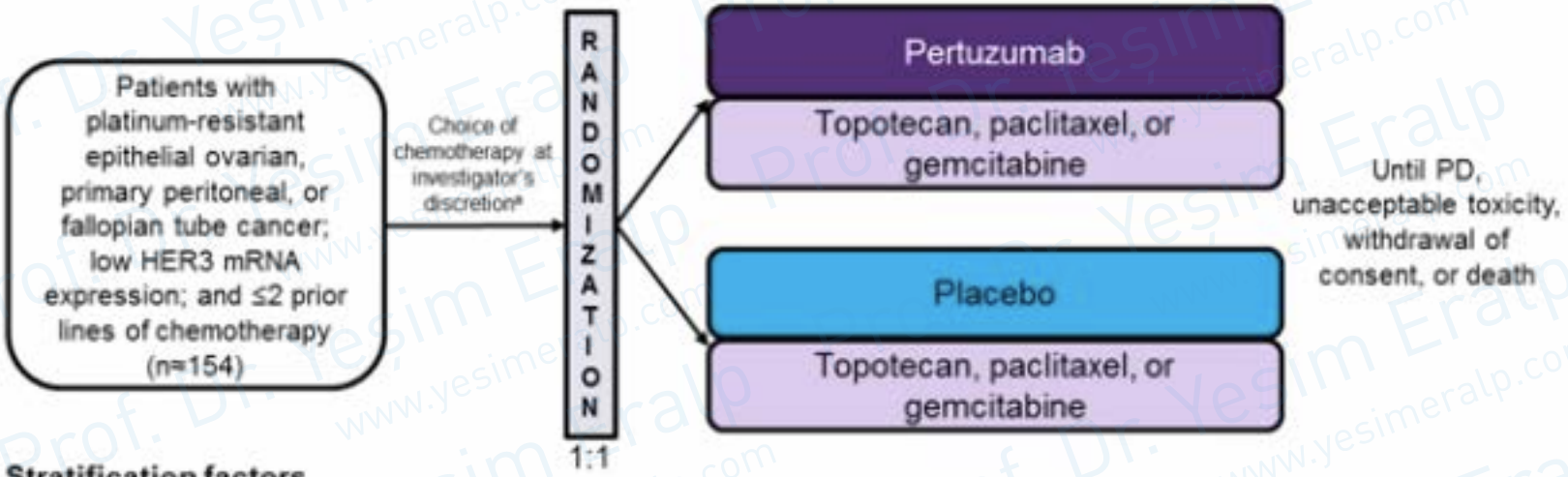


	Placebo + gem (N=24)	Pertuzumab + gem (N=37)
Median PFS, months	5.5	2.8
HR (95% CI)	1.68 (0.93–3.06)	



	Placebo + gem (N=35)	Pertuzumab + gem (N=26)
Median PFS, months	1.4	5.3
HR (95% CI)	0.32 (0.17–0.59)	

AGO-OVAR 2.20/PENELOPE: Part 2 study design

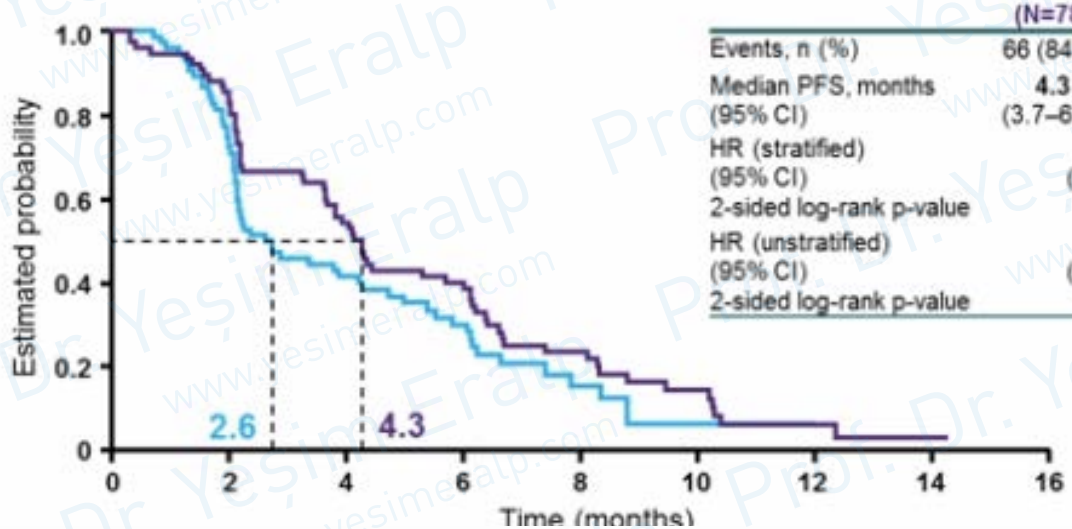


Stratification factors

- Selected chemotherapy cohort (topotecan vs paclitaxel vs gemcitabine)
- Previous anti-angiogenic therapy (yes vs no)
- Treatment-free interval from last platinum cycle to PD after platinum therapy (<3 vs 3–6 months)

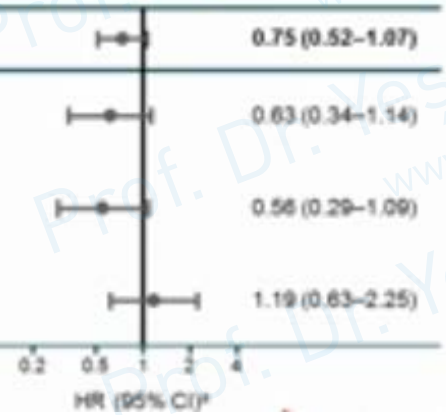
Selected chemotherapy[a]	Topotecan	25 (32.1)	24 (30.8)
	Paclitaxel	26 (33.3)	28 (35.9)
	Gemcitabine	27 (34.6)	26 (33.3)
Previous anti-angiogenic therapy[a]		27 (34.6)	30 (38.5)
Platinum-free interval, months[a]	<3	19 (24.4)	21 (26.9)
	3–6	59 (75.6)	57 (73.1)

PENELOPE & PFS



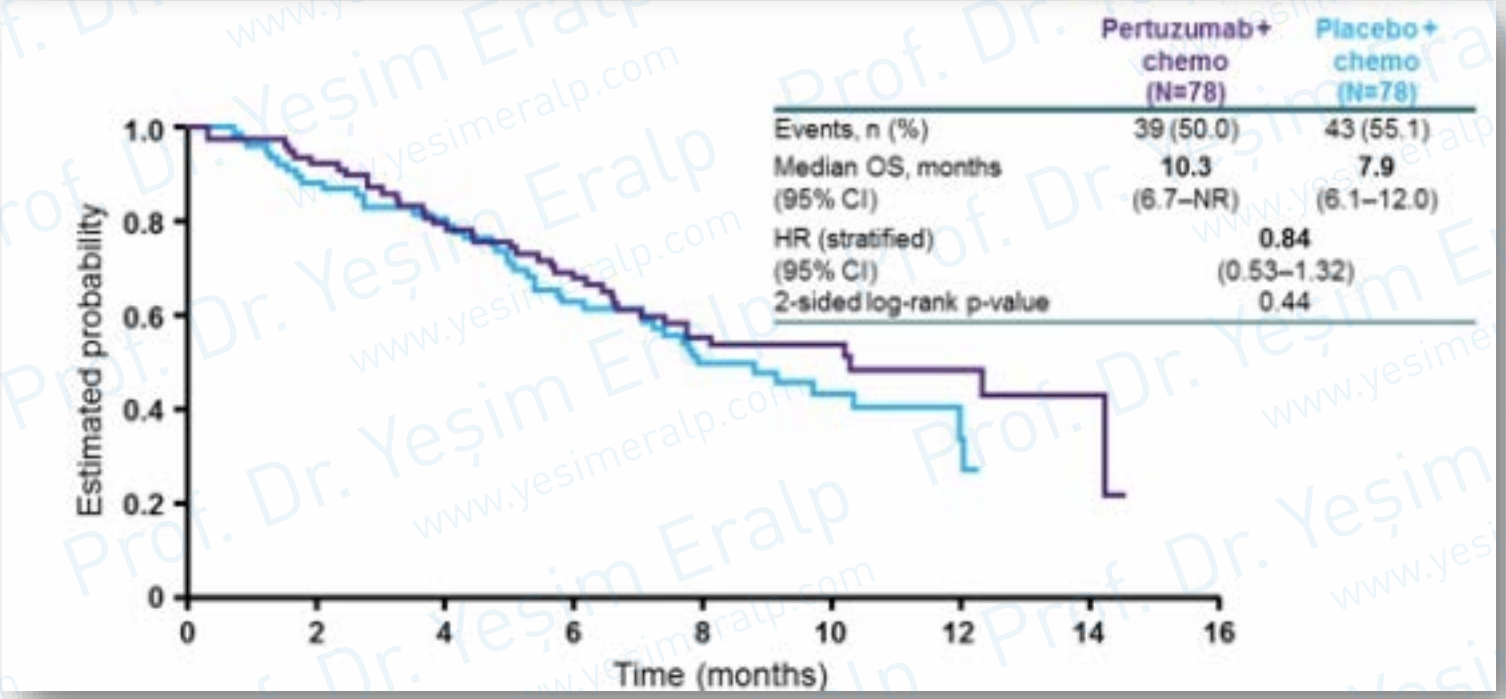
	Pertuzumab + chemo (N=78)	Placebo + chemo (N=78)
Events, n (%)	66 (84.6)	60 (76.9)[a]
Median PFS, months (95% CI)	**4.3** (3.7–6.0)	**2.6** (2.1–4.3)
HR (stratified) (95% CI)	**0.74** (0.50–1.11)	
2-sided log-rank p-value	0.14	
HR (unstratified) (95% CI)	**0.75** (0.52–1.07)	
2-sided log-rank p-value	0.12	

Chemotherapy	No. of events/patients (%) Pertuzumab + chemo	No. of events/patients (%) Placebo + chemo	Median PFS, months Pertuzumab + chemo	Median PFS, months Placebo + chemo	HR (95% CI)[a]
All	**66/78 (84.6)**	**60/78 (76.9)**	**4.3**	**2.6**	**0.75 (0.52–1.07)**
Gemcitabine	24/27 (88.9)	21/26 (80.8)	4.3	2.1	0.63 (0.34–1.14)
Paclitaxel	20/26 (76.9)	21/28 (75.0)	6.4	4.2	0.56 (0.29–1.09)
Topotecan	22/25 (88.0)	18/24 (75.0)	2.8	2.7	1.19 (0.63–2.25)



[a]Unstratified analysis

PENELOPE & OS: Interim Analiz



- Platin-dirençli hastalıkta ilk biyo-belirteç bazlı çalışma
- PFS; HR:0.74; p:NS
  - Gemsitabin ve paklitaksel ile avantaj
- Henüz GS avantajı yok; veri olgunlaşması bekleniyor

Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with previously treated, recurrent or refractory ovarian cancer: a phase Ib, open-label expansion trial

ABSTRACT 5509

Avelumab (MSB001071

- Fully human anti-PD-L1 IgG1 antibody

Patients

Patients with refractory or recurrent ovarian cancer (n=75)

- ECOG PS 0 or 1
- No PD-L1 preselection

Dosing

Avelumab 10 mg/kg IV Q2W until progression

Objectives

Primary: safety and tolerability

Select secondary: ORR, PFS, OS, PD-L1 status

RECIST 1.1 and irRC

Mary Disis,[1] Manish R. Patel,[2] Shubham Pant,[3] Jeffrey R.

