Over Kanserinin Güncel Sistemik Tedavisi

Dr.Ümmügül Üyetürk

Türk Tıbbi Onkoloji Sanal Kongresi 13-15 Kasım 2020

Sunum Planı

- Over kanseri,
- Erken evrede tedavi,
- İleri evrede tedavi,
- İdame tedavi,
- Nüks hastalıkta tedavi….

- %95’i epitelyal hücrelerden köken alır (germ hücreli tümör ve seks-kord stromal tümörler nadir),
- Ortalama tanı yaşı 55-64 (Herediter olanlar daha genç yaş),
- Yüksek mortalitesi olduğu dönem 65-74 yaş,

- Yaşam boyu over kanseri riski % 1.3(1/77)..
- Kadın genital sisteminde 2.sıklıkta görülmekte,
- Çoğu zaman erken belirti vermediği ve duyarlı bir kanser tarama testi olmadığı için ileri evrede tanı almakta.

- Hastaların yaklaşık %60 ileri evrede tanı,
- Hastaların %70'i birinci sıra tedaviden sonra ilk 3 yıl içinde nüks,
- Yeni tanı konmuş ileri evre over kanserli hastada
  5 yıllık sağkalım oranı %30-50,

Over Kanseri

Females

Lung & bronchus	66,020	23%
Breast	41,760	15%
Colon & rectum	23,380	8%
Pancreas	21,950	8%
Ovary	13,980	5%
Uterine corpus	12,160	4%
Liver & intrahepatic bile duct	10,180	4%
Leukemia	9,690	3%
Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	7,850	3%
All Sites	**285,210**	**100%**

Ölüm Oranı

Kadınlarda kansere bağlı ölüm nedenleri arasında 5.sırada…..

Siegel RL, Miller KD, Jemal A. CA Cancer J Clin. 2019;69(1):7-34.

Over Kanseri

Figo Evresi		Sıklık	Sağkalım
1	Overde sınırlı	%20	%73
2	Pelviste sınırlı	%5	%45
3	Periton veya lenf bezi metastazı	%58	%21
4	Uzak metastaz	%17	%<5

Bhatla N, Denny L.FIGO Cancer Report 2018. Int J Gynaecol Obstet. 2018 Oct;143 Suppl 2:2-3.

1-Over Kanserinde Erken Evrede Tedavi

- Erken evrede hangi hastalara tedavi verilmeli?
- Hangi kemoterapi tercih edilmeli?
- Tedavi süresi ne olmalı?

- Erken evre over kanserinde
- Yüksek riskli hastalar tedavi almalı,

- **<u>Kimler yüksek riskli</u>**?

- **Evre 1a/b**

  -Yüksek grade seröz karsinoma,

  -Endometrioid karsinoma grade 2/3
- **Evre Ic**

  -Müsinöz karsinoma,

  -Düşük grade seröz karsinoma,

  -Endometrioid karsinoma grade1
- **Berrak hücreli karsinoma,**
- **Karsinosarkoma**,

Table 2. Summary of published studies of adjuvant chemotherapy in ovarian cancer allowing inclusion of patients with early-stage disease (I and/or IIA) and with available (ICON3) or reported (others) early-stage analyses

Study	Number	Eligibility	%			Control arm	Research arm	No. of cycles	Recruit	HR
			I	II	III/IV					
ICON1 [7] 2003	477	Uncertain of benefit from chemotherapy	93	6	1	Observation	Platinum based (most carboplatin/CAP)	6	08/91-04/00	Overall OS HR = 0.71, 95% CI 0.52–0.98, $P = 0.04$
ACTION 2010 [18]	448	Ia–Ib, grade II–III; all stages Ic and IIa, and all stages I–IIa with clear-cell	93	7	0	Observation	Platinum based	6	11/90-01/00	Overall CSS HR = 0.73, 95% CI 0.48–1.13, $P = 0.16$
ICON3 [14]	2074	FIGO stage I–IV	9	11	80	Carboplatin AUC5 'or' Cyclophosphamide 500 mg/m^2 Doxorubicin 50 mg/m^2 Cisplatin 50 mg/m^2	Paclitaxel (175 mg/m^2, 3 h) Carboplatin AUC5	6	02/95-10/98	Stage I OS HR = 0.98, 95% CI 0.49–1.93, $P = 0.94$
GOG157 [10]	427	FIGO stage Ia/b grade 3, clear cell, Ic and completely resected stage II	69	31	0	Paclitaxel (175 mg/m^2, 3 h) Carboplatin AUC 7.5 [3 cycles]	Paclitaxel (175 mg/m^2, 3 h) Carboplatin AUC7.5 [six cycles]	3 versus 6	03/95–05/98	Overall RFS HR = 0.761, 95% CI 0.51–1.13, $P = 0.18$
AGO-OVAR/ GINECO/NSGO [11]	1742	All	8	10	82	Paclitaxel (175 mg/m^2, 3 h) Carboplatin AUC5	Paclitaxel (175 mg/m^2, 3 h) Carboplatin AUC5 Gemcitabine 800 mg/m^2 day 1/day 8	6	2002–2004	Stage I/IIA OS HR = 3.28, 95% CI 0.89–12.11, $P = 0.06$ (in favour of standard arm, but events scarce)
JGOG [12]	631	FIGO ≥stage II	0	18	82	Paclitaxel (175 mg/m^2, 3 h) Carboplatin AUC6	Paclitaxel (80 mg/m^2 day 1, 8, 15) Carboplatin AUC6	6	04/03-12/05	Stage II PFS ($n = 116$) HR = 0·81, 95% CI 0·36–1·82
GOG-175 [13]	542	FIGO stage 1A/B grade 3/clear cell or 1C/II	72	28	0	Paclitaxel (175 mg/m^2, 3 h) Carboplatin AUC6	Paclitaxel (175 mg/m^2, 3 h) Carboplatin AUC6 followed by Paclitaxel (40 mg/m^2, 1 h) q1w	6 24 weeks	09/98-12/06	All RFS HR = 0.81, 95% CI 0.57–1.15

Collinson F,et al; ICON1 collaborators. Optimal treatment of early-stage ovarian cancer.Ann Oncol. 2014 Jun;25(6):1165-71

Table 1. Summary of randomised phase 3 studies of weekly vs. 3 weekly paclitaxel

Study and phase	Population	No. of patients	Dose and schedule	Median PFS	Median OS	Response rate (%)
JGOG 3016 Katsumata et al. [5], phase III	Stage II–IV EOC	637	(A) C AUC 6 D1, P 80 mg/m² over 1 hr D1, 8, 15 (B) C AUC 6 D1, P 180 mg/m² over 3 hr D1	28.2 m vs. 17.5 m (HR=0.76; p=0.0037)	Median OS 100.5 m vs. 62.2 m (HR=0.79; p=0.039)	Overall response rate 56% vs. 53% (p=0.72)
ICON8 Clamp et al. [16], phase III (abstract form)	FIGO IC–IV (high risk FIGO IC–IIA)	1,566 Predominantly European	(A) C AUC 5 D1, P 175 mg/m² over 3 hr D1 (B) C AUC 5, P 80 mg/m² over 1 hr D1, 8, 15 (C) C AUC 2 D1, 8, 15, P 80 mg/m² over 1 hr D1, 8, 15	24.4 m vs. 24.9 m vs. 25.3 m (HR=0.92 – arms B vs. A) (HR=0.94 – arms C vs. A)	-	-
MITO-7 Pignata et al. [15], phase III	FIGO IC–IV	822	(A) C AUC 6, P 175 mg/m² D1 (B) C AUC 2, P 60 mg/m² D1, 8, 15	17.3 m vs. 18.3 m (HR=0.96; p=0.66)	2-yr OS 78.9% vs. 77.3% (HR=1.2; p=0.22)	Objective response 58% vs. 56% (p=0.63)

Lee MX et al.Weekly versus 3-weekly paclitaxel in combination with carboplatin in advanced ovarian cancer: which is the optimal adjuvant chemotherapy regimen?J Gynecol Oncol. 2018 Nov;29(6):e96

Erken evre over kanserinde tedavi Özet;

- 1-Kemoterapi mi takip mi?
- Gözleme göre kemoterapi genel sağkalım faydası(ICON 1),
- 2-Hangi kemoterapi tercih edilmeli?
- Siklofosfamid+adriyamisin+sisplatin ve karboplatin+ paklitaksel ve karboplatin karşılaştırılması etkinlik aynı toksisite profili dikkat edilecek(ICON3)
- 3-Karboplatin paklitaksel mi?Yoksa Sisplatin paklitaksel mi?
- Eşit etkinlik ama karboplatin paklitaksel daha iyi tolerasyon ve hayat kalitesi (GOG 158)

- 4- 3 kür mü yoksa 6 kür mü verelim?
- 6 kürün nüks oranını azaltmada ek faydası yok, hatta daha toksik olabilir(GOG 157)
- 5-Karboplatin paklitaksel kemoterapisini nasıl verelim?
- (Karboplatin+ paklitaksel 3 haftada bir veya

  Karboplatin 3 haftada+ paklitaksel haftada bir veya

  Karboplatin+ paklitaksel haftada bir)
- Karboplatin paklitaksel 3 haftada bir veya karboplatin 3 haftada paklitaksel haftada bir haftalık paklitaksel grubu daha etkin (JGOG 3016)*
- Bu tedaviler arasında fark yok(MİTO 7,GOG252,ICON 8)