Characteristics	n=75
Median age, years (range)	62 (38-84)
ECOG PS, n (%)	
0	31 (41.3)
1	44 (58.7)
# of prior regimens for locally advanced or metastatic disease, excluding adjuvant, n (%)	
≥3	51 (68.0)
2	10 (13.3)
≤1	14 (18.7)
Median (range)	4.0 (0-10)

Characteristics	n=75
Histology, n (%)	
Serous	53 (70.7)
Clear cell	2 (2.7)
Endometrioid	1 (1.3)
Mucinous	1 (1.3)
Transitional cell	1 (1.3)
Other*	17 (22.7)
Median time since metastatic disease, months (range)	29.0 (4.7, 206.5)

Data cutoff date: 13 February 2015

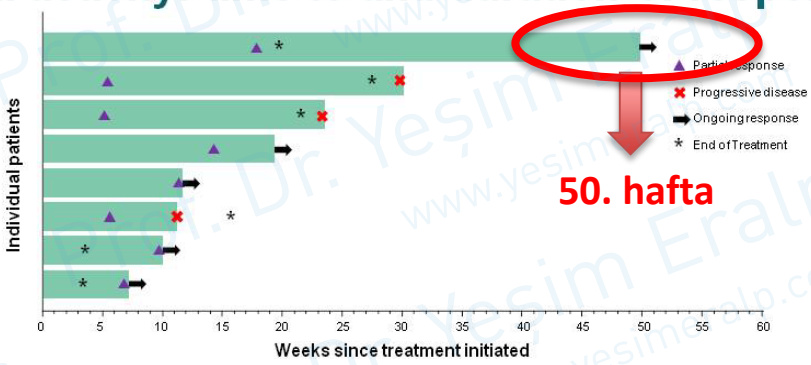
* Other denotes patients who were uncoded (13), missing (1), or

Best overall response by RECIST 1.1, unconfirmed*	Ovarian (n=75) n (%)
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)**
Disease control rate (DCR)†	41 (54.7)

Median duration of F/U: 5 months (range, 3-15 mos)

* There "not evaluable" information

Clinical activity: time to and duration of response



- Median time to response: 9 weeks (range, 5-18 wks)
- Median duration of response: 21 weeks (95% CI: 6, not estimable)
- Response ongoing in 5 of 8 patients (62.5%) at time of analysis

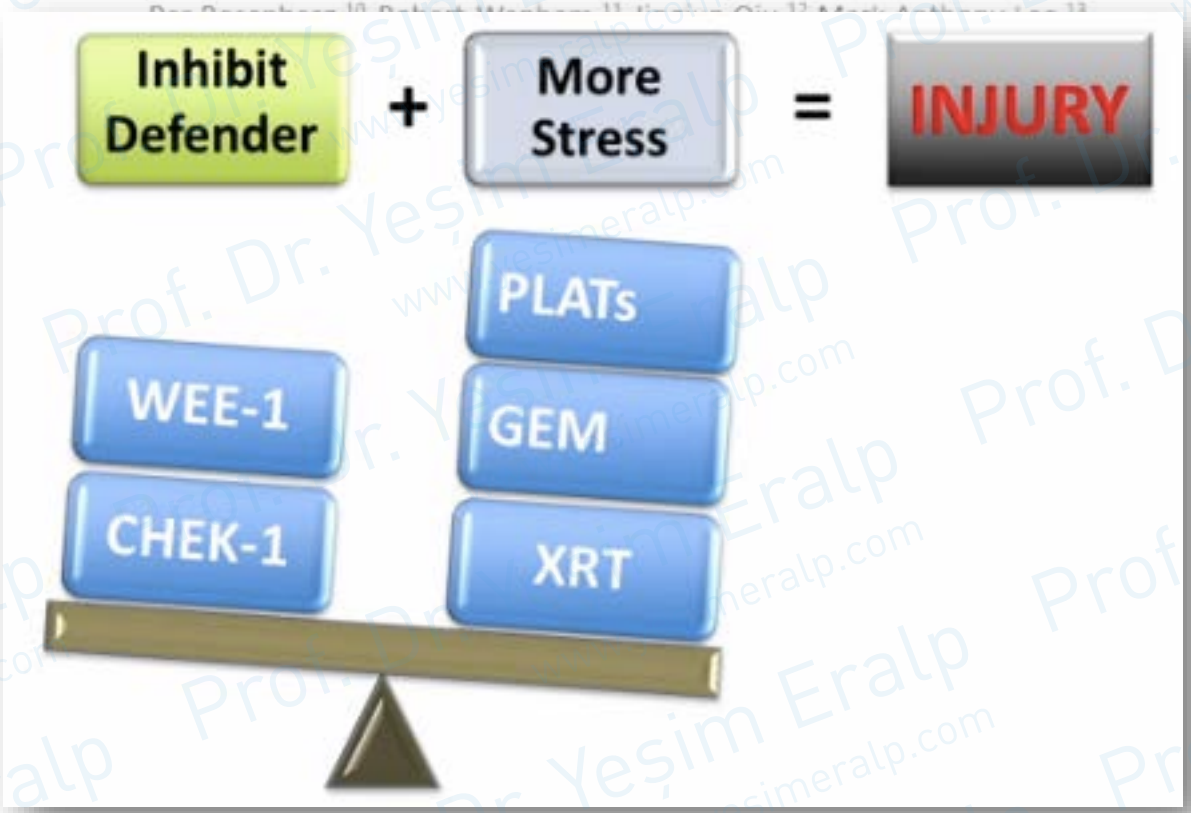
Sonuç: İmmun Checkpoint İnhibitörleri

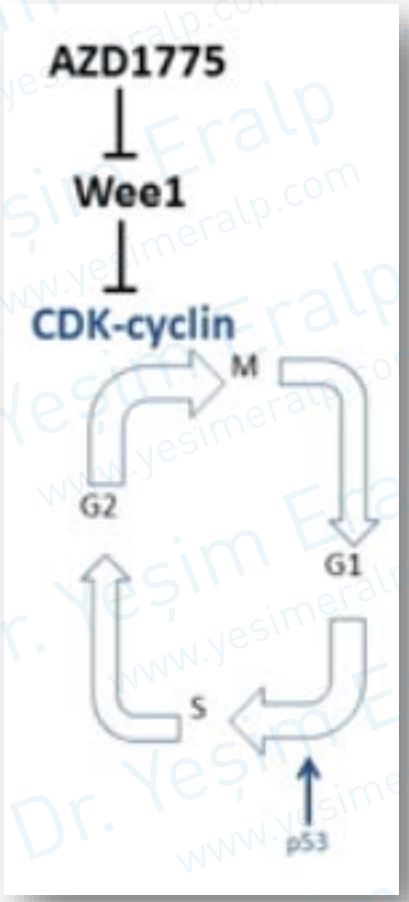
- Avelumab:
  - Nüks over kanserinde anti-checkpt inh ile en büyük çalışma
  - DCR: %54; ORR: %10
  - Kabul edilebilir toksisite
  - Berrak hücreli 2 hastanın tümünde yanıt var !
  - Faz III çalışma planlanıyor
- Pembrolizumab:
  - ORR: %11.5 (yoğun öncül tedavili hastalar)
  - Uzun süreli yanıt
  - Biyo-belirteç analizi devam ediyor

An international, biomarker-directed, randomized, Phase II trial of AZD1775 plus paclitaxel and carboplatin for the treatment of women with platinum-sensitive, *TP53*-mutant ovarian cancer

ABSTRACT #5506

Amit M Oza,[1] Johanne Weberpals,[2] Diane Provencher,[3] Eva-Maria Grischke,[4] Marcia Hall,[5] Denise Uyar,[6] Maria Diz,[7] Frederik Marmé,[8] Alexey Kuzmin,[9]





N=121

- Non-low-grade ovarian/fallopian tube/primary peritoneal cancer
- Loss-of-function mutation in *TP53*
- Platinum sensitive; progression ≥6 months after completion of prior platinum therapy

n=59 → AZD1775 (225 mg bid for 2.5 days; capsules) + P (175 mg/m²; IV) and C (AUC5; IV) on day 1

n=62 → Placebo (bid for 2.5 days) + P (175 mg/m²; IV) and C (AUC5; IV) on day 1

Double-blind randomization (1:1)

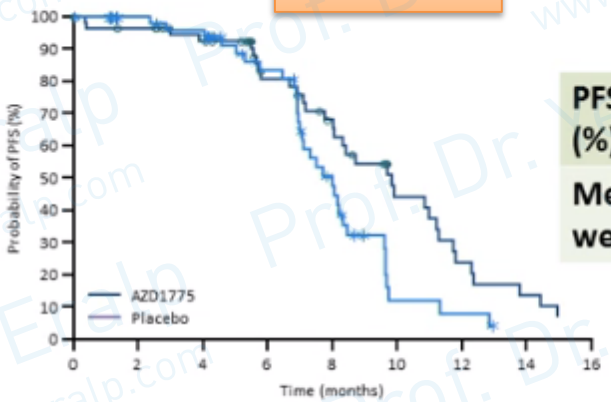
Treatment until progression or completion of 6 x 21-day cycles

- CT scans every 6 weeks
- CA-125 levels (GCIG criteria) every 3 weeks
- Adverse events (NCI CTCAE v4.0)

Primary objectives:
- PFS (enhanced RECIST v1.1, independent central review)
- Safety and tolerability

Secondary objectives:
- PFS (RECIST v1.1)
- ORR (enhanced RECIST v1.1, CA-125 levels)
- OS

PFS



	AZD1775 + P/C n=59	P/C n=62
PFS events, n (%)	34 (57.6)	32 (51.6)
Median PFS, weeks	42.86	34.86

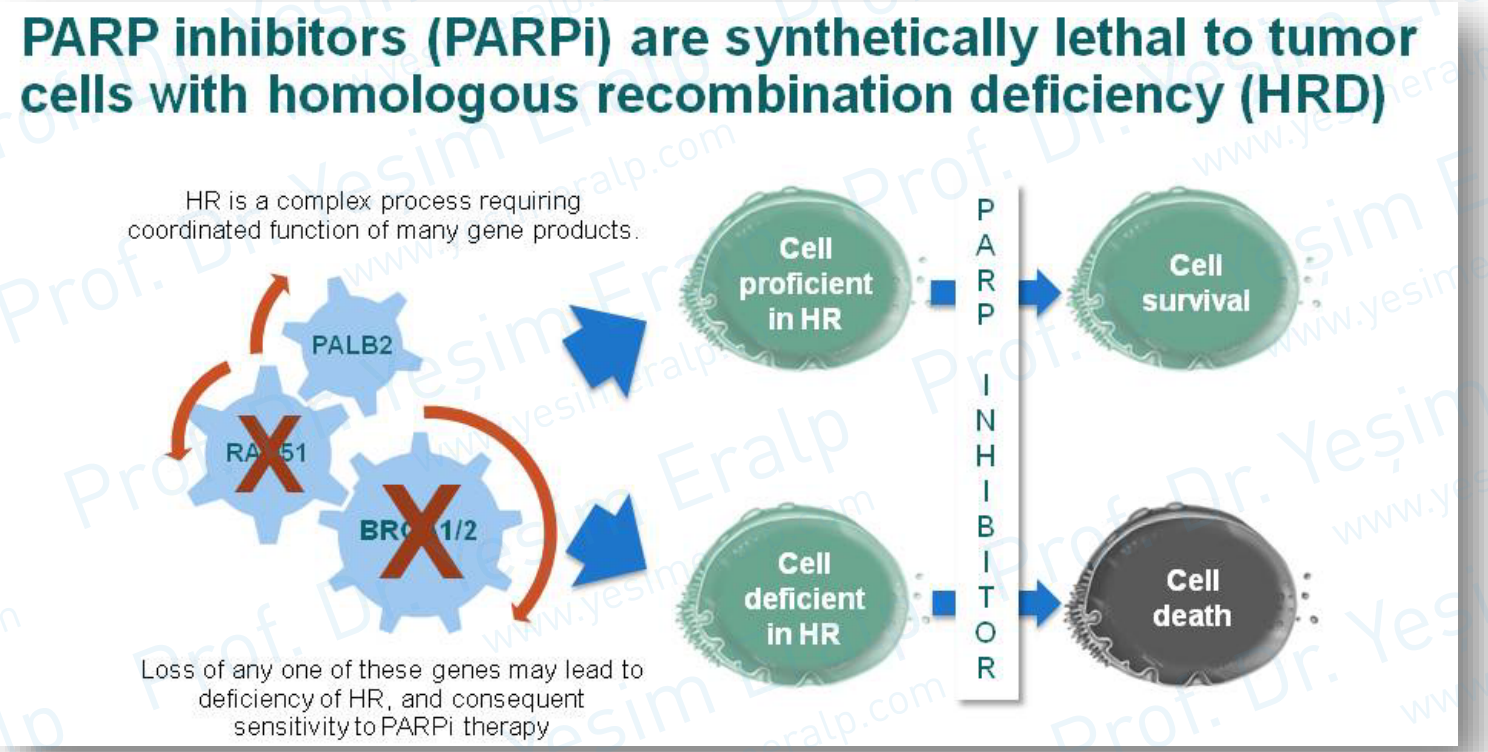
HR=0.55
80% CI 0.39, 0.79
95% CI 0.32, 0.95
P=0.030

Oza and colleagues

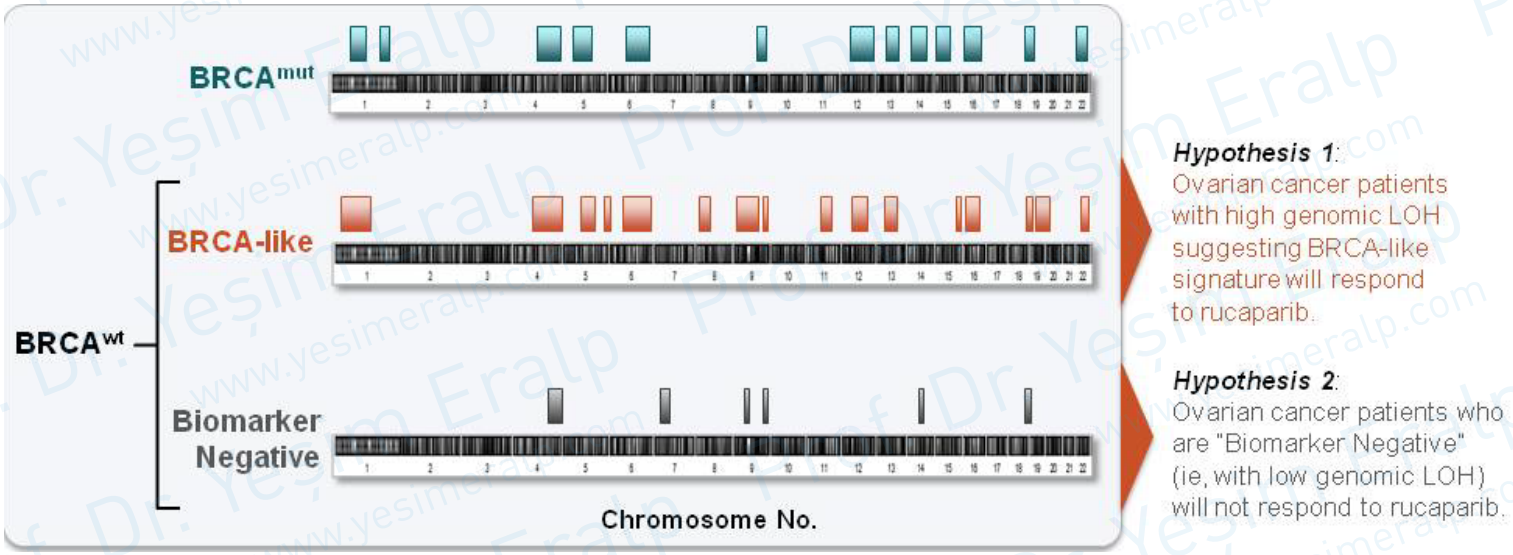
Results of ARIEL2: A phase 2 trial to prospectively identify ovarian cancer patients likely to respond to rucaparib using tumor genetic analysis

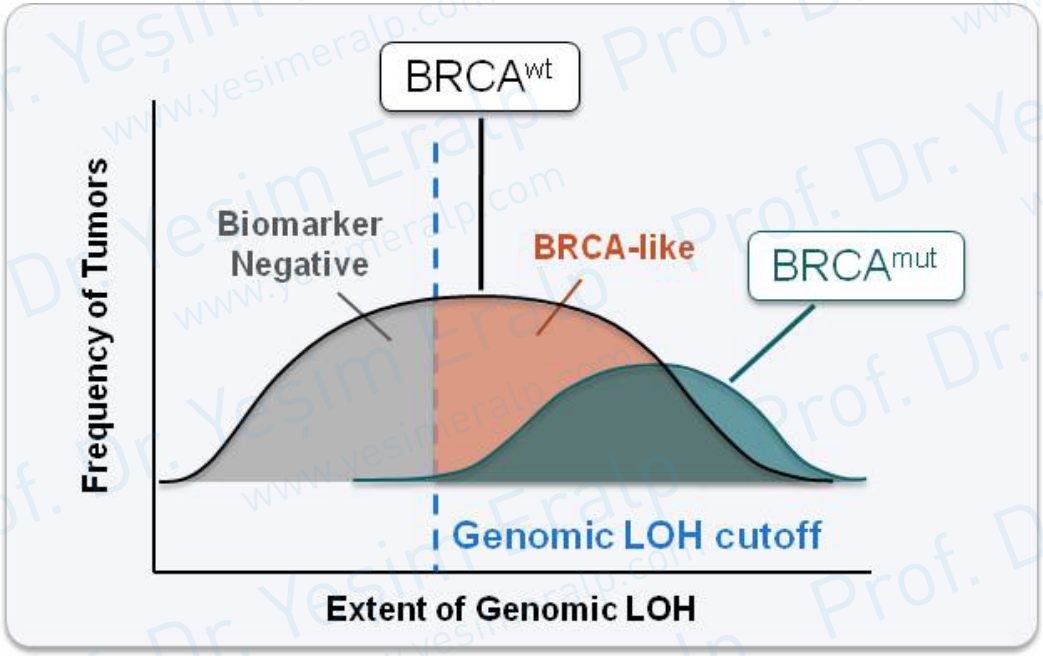
Iain McNeish,[1] Amit Oza,[2] Robert L. Coleman,[3] Clare Scott,[4] Gottfried Konecny,[5] Anna Tinker,[6] David M.

PARP inhibitors (PARPi) are synthetically lethal to tumor cells with homologous recombination deficiency (HRD)



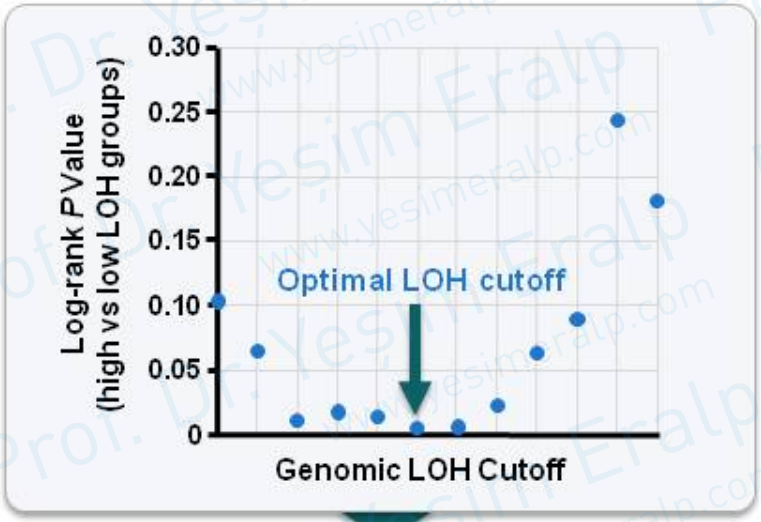
HRD genomik LOH'ya neden olur; bu genomik değişiklik NGS ile belirlenebilir