- 6-İdame paklitaksel vermek faydalı mı?
- 3 kür karboplatin paklitaksel tedavisine 24 hafta paklitaksel eklemenin nüksüz süreyi uzatmada faydası yok(GOG 175)
- 7-Karboplatin paklitaksele (gemsitabin, liposomal doksorubisin veya topotekan) eklemenin faydası var mı?
- İlaç eklemenin etkinliği iyileştirmede faydası yok(AGO-OVAR-9, GOG 0182–ICON5)

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PRINCIPLES OF SYSTEMIC THERAPY

Primary Systemic Therapy Regimens[a] - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

STAGE I DISEASE			
• High-grade serous • Endometrioid (Grade 2/3) • Clear cell carcinoma[b] • Carcinosarcoma[b]	**Preferred Regimens** • Paclitaxel 175/carboplatin[d]	**Other Recommended Regimens** • Carboplatin/liposomal doxorubicin • Docetaxel/carboplatin	**Useful in Certain Circumstances** • Carboplatin (if elderly [age >70] and/or for those with comorbidities) For carcinosarcoma: • Carboplatin/ifosfamide • Cisplatin/ifosfamide • Paclitaxel/ifosfamide (category 2B)
Mucinous Carcinoma (stage IC)[b]	**Preferred Regimens** • Paclitaxel 175/carboplatin[d] • 5-FU/leucovorin/oxaliplatin • Capecitabine/oxaliplatin	**Other Recommended Regimens** • Carboplatin/liposomal doxorubicin • Docetaxel/carboplatin	**Useful in Certain Circumstances** • Carboplatin (if elderly [age >70] and/or for those with comorbidities)
Low-Grade Serous (stage IC)/Grade I Endometrioid (stage IC)[b,c]	**Preferred Regimens** • Paclitaxel 175/carboplatin[d]	**Other Recommended Regimens** • Carboplatin/liposomal doxorubicin • Docetaxel/carboplatin • Hormone therapy (aromatase inhibitors [anastrozole, letrozole, exemestane], leuprolide acetate, tamoxifen) (category 2B)	**Useful in Certain Circumstances** • Carboplatin (if elderly [age >70] and/or for those with comorbidities)

Stage II–IV (See OV-C, 5 of 10)

Primary Systemic Therapy Dosing (See OV-C, 6 of 10)

[a] See Discussion for references.
[b] There are limited data on the primary systemic therapy regimens for these LCOC.
[c] Borderline disease with invasive implants may be treated as low-grade serous disease. See LCOC-6 and LCOC-7.
[d] Elderly patients and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Guidelines. Based on clinical judgment and expected tolerance to therapies, alternate dosing (see OV-C, 6 of 10) may be appropriate for elderly patients with epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). Algorithms have been developed for predicting chemotherapy toxicity. See the NCCN Guidelines for Older Adult Oncology.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

İleri Evre Over Kanserinde Tedavi

- CA-125,görüntüleme yöntemleri ve laporoskopi önemli,
- Sitoredüksiyon için maksimum efor,
- Cerrahide amaç R0 rezeksiyon (optimal),

- Eğer R0 rezeksiyon karsinomatozis yüzünden mümkün değilse,
- Yaş veya performansı cerrahi için uygun değilse,
- Neoadjuvan 3 kür kemoterapi sonrası interval debulking için değerlendirilmeli,

- Sistemik tedavi karboplatin paklitaksel ve bevacizumab tercih edilmeli,

- -(International Collaboration on Ovarian Neoplasms)ICON -7,
- -GOG- 0218 çalışmaları,

ICON7 N=1528	Perren TJ	**Chemotherapy + bevacizumab** vs **chemotherapy** PFS: **21.8** vs **20.3** months[4] OS: **45.5** vs **44.6** months[5]	N Engl J Med, 2011[4]
GOG-0218 N=1873	Burger RA	**Chemotherapy + bevacizumab** vs **chemotherapy** PFS: **14.1** vs **10.3** months*[6] OS: **43.4** vs **41.1** months†[7]	N Engl J Med 2011[6]

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

Amit M Oza, Adrian D Cook, Jacobus Pfisterer, Andrew Embleton, Jonathan A Ledermann, Eric Pujade-Lauraine, Gunnar Kristensen, Mark S Carey, Philip Beale, Andrés Cervantes, Tjoung-Won Park-Simon, Gordon Rustin, Florence Joly, Mansoor R Mirza, Marie Plante, Michael Quinn, Andrés Poveda, Gordon C Jayson, Dan Stark, Ann Marie Swart, Laura Farrelly, Richard Kaplan, Mahesh K B Parmar, Timothy J Perren, for the ICON7 trial investigators*

- Faz III, 18 Aralık 2006-16 Şubat 2009,
- 263 merkez,Avrupa(11 ülke),Kanada, Avusturalya, Yeni Zelanda,
- Yeni tanı, yüksek riskli evre 1-IIa (Grade 3 ve berrak hücre histoloji) veya
- İleri evre IIb-IV,
- ECOG 0-2,
- 1528 hasta

Paklitaksel
175 mg/m2(3 saat)
Karboplatin
5 veya 6 AUC
21 günde bir
764 hasta

Paklitaksel
175 mg/m2
Karboplatin
5 veya 6 AUC
Bevacizumab
7.5 mg/kg
21 günde bir
764 hasta

Bevacizumab
12 siklus
veya
progresyon

Oza AM,et al.Lancet Oncol. 2015; 16(8): 928–36.

	All patients		High-risk patients	
	Standard therapy (n=764)	**Bevacizumab (n=764)**	**Standard therapy (n=254)**	**Bevacizumab (n=248)**
Overall survival				
Follow-up duration (months)	48·6 (24·3–56·0)	48·8 (28·2–56·4)	29·0 (14·1–50·7)	38·9 (21·1–52·5)
Deaths	352 (46%)	362 (47%)	174 (69%)	158 (64%)
Median overall survival (months; 95% CI)	58·6 (53·5–67·5)	58·0 (52·4–66·9)	30·2 (27·0–34·3)	39·7 (36·0–44·2)
Log-rank test p value	p=0·85		p=0·03	
HR (95% CI)	0·99 (0·85–1·14)		0·78 (0·63–0·97)	
Non-proportionality p value*	p=0·02		p=0·01	
(Restricted) mean survival time (months; 95% CI)†	44·6 (43·2–45·9)	45·5 (44·2–46·7)	34·5 (32·0–37·0)	39·3 (37·0–41·7)
Restricted mean survival time difference (95% CI)	0·9 (−0·8 to 2·6)		4·8 (1·5–8·1)	
Progression-free survival				
Follow-up duration (months)	16·3 (8·8–48·4)	19·4 (12·7–45·3)	10·1 (7·7–18·2)	15·6 (9·9–21·7)
Disease progression	526 (74%)	554 (73%)	228 (90%)	223 (90%)
Median progression-free survival (months; 95% CI)	17·5 (15·7–18·7)	19·9 (19·1–22·0)	10·5 (9·3–12·0)	16·0 (14·2–17·8)
Log-rank test p value	p=0·25		p=0·001	
HR (95% CI)	0·93 (0·83–1·05)		0·73 (0·61–0·88)	
Non-proportionality p value*	p<0·0001		p<0·0001	
(Restricted) mean survival time (months; 95% CI)†	27·7 (26·1–29·2)	29·2 (27·7–30·7)	15·9 (14·1–17·7)	20·0 (18·1–21·8)
Restricted mean survival time difference (95% CI)	1·6 (−0·6 to 3·7)		4·1 (1·4–6·7)	

Oza AM,et al.Lancet Oncol. 2015; 16(8): 928–36.