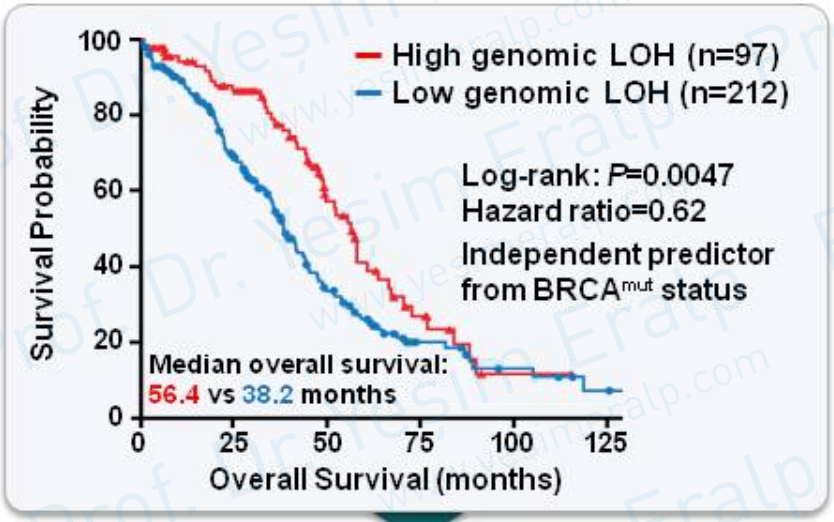




Initial genomic LOH cutoff derived from public data and prospectively tested in ARIEL2

TCGA and AOCS overall survival data used to develop LOH cutoff to identify HGOC patient tumors with BRCA-like signature





Prospective testing of prespecified cutoff in ARIEL2

The Cancer Genome Atlas (TCGA) Research Network. *Nature*. 2011;474:609-615;
Wang ZC et al; Australian Ovarian Cancer Study (AOCS). *Clin Cancer Res*. 2012;18:5806-5815.

Key Eligibility (N=180)

- High-grade serous or endometrioid OC
  - Known gBRCA enrollment capped at N=15
- ≥1 prior platinum chemotherapy
- Platinum-sensitive, relapsed, measurable disease
- Tumor tissue (screening biopsy and archival)

NGS of **tumor tissue** allows patients to be classified

600 mg BID rucaparib until disease progression

BRCA^{mut}

BRCA-like

Biomarker Negative

Analysis of HRD Subgroups

Primary endpoint

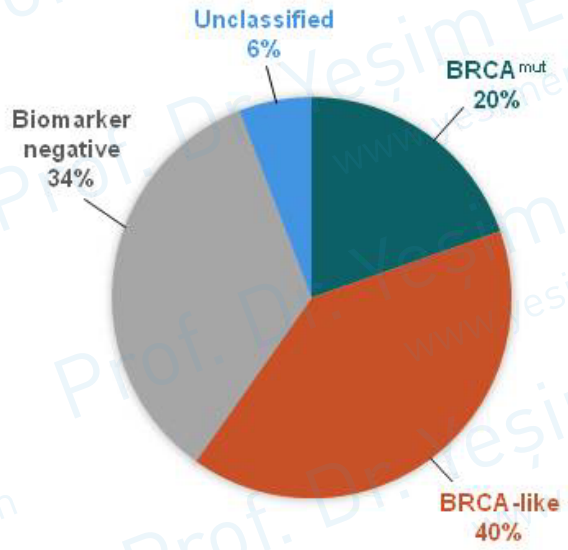
- PFS

Secondary endpoints

- ORR
  - RECIST
  - RECIST + CA-125
- Safety
- PK

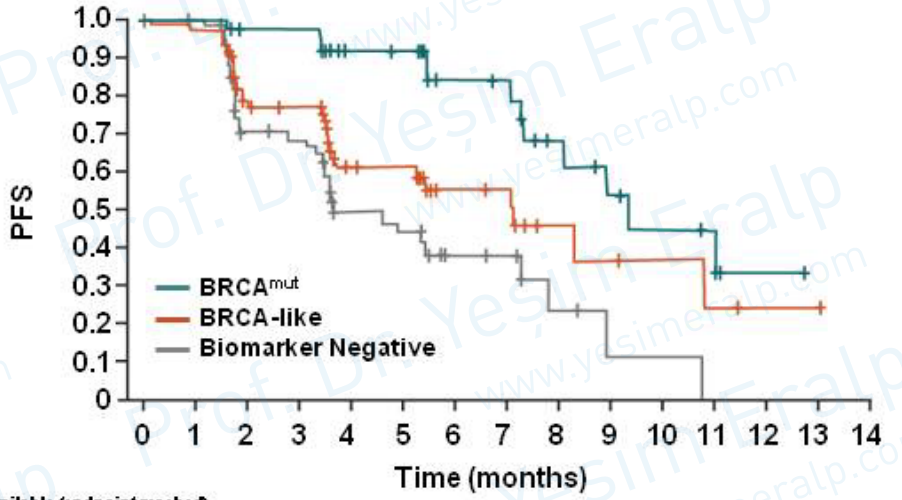
Parameter	Total (N=204)
Median age, years (range)	65 (31–86)
ECOG PS grade	
0 / 1 / Pending (%)	67 / 30 / 3
Diagnosis	
Epithelial ovarian cancer (%)	80
Primary peritoneal / fallopian tube cancer (%)	12 / 7 (1 unknown)
Histology	
Serous / endometrioid / mixed (%)	96 / 2 / 2
No. of prior treatment regimens	
Median no. of regimens (range)	1 (1–6)
1 (%)	57
≥2 (%)	43
Median no. of platinum-based regimens (range)	1 (1–5)
1 (%)	60
≥2 (%)	40

Distribution of HRD molecular subgroups



HRD Subgroup	Median PFS, mo (90% CI)	Overall Response Rate, % (N)	
		RECIST	RECIST + CA-125
$BRCA^{mut}$	9.4 (7.3, NR)	69 (27/39)	82 (32/39)
$BRCA^{wt}$ BRCA-like	7.1 (3.7, 10.8)	30 (22/74)	45 (33/74)
$BRCA^{wt}$ Biomarker Negative	3.7 (3.5, 5.5)	13 (8/62)	21 (13/62)

Progression-free survival by HRD molecular subgroup



Available (endpoint reached)

$BRCA^{mut}$	40 (0)	39 (0)	35 (1)	35 (1)	28 (3)	27 (3)	18 (5)	17 (5)	10 (8)	7 (10)	5 (11)	4 (11)	1 (12)	0 (12)
BRCA-like	81 (0)	72 (2)	48 (15)	45 (16)	24 (24)	23 (24)	13 (26)	12 (26)	5 (28)	4 (29)	3 (29)	2 (30)	1 (30)	1 (30)	0 (30)
Biomarker Negative	69 (0)	62 (0)	37 (17)	35 (18)	18 (27)	16 (29)	8 (31)	7 (31)	3 (33)	1 (34)	1 (34)	0 (35)		

HRD Subgroup	Median PFS, mo (90% CI)
$BRCA^{mut}$	9.4 (7.3, Not Reached)
BRCA-like	7.1 (3.7, 10.8)
Biomarker Negative	3.7 (3.5, 5.5)

Subgroup Comparison	Hazard Ratio (90% CI)
$BRCA^{mut}$ vs Biomarker Negative	0.47 (0.35, 0.64)
BRCA-like vs Biomarker Negative	0.61 (0.41, 0.92)

CI=confidence interval.

Rucaparib ovarian cancer trials enrolling in 2015

The HRD algorithm will be applied prospectively to two ongoing trials

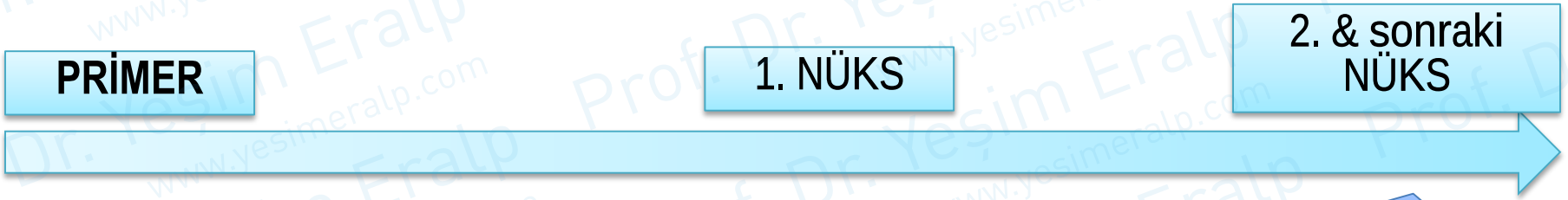
ARIEL2 Part 2 (N=300)

Single arm in HGOC patients who have received ≥3 prior chemotherapy regimens (NCT01891344)

ARIEL3 (N=540)

Randomized maintenance study rucaparib vs placebo in HGOC patients who have received ≥2 platinum regimens (NCT01968213)

2014....



Carboplatin + Paklitaksel + BEV

GOG 218
ICON 7

Bio-belirteç ??

Platin Duyarlı

Carbo-CT + BEV

Carbo-CT + CEDIRANIB

Carbo-CT ➡ OLEPARIB*

OCEANS
ICON 6
STUDY 19

OLAPARIB + CEDIRANIB

PAZOPANIB İDAME (AGO-OVAR 16)

MUC-1 İDAME (CAN 003)

Platin Dirençli

CT + BEV

AURELIA

Anjiogenez direnci ??

PAZOPANIB + PAC (MITO-11)

MEK inh. ??

*: sadece idame & BRCA mut taşıyıcıları

2015 & ....

PRİMER | **1. NÜKS** | **2. & sonraki NÜKS**

Carboplatin + Paklitaksel + BEV

Platin Duyarlı

Carbo-CT + BEV

Carbo-CT + CEDIRANIB

Carbo-CT ➡ OLEPARIB*

OCEANS,ICON 6,STUDY 19

Platin Dirençli

CT + BEV

AURELIA

PERTUZUMAB +PAC/GEM (⬇ HER-3 EXPR)

PENELOPE

GOG 218
ICON 7

CD 31 +

RUCAPARIB (BRCAm & BRCA-like)

ARIEL 2

PAZOPANIB + PAC

MITO 11

OLAPARIB + CEDIRANIB

PAZOPANIB İDAME (AGO-OVAR 16)

AZD 1775+ PAC-Carbo (p53 mut+)

İmmun Checkpt İnhibitörleri AVELUMAB / PEMBRO (MSI-H ?)