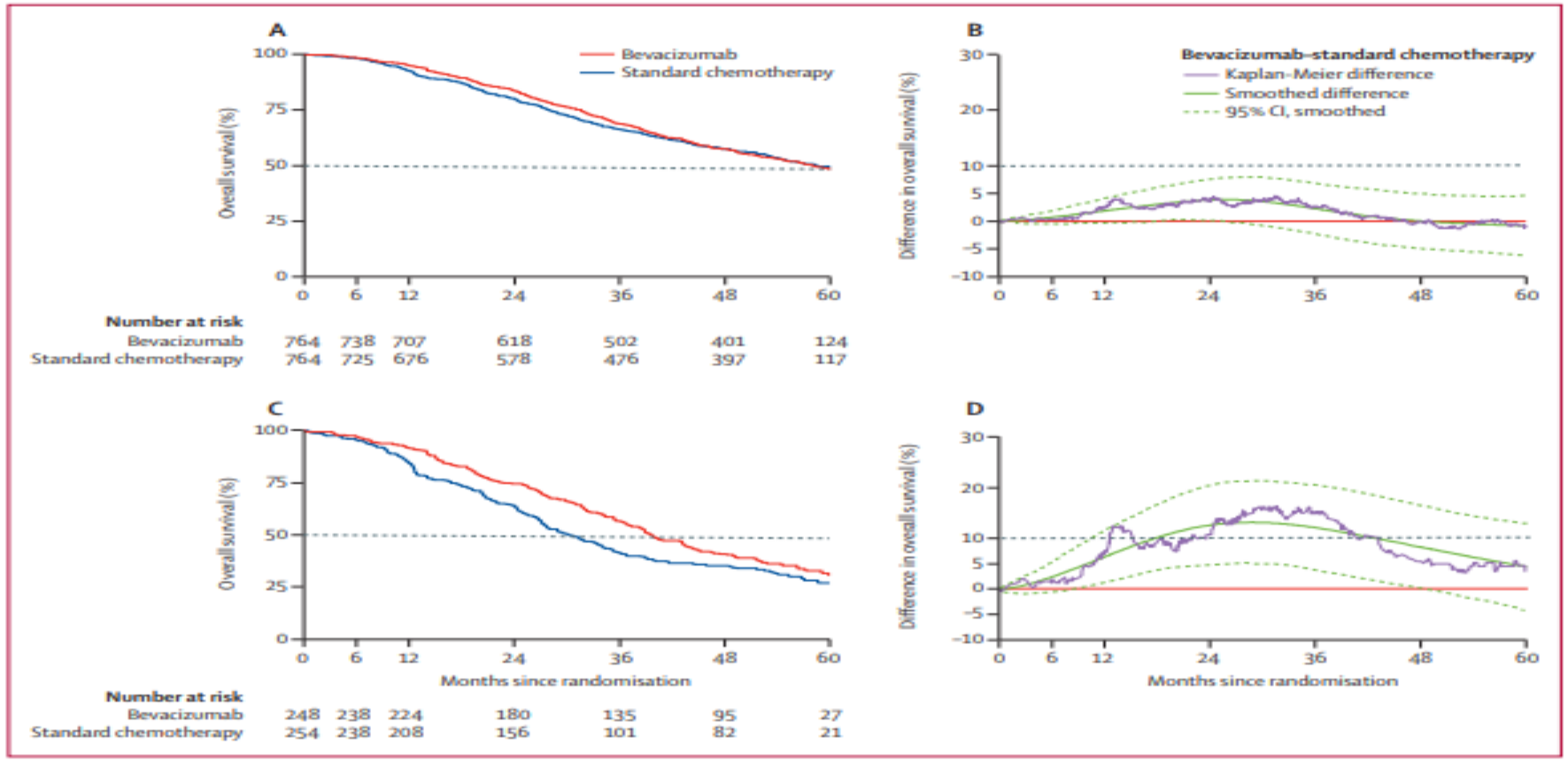

***Figure 2:* Overall survival**

(A) Overall survival in all patients. (B) Difference in overall survival between all patients in the two groups. (C) Overall survival in high-risk patients. (D) Difference in overall survival between high-risk patients in the two groups.

- Sonuç olarak;

- Platin bazlı kemoterapiye bevacizumab eklemek tüm çalışma grubunda genel sağkalımda iyileşme sağlamazken,
- Özellikle yüksek riskli hastalarda fayda sağladığı sonucuna ulaşmışlar.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D., Gini F. Fleming, M.D., Bradley J. Monk, M.D., Helen Huang, M.S., Robert S. Mannel, M.D., Howard D. Homesley, M.D., Jeffrey Fowler, M.D., Benjamin E. Greer, M.D., Matthew Boente, M.D., Michael J. Birrer, M.D., Ph.D., and Sharon X. Liang, M.D., for the Gynecologic Oncology Group*

- GOG 0218
- Faz III,
- Yeni tanı
- Evre III(optimal, suboptimal), Evre IV
- ECOG 0-2,
- 1873 hasta

Paklitaksel
175 mg/m2
Karboplatin
6 AUC
623 hasta

→ plasebo

Paklitaksel
175 mg/m2
Karboplatin
6 AUC
Bevacizumab
15mg/kg
625 hasta

→ plasebo

Paklitaksel
175 mg/m2
Karboplatin
6 AUC
Bevacizumab
15 mg/kg
623 hasta

→ Bevacizumab 15 mg/kg
15 ay

Burger RA,et al.N Engl J Med. 2011;365(26):2473-83.

- PSK standart kemoterapi kolunda 10.3 ay, bevacizumab kolunda11.2 ay ve idame bevacizumab kolunda 14.1 ay ($p<.01$)

- GSK standart kemoterapi kolunda 39.3 ay, bevacizumab kolunda 38.7 ay ve idame bevacizumab kolunda 39.7 ay ($p=.45$)

Burger RA,et al.N Engl J Med. 2011;365(26):2473-83.

- Özellikle asitli hastalarda;
- PSK idame bevacizumablı kolda 15.2 ayken sadece kemoterapi kolunda 10.4 ay ($p<.001$),
- GSK idame bevacizumablı kolda 43.3 ayken sadece kemoterapi kolunda 39.9 ay ($p=.035$).

Burger RA,et al. N Engl J Med. 2011;365(26):2473-83.

- Sonuç olarak,
- Karboplatin paklitaksel kemoterapisiyle birlikte kullanımdan sonra 10 ay kadar bevacizumab kullanımı
- ileri evre epitelyal over kanserli hastalarda progresyonsuz sağkalımı yaklaşık 4 ay kadar uzatmakta,

PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens[a] - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

STAGE II–IV DISEASE			
• **High-grade serous** • **Endometrioid (Grade 2/3)** • **Clear cell carcinoma[b]** • **Carcinosarcoma[b]**	**Preferred Regimens** • Paclitaxel 175/carboplatin[d] • Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[e] (ICON-7 & GOG-218)	**Other Recommended Regimens** • Paclitaxel weekly/carboplatin weekly[d,f] • Docetaxel/carboplatin • Carboplatin/liposomal doxorubicin • Paclitaxel weekly/carboplatin q3weeks	**Useful in Certain Circumstances** • IP/IV paclitaxel/cisplatin (for optimally debulked stage II–III disease) • For carcinosarcoma: ▸ Carboplatin/ifosfamide ▸ Cisplatin/ifosfamide ▸ Paclitaxel/ifosfamide (category 2B) • Carboplatin (if elderly [age >70] and/or for those with comorbidities)
Mucinous Carcinoma[b]	**Preferred Regimens** • Paclitaxel 175/carboplatin[d] • Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[e] (ICON-7 & GOG-218) • 5-FU/leucovorin/oxaliplatin ± bevacizumab[e] (category 2B for bevacizumab) • Capecitabine/oxaliplatin ± bevacizumab[e] (category 2B for bevacizumab)	**Other Recommended Regimens** • Paclitaxel weekly/carboplatin weekly[d,f] • Docetaxel/carboplatin • Carboplatin/liposomal doxorubicin • Paclitaxel weekly/carboplatin q3weeks	**Useful in Certain Circumstances** • Carboplatin (if elderly [age >70] and/or for those with comorbidities)
Low-Grade Serous/Grade I Endometrioid[b,c]	**Preferred Regimens** • Paclitaxel 175/carboplatin[d] • Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[e] (ICON-7 & GOG-218)	**Other Recommended Regimens** • Paclitaxel weekly/carboplatin weekly[d,f] • Docetaxel/carboplatin • Carboplatin/liposomal doxorubicin • Paclitaxel weekly/carboplatin q3weeks • Hormone therapy (aromatase inhibitors [anastrozole, letrozole, exemestane], leuprolide acetate, tamoxifen) (category 2B)	**Useful in Certain Circumstances** • Carboplatin (if elderly [age >70] and/or for those with comorbidities)

Primary Systemic Therapy Dosing (See OV-C, 6 of 10)

[a] See Discussion for references.
[b] There are limited data on the primary systemic therapy regimens for these LCOC.
[c] Borderline disease with invasive implants may be treated as low-grade serous disease. See LCOC-6 and LCOC-7.
[d] Elderly patients and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Guidelines. Based on clinical judgment and expected tolerance to therapies, alternate dosing (see OV-C, 6 of 10) may be appropriate for elderly patients with epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). Algorithms have been developed for predicting chemotherapy toxicity. See the NCCN Guidelines for Older Adult Oncology.
[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[f] Regimen may be considered for those with poor performance status.

Nüks Over Kanserlerinde Tedavi

- Hastanın performans durumu,
- Nüks yeri ve zamanı,
- Metastaz yer(ler)i, tümör yükü
- Önceki tedaviler;

  -Etki ve yan etki,

  -Tedaviler arası süre(Son kemoterapiden itibaren geçen süre)

Nüks Over Kanserlerinde Tedavi

- Platin dirençli hastalık,
- Platin duyarlı hastalık,

Platin Dirençli ve Duyarlı Hastalık Tanımı?

Platin Dirençli

Platin Refrakter

Tedavi altında progresyon veya en iyi yanıt stabil hastalık,

Platin Dirençli

Tedavi tamamlandıktan <6 ay tekrarlayan hastalık,

Platin Duyarlı

Kısmi Platin Duyarlı

Tedavi tamamlandıktan 6 -12 ay tekrarlayan hastalık,

Platin Tam Duyarlı

Tedavi tamamlandıktan >12 ay tekrarlayan hastalık,

Nüks Over Kanseri

- Platin Dirençli

  AURELİA

- Platin Duyarlı

  GOG- 0213 ve

  OCEANS

Platin Dirençli

VOLUME 32 · NUMBER 13 · MAY 1 2014
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial

2.Sıra

Platin bazlı kemoterapiyi ≥4 siklus aldıktan sonra ≤6 ay progresyon görülen hastalık,

Primer sonlanım noktası progresyonsuz sağkalım

ECOG 0-2

Bevacizumab;
10 mg/kg/gün 15 günde bir veya
15 mg/kg/gün 21 günde bir uygulanmış

Paklitaksel
80 mg/m2 1,8,15,22gün
4 haftada bir

Pegile lipozomal doksurobisin
40 mg/m2
4 haftada bir

Topotekan
4 mg/m2
1,8,15. gün
4 haftada bir

Topotekan
1.75 mg/m2/gün
1-5 gün
3 haftada bir

Pujade-Lauraine E, et al. J Clin Oncol. 2014;32:1302-8.