ENDOMETRİUM KANSERİ

	Type I	Type II
Clinical, endocrinological, and morphological components (Bokhman classification[5])		
Distribution	60–70%	30–40%
Reproductive function	Decreased	No disturbances
Onset of menopause	After age 50 years	Younger than age 50 years
Background endometrium	Hyperplasia	Atrophy
Oestrogen associated	Yes	No
Associated obesity, hyperlipidaemia, and diabetes mellitus	Yes	No
Tumour grade	Low (grades 1–2)	High (grade 3)
Myometrial invasion	Superficial	Deep
Potential for lymphogenic metastatic spread	Low	High
Prognosis	Favourable	Unfavourable
Sensitivity to progestagens	High	Low
Outcome (5-year survival)	86%	59%
Clinicopathological and molecular correlates[7–10]		
Prototypical histological type	Endometrioid	Serous
Oestrogen-receptor or progesterone-receptor expression	High	Low
Stage at diagnosis	Early (FIGO stage I–II)	Advanced (FIGO stage III–IV)

Bokhman JV.

Gynecol Oncol 1983; **15**: 10–17.

Endometrium kanseri genotipler: Kanser Genom Projesi

	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 ($2{\cdot}9 \times 10^{-6}$ mutations/Mb)	Low ($2{\cdot}3 \times 10^{-6}$ 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

PTEN, PI3CK, KRAS mutasyonları tüm gruplarda mevcut

Kandoth C,
Nature 2013; 497: 67–73.
Rajmohan Murali,
Lancet Oncol 2014; 15: e268–78

Endometrium Kanseri Hedefe Yönelik Tedaviler: Tek ajan çalışmalar

Drug	Response rate (%)	Authors (Refs.)
Angiogenesis inhibitors		
Bevacizumab	13.5	Aghajanian *et al* (22)
Aflibercept	6.8	Coleman *et al* (24)
Thalidomide	12.5	McMeekin *et al* (25)
EGFR inhibitors		
Gefitinib	3.4	Leslie *et al* (26)
Erlotinib	4.3	Jasas *et al* (27)
HER2 inhibitors		
Trastuzumab	0.0	Fleming *et al* (29)
mTOR inhibitors		
Temsirolimus (first-line)	26.0	Oza *et al* (33)
Ridaforolimus	28.9 (CBR)	Colombo *et al* (34)

İleri Evre Endometrial Kanser Tedavi Zorlukları

- Mevcut tedavi seçeneklerinin yetersizliği
  - Onaylı hedefe yönelik tedavi yok…
- Çoğu yaşlı hasta; komorbidite varlığı
- Biyo-belirteç eksikliği

	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 ($2{\cdot}9 \times 10^{-6}$ mutations/Mb)	Low ($2{\cdot}3 \times 10^{-6}$ 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
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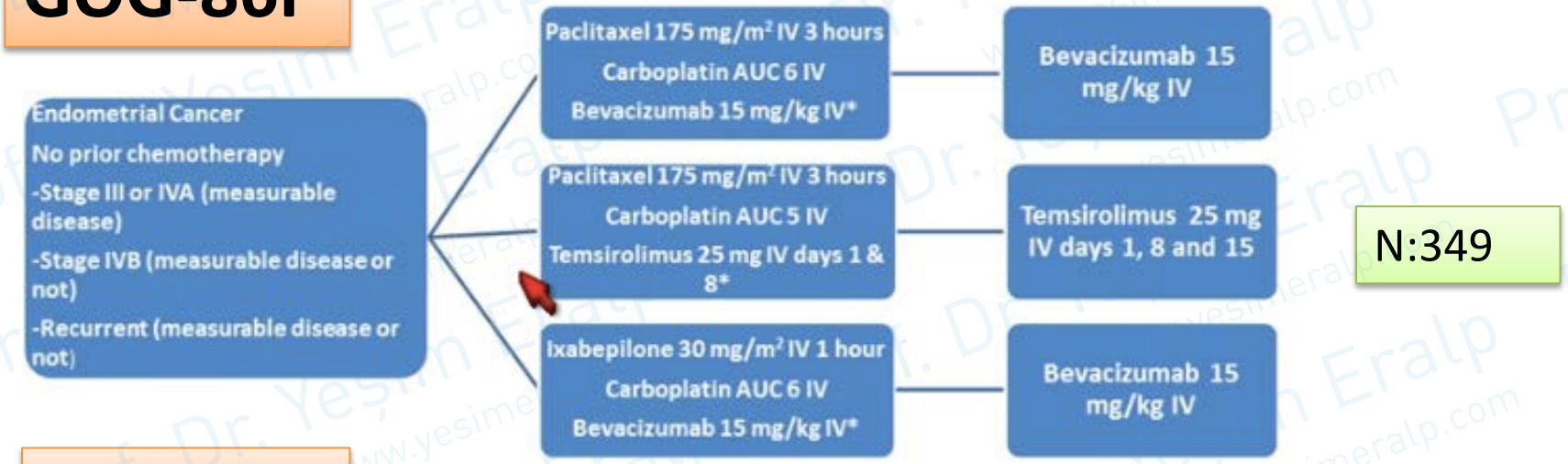
Progression-free survival	Good	Intermediate	Intermediate	Poor

Lancet Oncol 2014; 15: e268–78 *Nature* 2013; 497: 67–73.

İleri Evre Endometrial Kanser Tedavi Seçenekleri

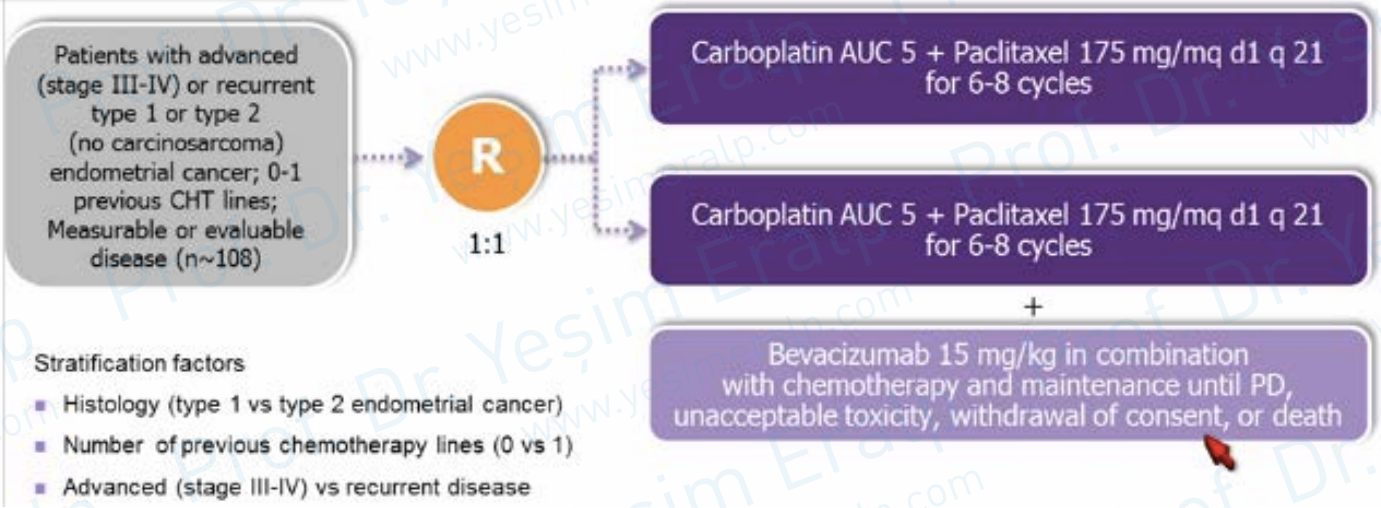
- GOG 209: ilk seçim kombinasyon KT
  - PAC + Carbo vs PAC (non-inf) → PFS: 14 ay
- İkinci seçim: tek ajan KT
  - PAC, DOX; IXA → PFS: 4 ay
- Endokrin tedavi :
  - HR (+) düşük gradlı hastalık

GOG-86P



N:349

MITO-2



N:108

Yanıt Oranları

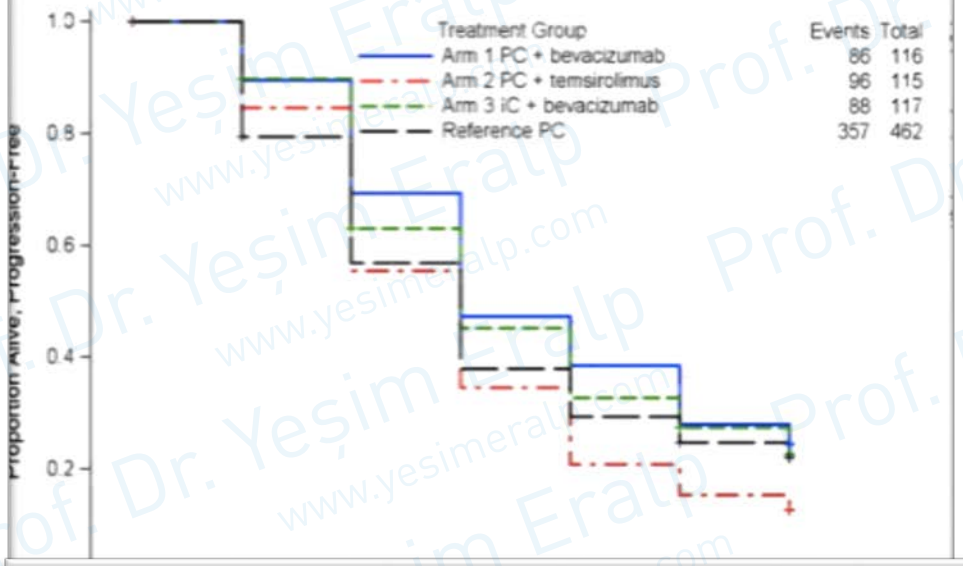
GOG-86P

	PC + Bevacizumab (n=116)	PC + Temsirolimus (n=115)	IC + Bevacizumab (n=118)	GOG209 PC Historical Reference (n= 462)
Complete Response (CR)	22 (24.7%)	14 (16.5%)	9 (10.6%)	40 (10.8%)
Partial Response (PR)	31 (34.8%)	33 (38.8%)	36 (42.4%)	149 (40.4%)
Objective Response Rate (CR + PR)	**53 (59.5%)**	**47 (55.3%)**	**45 (52.9%)**	**189 (51.2%)**