Paklitaksel grubunda

PSK kemoterapi grubunda 3.9 ayken bevacizumab grubunda 10.4 ay,

Median GSK kemoterapi grubunda13.2 ayken, bevacizumab grubunda 22.4 ay,

- **Topotekan grubunda**
- PSK kemoterapi grubunda 2.1 ayken bevacizumab grubunda 6.2 ay,
- GSK kemoterapi grubunda 13.3 ayken, bevacizumab grubunda 13.8 ay,

Pegile lipozomal doksurobisin grubunda

PSK kemoterapi grubunda 3.5 ayken bevacizumab grubunda 5.1 ay,

GSK kemoterapi grubunda 14.1 ayken, bevacizumab grubunda 13.7 ay,

Pujade-Lauraine E, et al. J Clin Oncol 2014;32:1302-8

- Kemoterapi grubunda progresyonsuz sağkalım 3.4 ay iken kemoterapi ve bevacizumab gruplarında 6.7 ay,
- Genel cevap oranı %11.8 karşı %27.3 (p 0.001).
- Median sağkalım oranı kemoterapi gruplarında 13.3(11.9-16.4) aya karşı bevacizumab gruplarında 16.6(13.7-19.0) ay

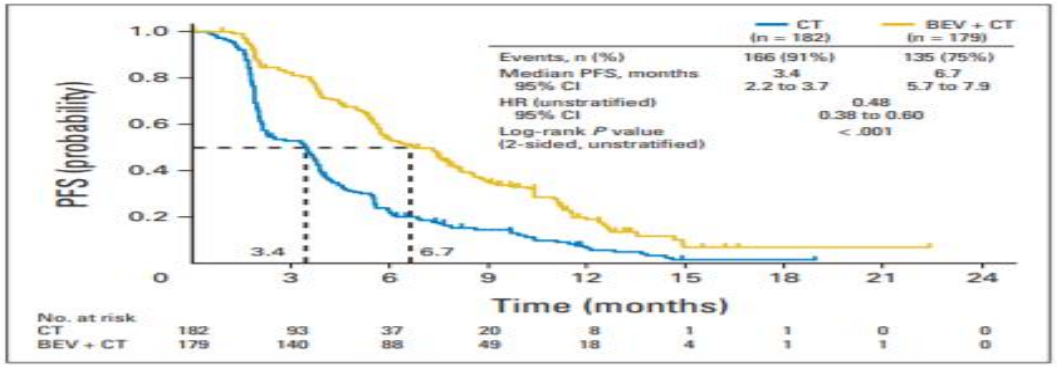

Fig 2. Progression-free survival (PFS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.

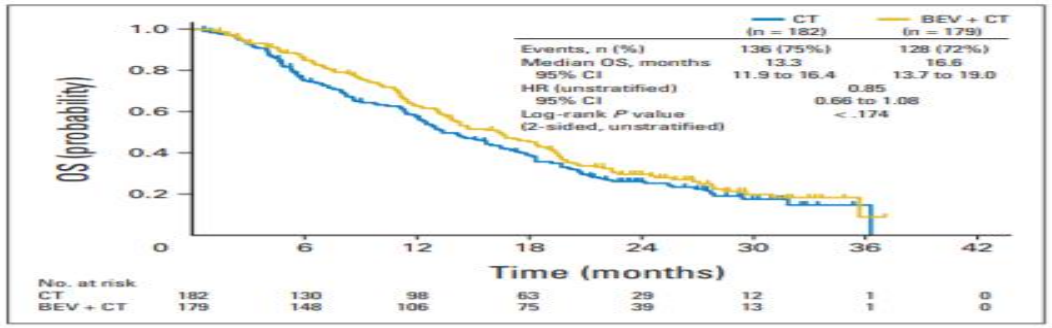

Fig 3. Overall survival (OS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.

Pujade-Lauraine E, et al. J Clin Oncol. 2014;32:1302-8

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[j]/Fallopian Tube/Primary Peritoneal Cancer[k]

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens		Useful in Certain Circumstances
Cytotoxic Therapy	Cytotoxic Therapy[r]		Immunotherapy
Cyclophosphamide (oral)/bevacizumab[e,22]	Capecitabine	Oxaliplatin	Pembrolizumab (for MSI-H or dMMR solid tumors)[t,21]
Docetaxel[23]	Cyclophosphamide	Paclitaxel	Hormone Therapy
Etoposide, oral[24]	Doxorubicin	Paclitaxel, albumin bound	Fulvestrant (for low-grade serous carcinoma)
Gemcitabine[25,26]	Ifosfamide	Pemetrexed	Targeted Therapy (single agents)
Liposomal doxorubicin[25,26]	Irinotecan	Sorafenib/topotecan[31]	Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[t]
Liposomal doxorubicin/bevacizumab[e,m,27]	Melphalan	Vinorelbine	Trametinib (for low-grade serous carcinoma)[20]
Paclitaxel (weekly)[28]			
Paclitaxel (weekly)/bevacizumab[e,m,27]			
Topotecan[29,30]			
Topotecan/bevacizumab[e,m,27]			
Targeted Therapy (single agents)	Targeted Therapy (single agents)		
Bevacizumab[e,m,9,10]	Pazopanib (category 2B)[18]		
Niraparib[o,11]	Hormone Therapy		
Olaparib[p,12]	Aromatase inhibitors (anastrozole, exemestane, letrozole)		
Rucaparib[q,13]	Leuprolide acetate		
	Megestrol acetate		
	Tamoxifen		

[e]An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[j]Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[k]Patients who progress on two consecutive 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.
[m]Contraindicated for patients at increased risk of GI perforation.
[o]For patients treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD defined by either: 1) a deleterious or suspected deleterious *BRCA* mutation; or 2) genomic instability and progression >6 months after response to the last platinum-based chemotherapy.
[p]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 two or more lines of chemotherapy.

Platinum-Sensitive Disease, see OV-C, 7 of 10

[q]For patients with deleterious germline and/or somatic *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 two or more lines of chemotherapy.
[r]Many of these single-agent cytotoxic therapy options have not been tested in patients who have been treated with modern chemotherapy regimens.
[t]Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: *BRCA1/2*, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

Platin Duyarlı

HHS Public Access
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Published in final edited form as:
Lancet Oncol. 2017 June ; 18(6): 779–791. doi:10.1016/S1470-2045(17)30279-6.

Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial

Robert L Coleman, Mark F Brady, Thomas J Herzog, Paul Sabbatini, Deborah K Armstrong, Joan L Walker, Byoung-Gie Kim, Keiichi Fujiwara, Krishnansu S Tewari, David M O'Malley, Susan A Davidson, Stephen C Rubin, Paul DiSilvestro, Karen Basen-Engquist, Helen Huang, John K Chan, Nick M Spirtos, Raheela Ashfaq, and Robert S Mannel

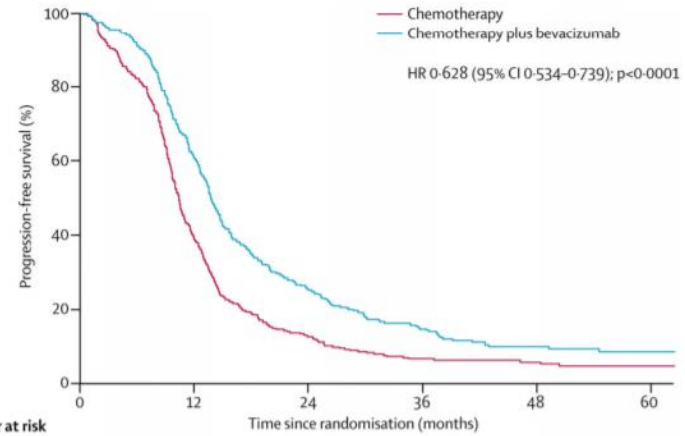
- GOG -0213
- Faz 3,
- Çok merkezli,67 Merkez(1 merkez Japonya ve Güney Kore, diğerleri Amerika)
- Birinci sıra tedaviyi en az 6 ay önce tamamlamış hastalar,
- 10 Aralık 2007-26 Ağustos 2011
- 673 hasta

Karboplatin
5 AUC
Paklitaksel
175 mg/m2
21 günde bir

Karboplatin
5 AUC
Paklitaksel
175 mg/m2
Bevacizumab
15 mg/kg
21 günde bir

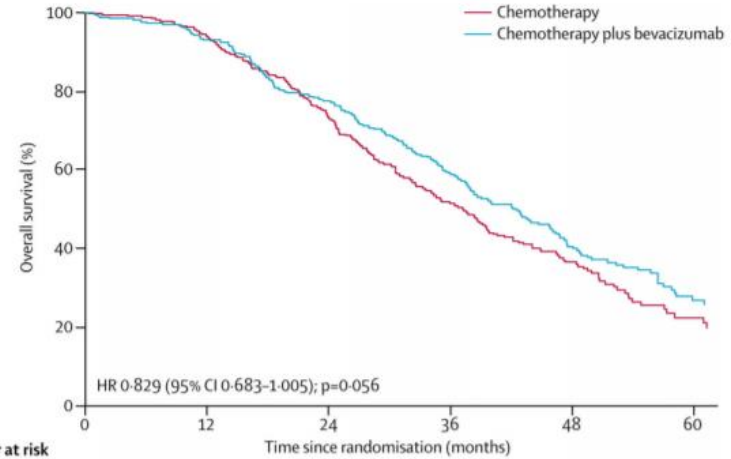
Bevacizumab
15 mg/kg
21 günde bir

Coleman RL, et al. Lancet Oncol. 2017;18:779-91.



Number at risk (number censored)						
Chemotherapy	337 (0)	125 (15)	40 (16)	20 (17)	12 (23)	5 (28)
Chemotherapy plus bevacizumab	337 (0)	201 (7)	84 (7)	46 (10)	16 (27)	9 (32)

Figure 4. Progression-free survival, adjusted for stratification factors

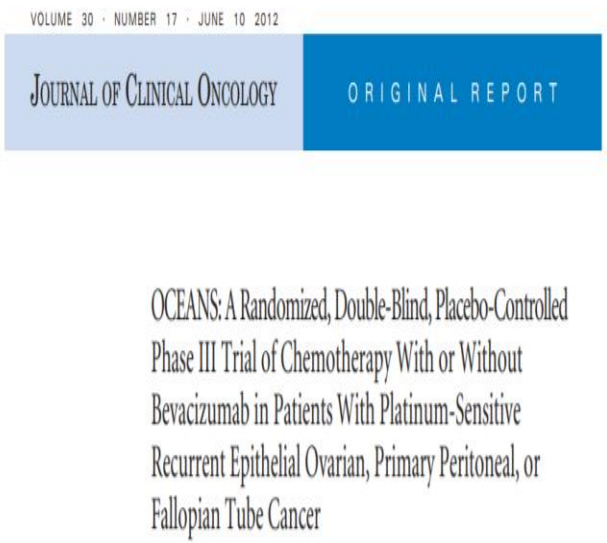


Number at risk (number censored)						
Chemotherapy	337 (0)	303 (15)	234 (17)	152 (30)	69 (77)	18 (109)
Chemotherapy plus bevacizumab	337 (0)	306 (8)	253 (9)	183 (20)	75 (82)	28 (110)

Figure 2. Primary analysis of overall survival, adjusted for stratification factors
Median overall survival is based on the originally submitted treatment-free interval data.

- Kemoterapi kolunda PSK 10.4 ayken bevacizumablı kolda 13.8 ay ($p<.0001$),
- GSK kemoterapi kolunda 37.3 ayken, bevacizumablı kolda 42.2 ay ($p=.056$),
- Platin duyarlı nüks hastalıkta standart kemoterapiye bevacizumab eklenmesi ve ardından progresyona kadar idame tedavisi sağkalım üzerinde iyileşmeye neden olmaktadır sonucuna ulaşılmış.

Coleman RL, et al. Lancet Oncol. 2017;18:779-91.



OCEANS
Faz III

2.Sıra (1.Sıra platin bazlı kemoterapiyi tamamladıktan ≥6 ay sonra nüks gösteren hastalık)

ECOG 0-1

484 hasta

Gemsitabin
1000 mg/m2 1,8 gün
Karboplatin
4 AUC

Gemsitabin
1000 mg/m2 1 ve 8 gün
Karboplatin
4 AUC
Bevacizumab
15 mg/kg

Aghajanian C,et al.Gynecol Oncol. 2015 ;139(1):10-6.

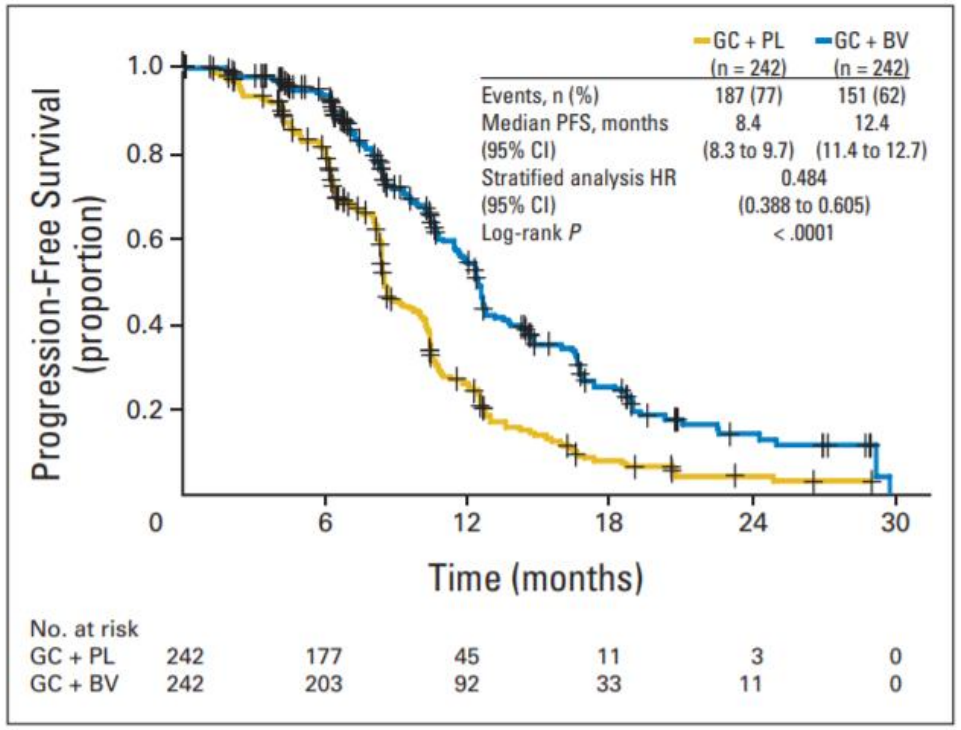
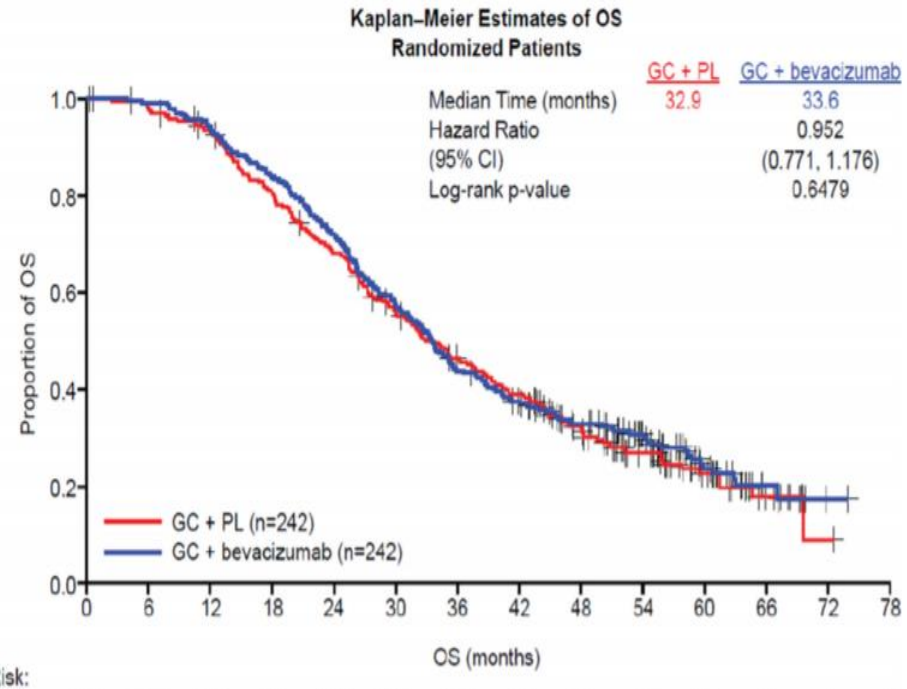


Fig 2. Kaplan-Meier estimates of progression-free survival (PFS) based on investigator assessment, censoring for non–protocol-specified therapy (randomly assigned patients). BV, bevacizumab; GC, gemcitabine plus carboplatin; HR, hazard ratio; PL, placebo.

- Gemsitabin karboplatin 1-6 siklusa bevacizumab eklenmesi, sonrasında bevacizumab progresyona kadar,
- PSK 8.4 aya karşın 12.4 ay(p<.0001),

Aghajanian C,et al.Gynecol Oncol 2015 ;139(1):10-6.