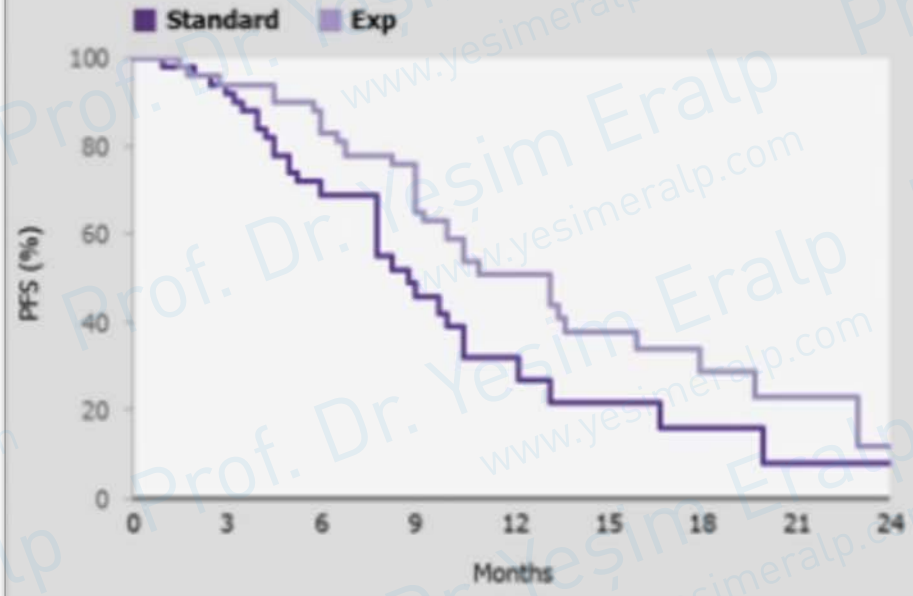
MITO-2

	CP N=46 (%) (CI 95%)	CP-B N=46 (%) (CI 95%)	P value
Objective response (CR+PR)	25 (54.3) (39.9-98.7)	33 (71.7) (58.7-84.7)	0.065
SD	20 (43.5) (29.2-57.8)	10 (21.7) (9.8-33.6)	
6-months non PD (%)	69%	83%	0.09
PD	1 (2.2) (-2.0-6.4)	3 (6.5) (-0.6-13.6)	

GOG86P: PFS

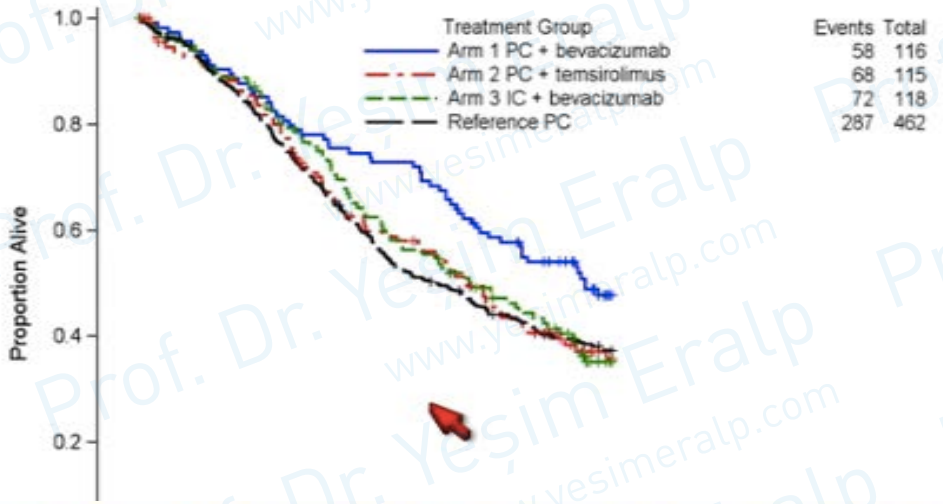


	vs Tarihi kontrol
PC + Bev	HR: 0.805
PC + Tem	HR: 1.22
IxaC + Bev	HR:0.87



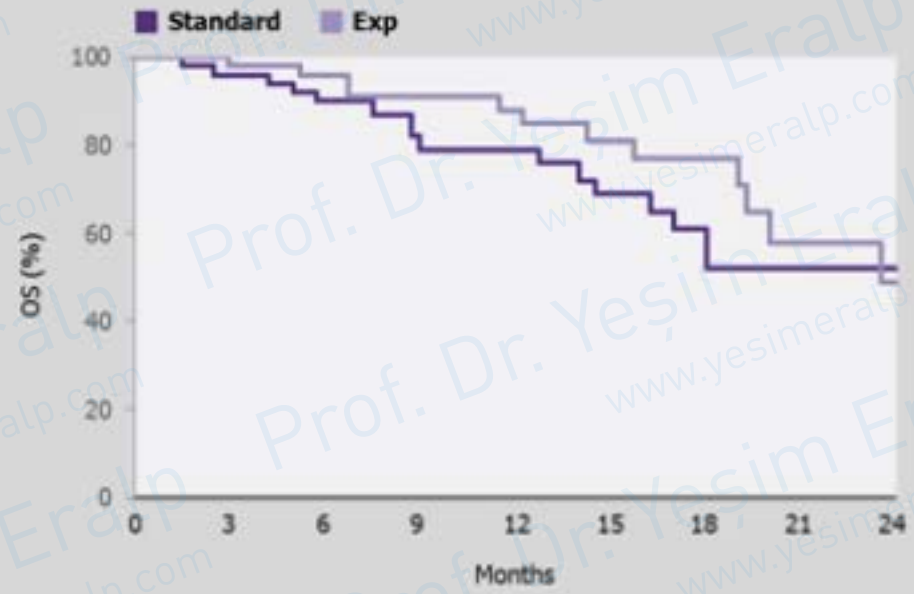
	CT (N=54)	CT-B (N=54)
Events, n	34	32
Median PFS, months (95% CI)	8.7 (6.3-11.2)	13 (9.2-16.8)
HR (stratified) (95% CI) **2-sided log-rank p-value**	0.59 (0.35–0.98) 0.036	

GOG86P: OS



Arm	*Median Point Estimate*
1	**34.0 (p<0.039)**
2	25.0
3	25.2
Reference	22.7

Overall survival (secondary endpoint): immature



	CT (N=54)	CT-B (N=54)
Events, n	17	12
Median OS, months (95% CI)	18 (6.3-11.2)	23.5 (9.2-16.8)
HR (stratified) (95% CI) 2-sided log-rank p-value	0.65 (0.31–1.36) 0.24	

GOG-86P & MITO-2

	LoRusso	Aghajanian
PFS experimental (p)	13 months (0.036)	NR
PFS control (p)	8.7 months	14 months (historical)
OS (p)	23.5 months (0.24)	34 months (0.039)
Carboplatin	AUC5	AUC6
Toxicity discon	10%	27%
Median bev cycles	10	12
Thromboembolic	11.5%	8.9%
Fistulation	1.9%	2.7%

- PAC + CARBO + Bev endometrium kanserinde standart tedavi olma yolunda…
  - Faz III veri bekleniyor

SERVİKS KANSERİ

Nüks, Metastatik Serviks Kanseri: Faz III Çalışmalar

		RR %	GS (ay)	PFS (ay)
GOG 110 [18]	Cisplatin 50 mg/m^2	17.8	8	3.2
	Cisplatin 50 mg/m^2 + DBD 180 mg/m^2	21.1	7.3	3.3
	Cisplatin 50 mg/m^2 + ifosfamide 5 g/m^2 + mesna	31.1	8.3	4.6
GOG 149 [19]	Cisplatin 50 mg/m^2 + ifosfamide 5 g/m^2	32	8.5	4.6
	Cisplatin 50 mg/m^2 + ifosfamide 5 g/m^2 + bleomycin 30 units	31.2	8.4	5.1
GOG 169 [20]	Cisplatin 50 mg/m^2	19	8.8	2.8
	Cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2	36	9.7	4.8
GOG 179 [21]	Cisplatin 50 mg/m^2	13	6.5	2.9
	Cisplatin 50 mg/m^2 + topotecan 0.75 mg/m^2 days 1–3	26	9.4	4.6
	MVAC	NA	NA	NA
GOG 204 [22]	Cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2	29.1	12.9	5.8
	Cisplatin 50 mg/m^2 + topotecan 0.75 mg/m^2 days 1–3	23.4	10.3	4.7
	Cisplatin 50 mg/m^2 + gemcitabine 1000 mg/m^2	22.3	10.3	4.6
	Cisplatin 50 mg/m^2 + vinorelbine 30 mg/m^2	25.9	10	4.0

Curr Opin Obstet Gynecol 2014, 26:314–321

GOG 240

Primer evre IVB veya nüks Serviks Kanseri

Daha önce KT uygulanmamış (KT-RT dışında)

RANDOMIZE

Regimen 1**
Paclitaxel* + CDDP 50 mg/m2

Regimen 2**
Paclitaxel* + CDDP 50 mg/m2 + Bevacizumab 15/mg/kg

Regimen 3**
Paclitaxel 175 mg/m2 over 3 hrs on day 1 +
Topotecan 0.75 mg/m2 over 30 mins days 1-3

Regimen 4**
Paclitaxel 175 mg/m2 over 3 hrs on day 1 +
Topotecan 0.75 mg/m2 over 30 mins days 1-3 +
Bevacizumab 15/mg/kg