A



- Gemsitabin karboplatin 1-6 siklusa bevacizumab eklenmesi, sonrasında bevacizumab progresyona kadar,
- GSK 32.9 aya karşı 33.6 ay (p=.65),

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[j]/Fallopian Tube/Primary Peritoneal Cancer[k]

Recurrence Therapy for Platinum-Sensitive Disease[l] (alphabetical order)

Preferred Regimens	Other Recommended Regimens[r]	Useful in Certain Circumstances
Carboplatin/gemcitabine[2] ± bevacizumab[e,m,n,3] Carboplatin/liposomal doxorubicin[4] ± bevacizumab[e,5] Carboplatin/paclitaxel[6] ± bevacizumab[e,m,n,7] Cisplatin/gemcitabine[8] <u>Targeted Therapy (single agents)</u> Bevacizumab[e,m,9,10] Niraparib[o,11] Olaparib[p,12] Rucaparib[q,13]	Carboplatin/docetaxel[14,15] Carboplatin/ paclitaxel (weekly)[16] Capecitabine Carboplatin[s,2] Cisplatin[6] Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Vinorelbine <u>Targeted Therapy</u> Niraparib/bevacizumab[e,17] Pazopanib (category 2B)[18] <u>Hormone Therapy</u> Aromatase inhibitors (anastrozole, exemestane, letrozole) Leuprolide acetate Megestrol acetate Tamoxifen	For mucinous carcinoma: • 5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[e,m] • Capecitabine/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[e,m] Carboplatin/paclitaxel, albumin bound (for confimed taxane hypersensitivity) Carboplatin/paclitaxel[s] (for age >70) Irinotecan/cisplatin (for clear cell carcinoma)[19] <u>Targeted Therapy (single agents)</u> Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[t] Trametinib (for low-grade serous carcinoma)[20] <u>Hormone Therapy</u> Fulvestrant (for low-grade serous carcinoma) <u>Immunotherapy</u> Pembrolizumab (for microsatellite instability-high [MSI-H] or mismatch repair-deficient [dMMR] solid tumors)[t,21]

Platinum-Resistant Disease, see OV-C, 8 of 10

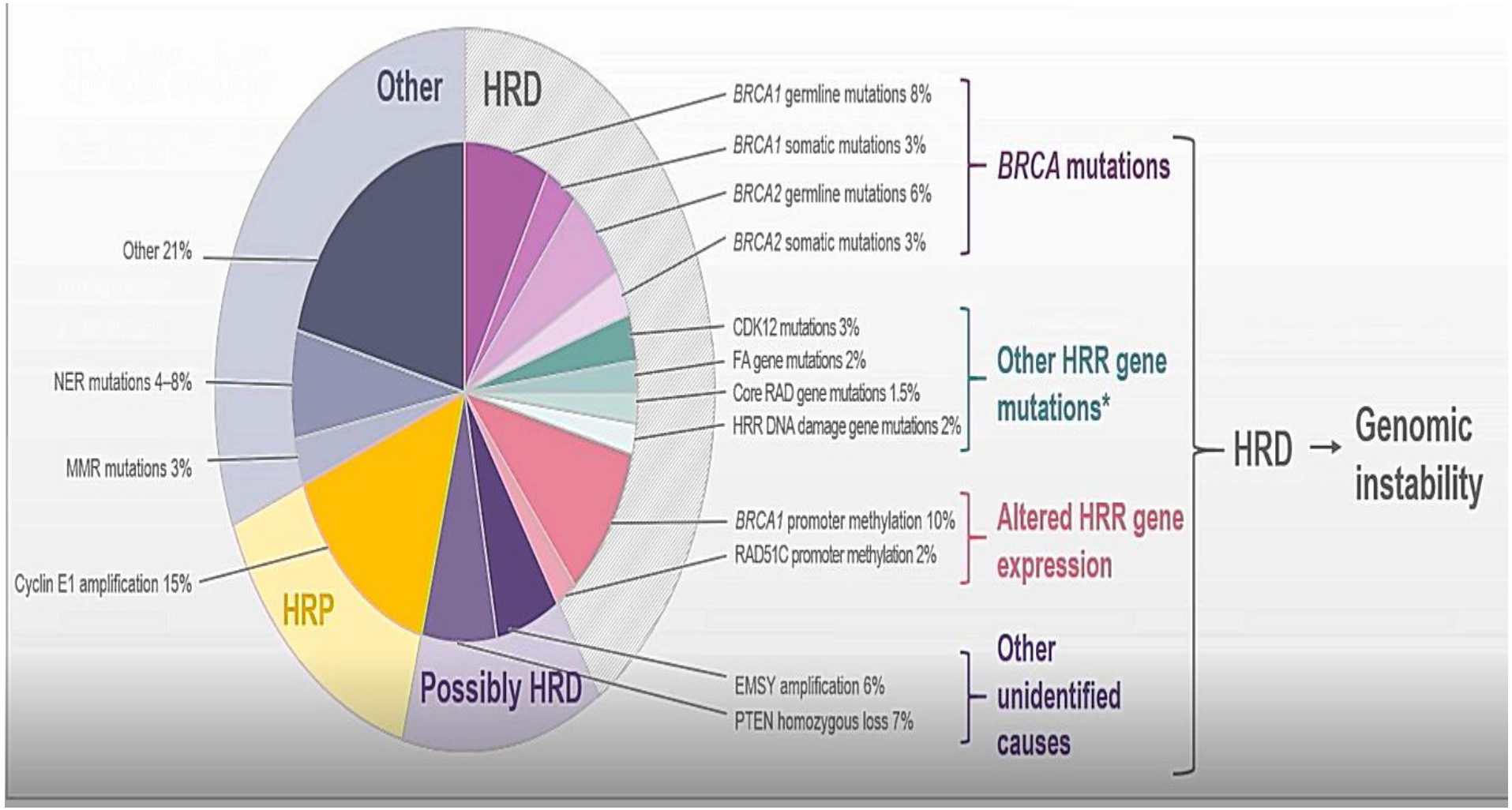
[e]An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[j]Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[k]Patients who progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. (Griffiths RW, et al. 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.
[l]In general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.
[m]Contraindicated for patients at increased risk of GI perforation.
[n]If response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity. Discontinue bevacizumab before initiating maintenance therapy with a PARP inhibitor.
[o]For patients treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD defined by either: 1) a deleterious or suspected deleterious *BRCA* mutation; or 2) genomic instability and progression >6 months after response to the last platinum-based chemotherapy.
[p]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 two or more lines of chemotherapy.
[q]For patients with deleterious germline and/or somatic *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 two or more lines of chemotherapy.
[r]Many of these single-agent cytotoxic therapy options have not been tested in patients who have been treated with modern chemotherapy regimens.
[s]For recommended dosing for elderly patients, see OV-C, 6 of 10.
[t]Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: *BRCA1/2*, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

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

Continued

Over Kanserinde İdame Tedavi

- Poli(ADP-ribose) polimeraz (PARP) inhibitörleri;
- Homolog rekombinasyon eksikliği olan (BRCA mutasyonu olan tümörler de dahil) kanserlerde tümör hücrelerini hedefleyerek ölümlerine neden olur.
- PARP inhibitörleri(olaparib, veliparib, niraparib, rucaparib ve talazoparib gibi) çalışmalarla değerlendirilmekte


Other
HRD
HRP
Possibly HRD
Other 21%
NER mutations 4–8%
MMR mutations 3%
Cyclin E1 amplification 15%
BRCA1 germline mutations 8%
BRCA1 somatic mutations 3%
BRCA2 germline mutations 6%
BRCA2 somatic mutations 3%
BRCA mutations
CDK12 mutations 3%
FA gene mutations 2%
Core RAD gene mutations 1.5%
HRR DNA damage gene mutations 2%
Other HRR gene mutations*
BRCA1 promoter methylation 10%
RAD51C promoter methylation 2%
Altered HRR gene expression
EMSY amplification 6%
PTEN homozygous loss 7%
Other unidentified causes
HRD → Genomic instability

Poli (ADP-riboz) polimeraz (PARP) İnhibitörleri

- **Olaparib** (150 mg tablet)
- Platin duyarlı, nüks, BRCA germline ve /veya somatik mutasyonlu,
- Monoterapi idame tedavisi olarak 3 veya daha fazla basamak tedavi almış hastalarda 2014 onay alan ilk ilaç.
- **SOLO-2 çalışması**: Ağustos 2017 idame tedavi,

- **Rucaparib** (300 mg tablet)
- Eylül 2016 BRCA mutasyonlu, platin dirençli hastada 3.basamakta onay)
- **ARİEL-3** platin duyarlı hastada idame rucaparib

- **Niraparib** (100mg kapsül) Mart 2017 onay,
- NOVA platin duyarlı hastalarda idame niraparib,

Olaparib

Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial

*Eric Pujade-Lauraine, Jonathan A Ledermann, Frédéric Selle, Val Gebski, Richard T Penson, Amit M Oza, Jacob Korach, Tomasz Huzarski, Andrés Poveda, Sandro Pignata, Michael Friedlander, Nicoletta Colombo, Philipp Harter, Keiichi Fujiwara, Isabelle Ray-Coquard, Susana Banerjee, Joyce Liu, Elizabeth S Lowe, Ralph Bloomfield, Patricia Pautier, the SOLO2/ENGOT-Ov21 investigators**

- gBRCA1/2 mutasyonu,
- Nüks hastalık
- Daha öncesinde ≥ 2 platin bazlı tedavi kısmi veya tam cevap

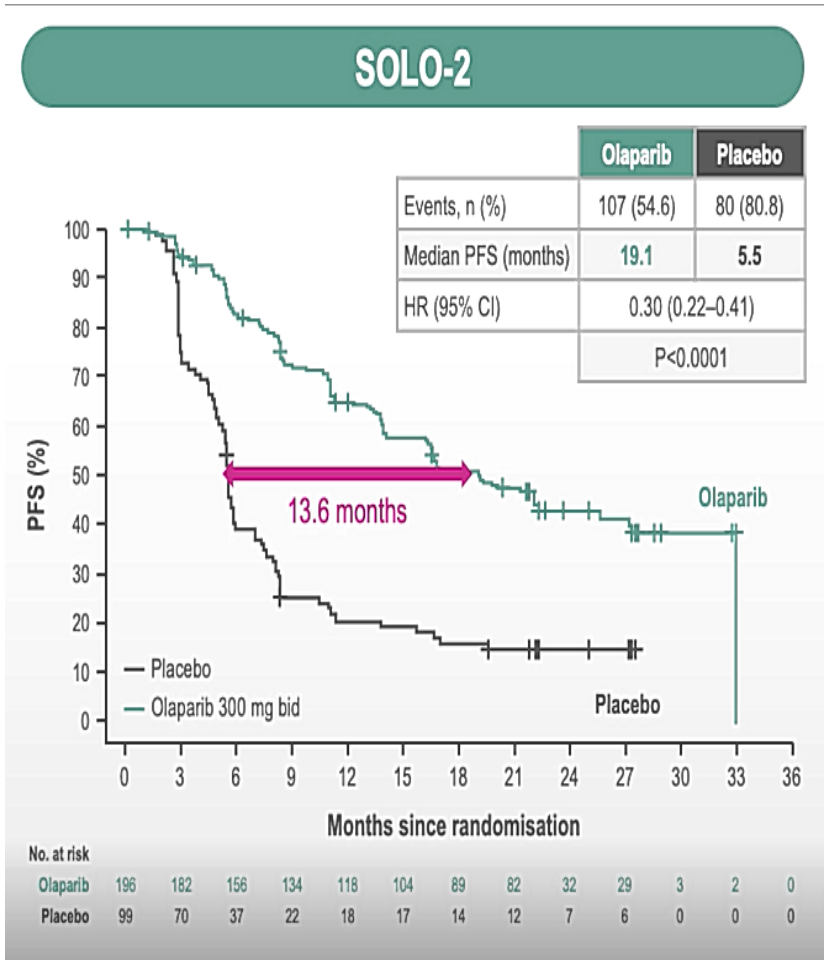
- 6-12 ay veya
- ≥12ay

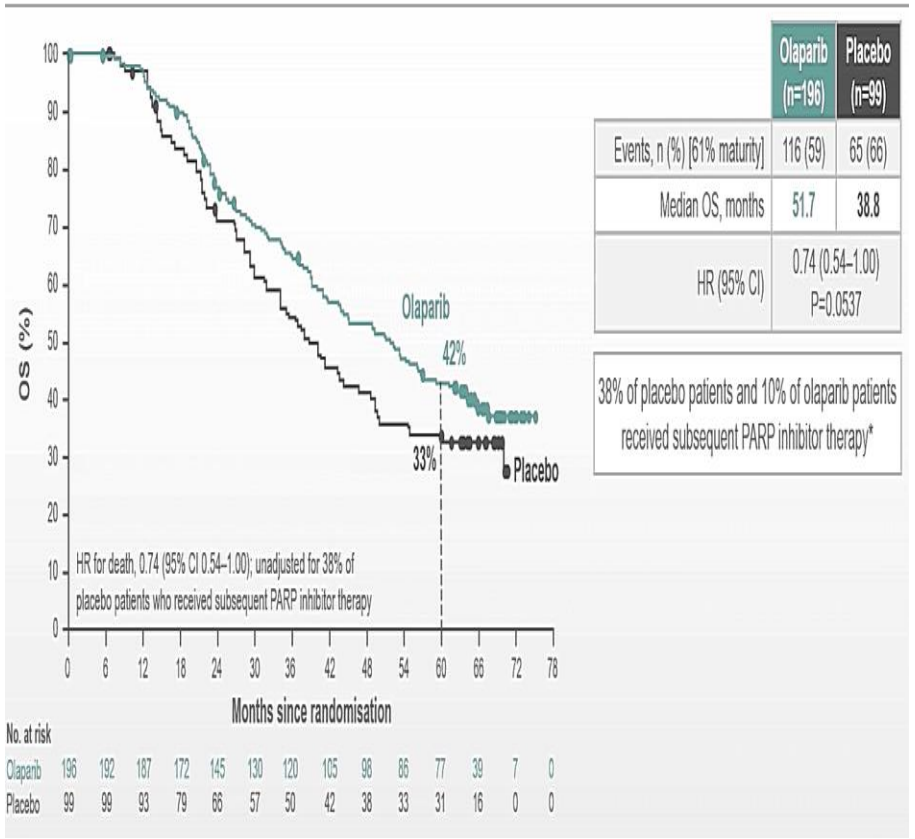
- 295 hasta

→ **Olaparib** 300 mg 2x1
196 hasta

→ Plasebo
99 hasta

Pujade-Lauraine et al.Lancet Oncol. 2017 ;18(9):1274-84.





Pujade-Lauraine et al.Lancet Oncol. 2017 ;18(9):1274-84

	Olaparib (n=195)	Placebo (n=99)
Median relative dose intensity*	98·4% (84·7–99·9)	99·4% (98·1–100·0)
Median daily dose (mg)	597·6 (541·3–600·0)	598·4 (593·0–600·0)
Dose interruptions	88 (45%)	18 (18%)
Dose reductions	49 (25%)	3 (3%)
Discontinuations	21 (11%)	2 (2%)

Data are median (IQR) or n (%). *See appendix p 7 for further details on the relative dose intensity.

Table 3: **Dose modifications and discontinuations owing to adverse events**

- Ciddi yan etkiler olaparib grubunda %19, plasebo grubunda %8,
- Olaparib grubunda grade 3 yan etki %32, en sık görülen yan etki %18 anemi, grade 4 yan etki %4,anemi,nötropeni ve lökopeni (%1)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

I. Ray-Coquard, P. Pautier, S. Pignata, D. Pérol, A. González-Martín, R. Berger, K. Fujiwara, I. Vergote, N. Colombo, J. Mäenpää, F. Selle, J. Sehouli, D. Lorusso, E.M. Guerra Alía, A. Reinthaller, S. Nagao, C. Lefeuvre-Plesse, U. Canzler, G. Scambia, A. Lortholary, F. Marmé, P. Combe, N. de Gregorio, M. Rodrigues, P. Buderath, C. Dubot, A. Burges, B. You, E. Pujade-Lauraine, and P. Harter, for the PAOLA-1 Investigators*

- Randomize,çift kör,Faz 3
- Yeni tanı,ileri evre, yüksek gradeli over kanseri,
- Birinci sıra platin+ taksan +bevacizumab tedavisinden sonra
- 2:1 randomizasyon
- Bütün hastalara bevcizumab 15 mg/kg 3 haftada bir 15 ay
- Olaparib 300 mg 2x1 veya plasebo kollarına 24 ay
- Primer sonlanım noktası hastalık progresyonu

- 806 hasta(537 olaparib,269 plasebo),
- 22.9 ay median takip süresi,

- Median PSK olaparib+ bevacizumab kolunda 22.1 ay, plasebo+ bevacizumab kolunda 16.6 ay p<.001)
- HRD (BRCA mutasyonu olanlar dahil)median PSK 37.2 aya karşın 17.7 ay,
- HRD(BRCA mutasyonu olanlar hariç) median PSK 28.1 aya karşın 16.6 ay,

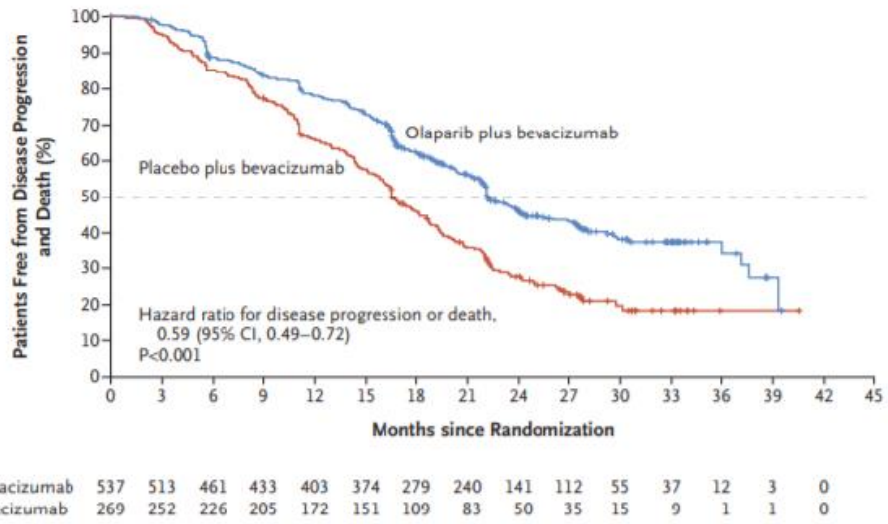


Figure 1. Kaplan–Meier Estimates of Investigator-Assessed Progression-free Survival.

Shown are Kaplan–Meier estimates of the rate of freedom from disease progression, as assessed by investigators, and from death. According to Kaplan–Meier estimates, the percentage of patients in the olaparib-plus-bevacizumab group and the placebo-plus-bevacizumab group who were free from disease progression and death was 78% and 66%, respectively, at 12 months; 62% and 46%, respectively, at 18 months; and 46% and 28%, respectively, at 24 months. The dashed horizontal line indicates the median value.