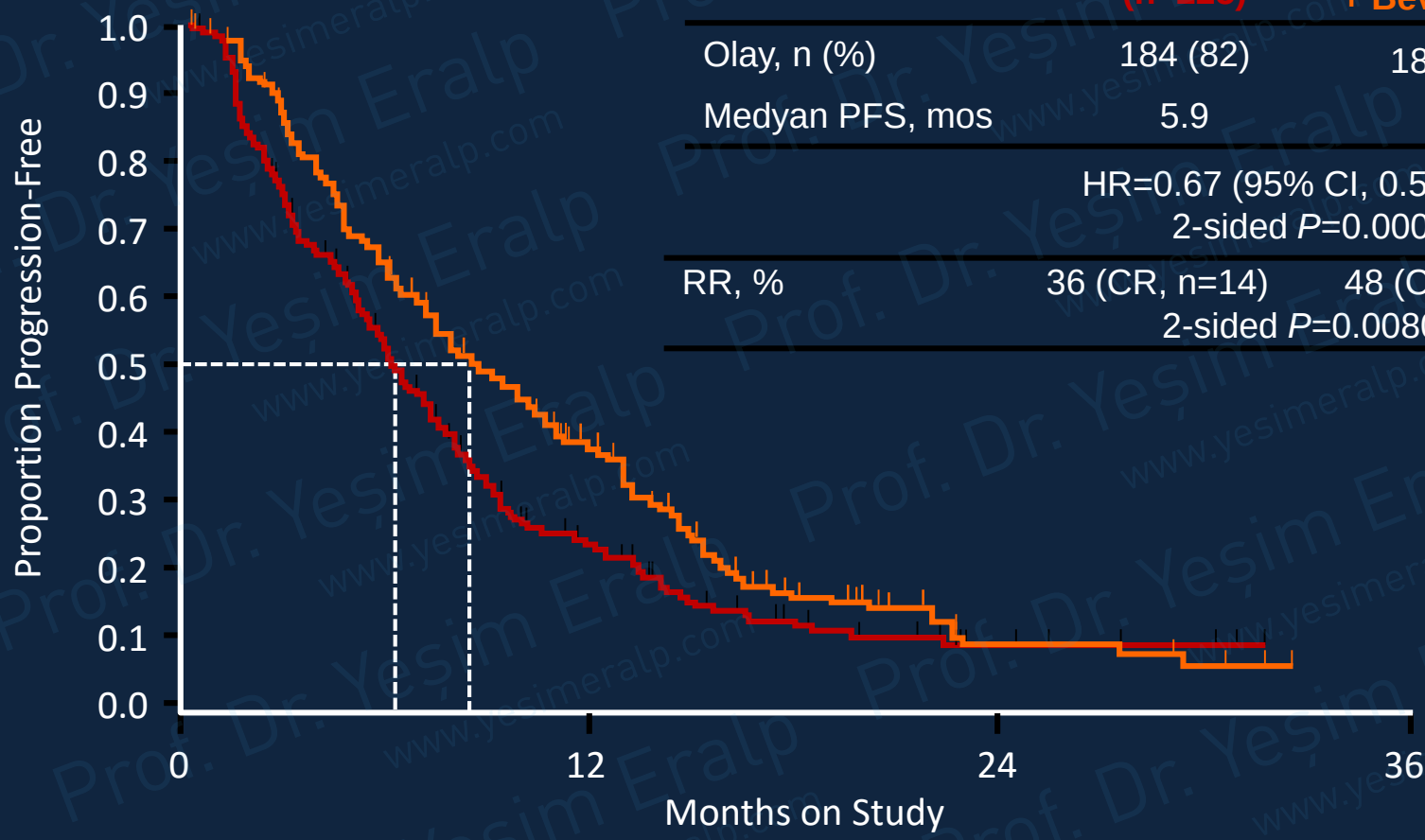
Hasta alımı: 2009-2012
n= 452
Hedef OS HR reduction: 30%

Tüm KOllar
Quality of life Değerlendirme:
Baseline
Before cycle 2
Before cycle 5
9 mo. after study entry at follow-up visit

* 135 mg/m2 over 24 or 175 mg/m2 over 3 hours
** Cycles repeated q21 days to progression/toxicity

Tewari KS et al N Engl J Med. 2014 Feb 20;370(8):734-43.

GOG 240 – Bevacizumab

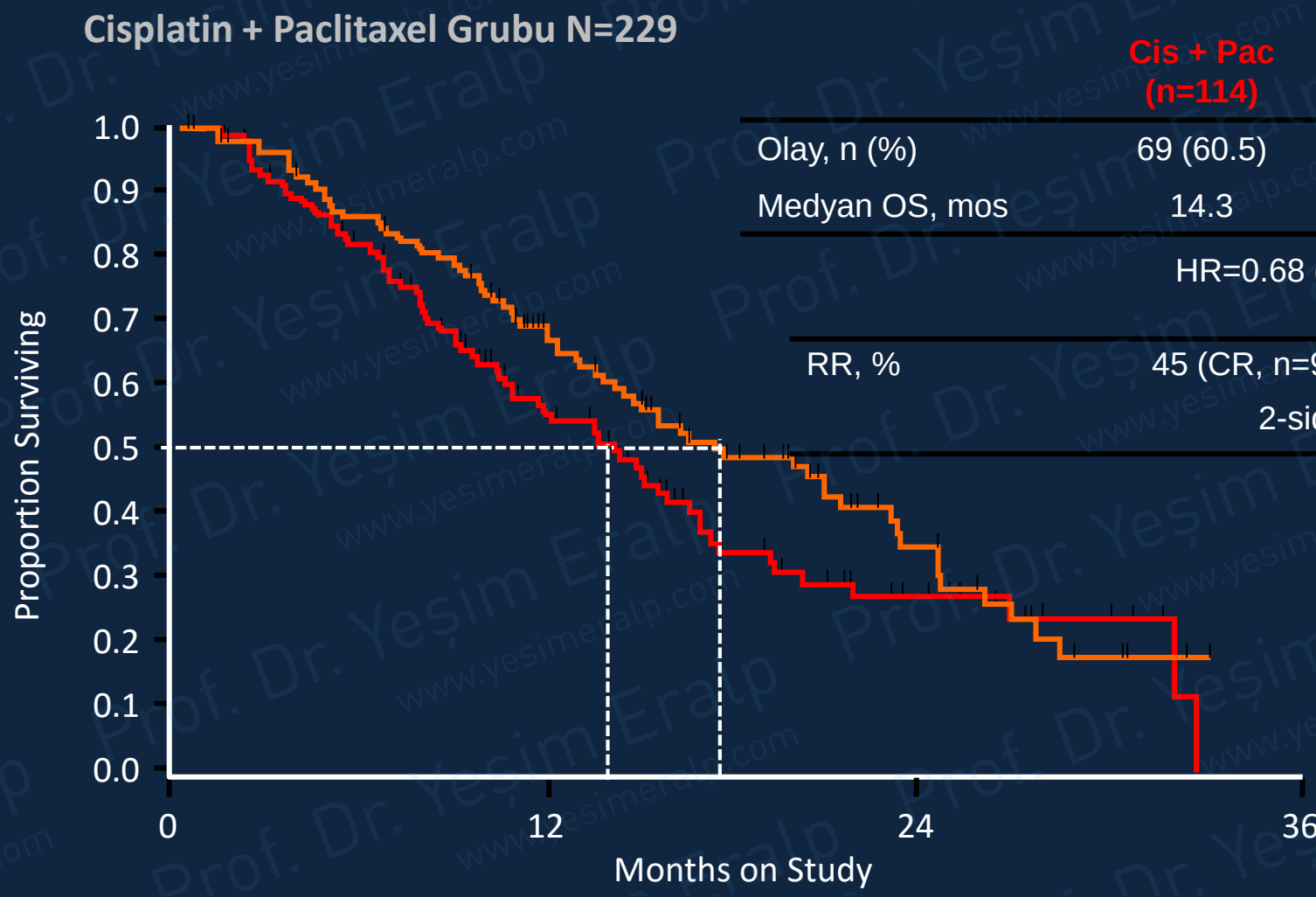


	Chemotherapy (n=225)	Chemotherapy + Bev (n=227)
Olay, n (%)	184 (82)	183 (81)
Medyan PFS, mos	5.9	8.2
	HR=0.67 (95% CI, 0.54-0.82) 2-sided *P*=0.0002	
RR, %	36 (CR, n=14)	48 (CR, n=28) 2-sided *P*=0.00807

Presented at ASCO 2013 by: Krishnansu S. Tewari, MD, FACOG, FACS

Tewari KS et al N Engl J Med. 2014 Feb 20;370(8):734-43.

GOG 240 – Bevacizumab



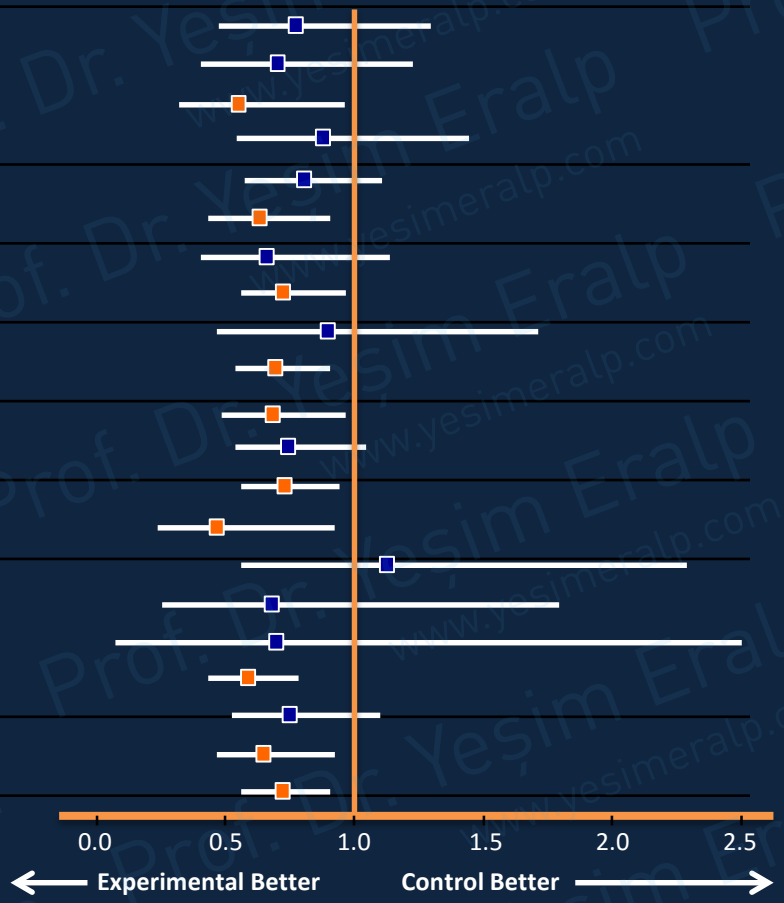
	Cis + Pac (n=114)	Cis + Pac + Bev (n=115)
Olay, n (%)	69 (60.5)	67 (58.3)
Medyan OS, mos	14.3	17.5
	HR=0.68 (95% CI, 0.48-0.97) *P*=0.0348	
RR, %	45 (CR, n=9)	50 (CR, n=17)
	2-sided *P*=0.5090	

Presented at ASCO 2013 by: Krishnansu S. Tewari, MD, FACOG, FACS

Tewari KS et al N Engl J Med. 2014 Feb 20;370(8):734-43.

GOG 240: OS & Prognostik Faktörler

Subgroup		No. of Patients
Age	Age ≤ 40 years	112
	40 < Age ≤ 48 years	111
	48 < Age ≤ 56 years	108
	56 years < Age	121
Performance Status	0	263
	1	189
Prior Platinum RT	No	115
	Yes	337
Disease Status	Advanced	76
	Recurrent/Persistent	376
Topotecan Treatment	No	229
	Yes	223
Race	Not Black	392
	Black	60
Histology	Adenocarcinoma	86
	Adenosquamous	44
	Other	12
	Squamous	310
Pelvic Disease	No	210
	Yes	242
Overall		452



= HR does not cross 1.0

Presented at ASCO 2013 by: Krishnansu S. Tewari, MD, FACOG, FACS

Tewari KS et al N Engl J Med. 2014 Feb 20;370(8):734-43.

GOG 240: Yan etki profili

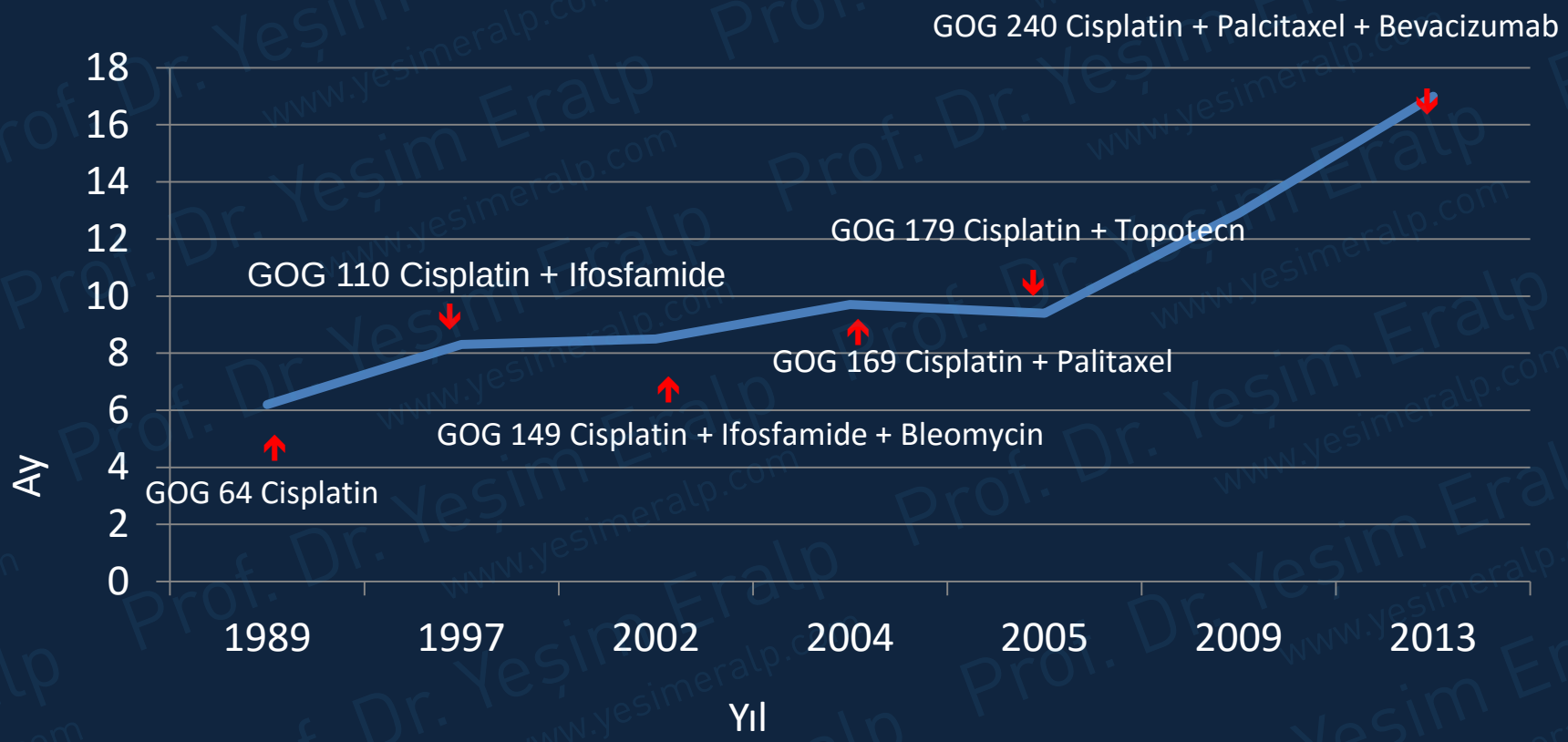
Adverse Event, n (%)	Chemo Alone (n=219)	Chemo + Bev (n=220)
Treatment cycles, median (range)	6 (0-30)	7 (0-36)
Grade 5 AE(s)	4 (1.8)	4 (1.8)
GI events, non-fistula (grade ≥2)	96 (44)	114 (52)
GI fistula (grade ≥3)*	0 (0)	7 (3)
GI perforation (grade ≥3)	0 (0)	5 (2)
GU fistula (grade ≥3)*	1 (0)	6 (2)
Hypertension (grade ≥2)*	4 (2)	54 (25)
Proteinuria (grade ≥3)	0 (0)	4 (2)
Pain (grade ≥2)	62 (28)	71 (32)
Neutropenia (grade ≥4)*	57 (26)	78 (35)
Febrile neutropenia (grade ≥3)	12 (5)	12 (5)
Thromboembolism (grade ≥3)*	3 (1)	18 (8)
Bleeding CNS (any grade)	0 (0)	0 (0)
GI (grade ≥3)	1 (0)	4 (1)
GU (grade ≥3)	1 (0)	6 (3)

*p<0.05

Presented at ASCO 2013 by: Krishnansu S. Tewari, MD, FACOG, FACS

Tewari KS et al N Engl J Med. 2014 Feb 20;370(8):734-43.

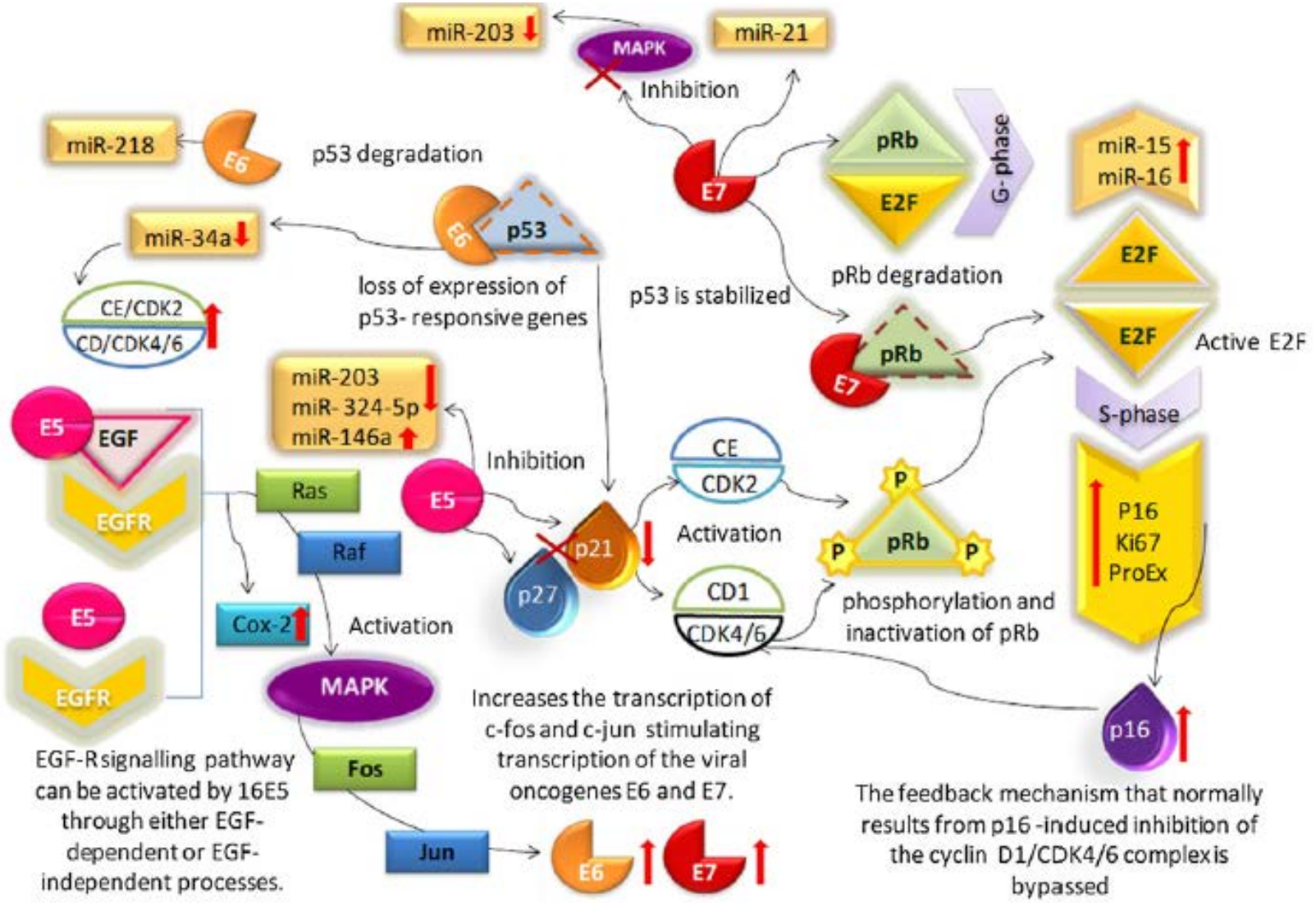
İleri Evre Serviks Kanserinde Sağkalım Eğilimi



Serviks Kanseri:
devam eden hedefe yönelik tedavi çalışmaları

Study	Estimated Enrollment	Phase	Regimen	Target	Primary endpoint
DDPDRO-002	30	I/II	Sorafenib with radiation and cisplatin	Multikinase	Determine the biologic activity of sorafenib in cervix cancer
NCT01229930	130	II	Carboplatin and paclitaxel with or without cediranib maleate	VEGF	Overall progression-free survival
NCT01065662	50	I/IB	Temsirolimus with cediranib	VEGF	Maximum tolerated dose of cediranib with temsirolimus
NCT01267253	51	II	Brivanib alaninate monotherapy	VEGF and FGFR	Progression-free survival for at least 6 months, objective tumor response, adverse events as assessed by NCI CTCAE v4.0
NCT00957411	76	II	Cisplatin and pelvic radiotherapy with or without cetuximab	EGFR	Recurrence-free survival at 2 years
NCT01158248	50	II	Panitunumab with cisplatin and radiotherapy	EGFR	Progression-free survival at 4 months and rate of skin and/or gastrointestinal toxicity CTCAE grade 4 at 4

HPV & Serviks Kanser Gelişimi



HPV:
Potansiyal Tedavi Hedefleri

- p16
- CDK 1,4,6
- EGFR
- MAPK
- Viral proteinler: E5,E6,E7

Viral bazlı kanser aşıları

Terapötik miRNA

TKI

SONUÇ: Jinekolojik Kanserlerde Hedefe Yönelik Tedaviler

- Birçok molekül; Değişken etkinlik
- Hedef ne olmalı: Genel sağkalım vs PFS

- Sorun:
  - Biyobelirteç yokluğu
  - Karsinogenezin temelinde yatan kilit hedefin bulunamamış olması