Clinical Trial > Lancet Oncol 2015 Jan;16(1):87-97. doi: 10.1016/S1470-2045(14)71135-0.
Epub 2014 Dec 4.

Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial

Amit M Oza [1], David Cibula [2], Ana Oaknin Benzaquen [3], Christopher Poole [4], Ron H J Mathijssen [5], Gabe S Sonke [6], Nicoletta Colombo [7], Jiří Špaček [8], Peter Vuylsteke [9], Holger Hirte [10], Sven Mahner [11], Marie Plante [12], Barbara Schmalfeldt [13], Helen Mackay [14], Jacqui Rowbottom [15], Elizabeth S Lowe [16], Brian Dougherty [17], J Carl Barrett [17], Michael Friedlander [18]

- Randomize,açık etiketli,faz 2,
- 12 Şubat-30 Temmuz 2010 ,12 ülke,43 merkez
- En az 3 sıra kemoterapi almış,Platin duyarlı,nüks over kanserli hastalar
- Karboplatin(4 AUC)+paklitaksel(175 mg/m²) ve bu tedaviye olaparib 200 mg 1-10 gün 21 günlük siklus sonrasında olaparib 400 mg 2x1 idame monoterapi
- Karboplatin(6 AUC)+paklitaksel(175 mg/m²) grupları olarak randomize

- 107 hastadan 41(%38) BRCA mutasyonu mevcuttu(20 olaparib ,21 kemoterapi grubu).

- PSK olaparib grubunda önemli oranda iyileşmiş olarak bulundu(median 12.2 aya karşın 9.6 ay p=.0012,BRCA mutasyonlu olanlarda p=0·0015)
- Ciddi yan etki kemoterapi+olaparib alanlarda 81 hastanın 12'inde (%15), sadece kemoterapi alan 75 hastanın 16'sında (%21) gözlendi.
- Sonuç olarak;
- Paklitaksel ve karboplatin tedavisini izleyen olaparib monoterapisi yönetilebilir ve kabul edilebilir toksisitesi ile özellikle BRCA mutant hastalarda PSK fayda sağlamaktadır.

Oza AM,et al.Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol2015 Jan;16(1):87-97

Rucaparib

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial

Robert L Coleman, Amit M Oza, Domenica Lorusso, Carol Aghajanian, Ana Oaknin, Andrew Dean, Nicoletta Colombo, Johanne I Weberpals, Andrew Clamp, Giovanni Scambia, Alexandra Leary, Robert W Holloway, Margarita Amenedo Gancedo, Peter C Fong, Jeffrey C Goh, David M O'Malley, Deborah K Armstrong, Jesus Garcia-Donas, Elizabeth M Swisher, Anne Floquet, Gottfried E Konecny, Iain A McNeish, Clare L Scott, Terri Cameron, Lara Maloney, Jeff Isaacson, Sandra Goble, Caroline Grace, Thomas C Harding, Mitch Raponi, James Sun, Kevin K Lin, Heidi Giordano, Jonathan A Ledermann*, on behalf of the ARIEL3 investigators†*

- Randomize, çift kör, faz 3
- 11 ülke,87 merkez
- 07.04.2014-19.07.2016,
- Platin duyarlı,
- Rucaparib 600 mg 2x1 veya plasebo
- 564 hasta(375 %66 rucaparib ve 189 %34 placebo)

- Median PSK BRCA mutasyonlu hastalarda 16·6 ayken plasebo grubunda 5.4 ay p<·0001,
- Bu hastaların HRD olanlarında[236(%63) ve 118(%62];

13.6 (10·9–16·2) aya karşı 5.4(5·1–5·6)ay p<·0001

- En sık görülen yan etki hb konsantrasyonunda düşüklük ve AST/ ALT yüksekliği olmuştur.

- Rucaparib platin duyarlı hastalarda idame tedavisinde PSK önemli iyileşme sağlamıştır sonucu

Niraparib

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, M. Fabbro, J.A. Ledermann, D. Lorusso, I. Vergote, N.E. Ben-Baruch, C. Marth, R. Mądry, R.D. Christensen, J.S. Berek, A. Dørum, A.V. Tinker, A. du Bois, A. González-Martín, P. Follana, B. Benigno, P. Rosenberg, L. Gilbert, B.J. Rimel, J. Buscema, J.P. Balser, S. Agarwal, and U.A. Matulonis, for the ENGOT-OV16/NOVA Investigators*

Faz 3,Platin duyarlı, >6 ay sonra nüks
≥ 2 platin bazlı rejim
Tam remisyon/kısmi remisyon veya progresyon, 553 hasta,
Primer sonlanım noktası progresyonsuz sağkalım

Niraparib 300 mg/gün 28 gün 1 kür

Germline BRCA mutasyon mevcut 203 hasta

- Niraparib 136 hasta
- plasebo 65 hasta

**Germline BRCA Mutasyonu Olmayan 350 hasta

- Niraparib 231 hasta
- Plasebo 114 hasta

Mirza MR, et al.N Engl J Med. 2016;375(22):2154-64.

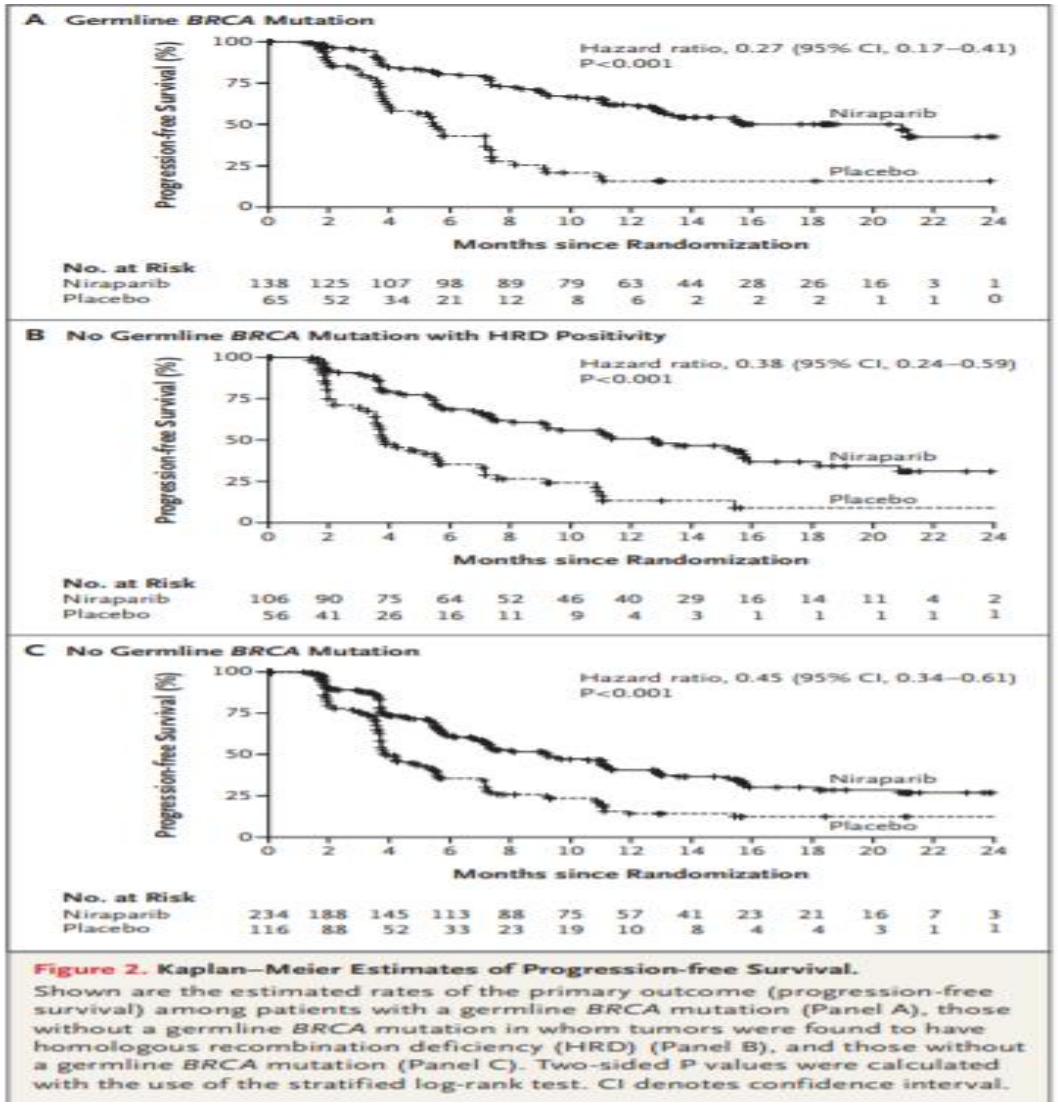


Figure 2. Kaplan–Meier Estimates of Progression-free Survival. Shown are the estimated rates of the primary outcome (progression-free survival) among patients with a germline *BRCA* mutation (Panel A), those without a germline *BRCA* mutation in whom tumors were found to have homologous recombination deficiency (HRD) (Panel B), and those without a germline *BRCA* mutation (Panel C). Two-sided P values were calculated with the use of the stratified log-rank test. CI denotes confidence interval.

- Homolog rekombinasyon eksikliği

- Niraparib grubunda plasebo grubuna göre BRCA mutasyonu olup olmamasından bağımsız olarak daha uzun PSK,

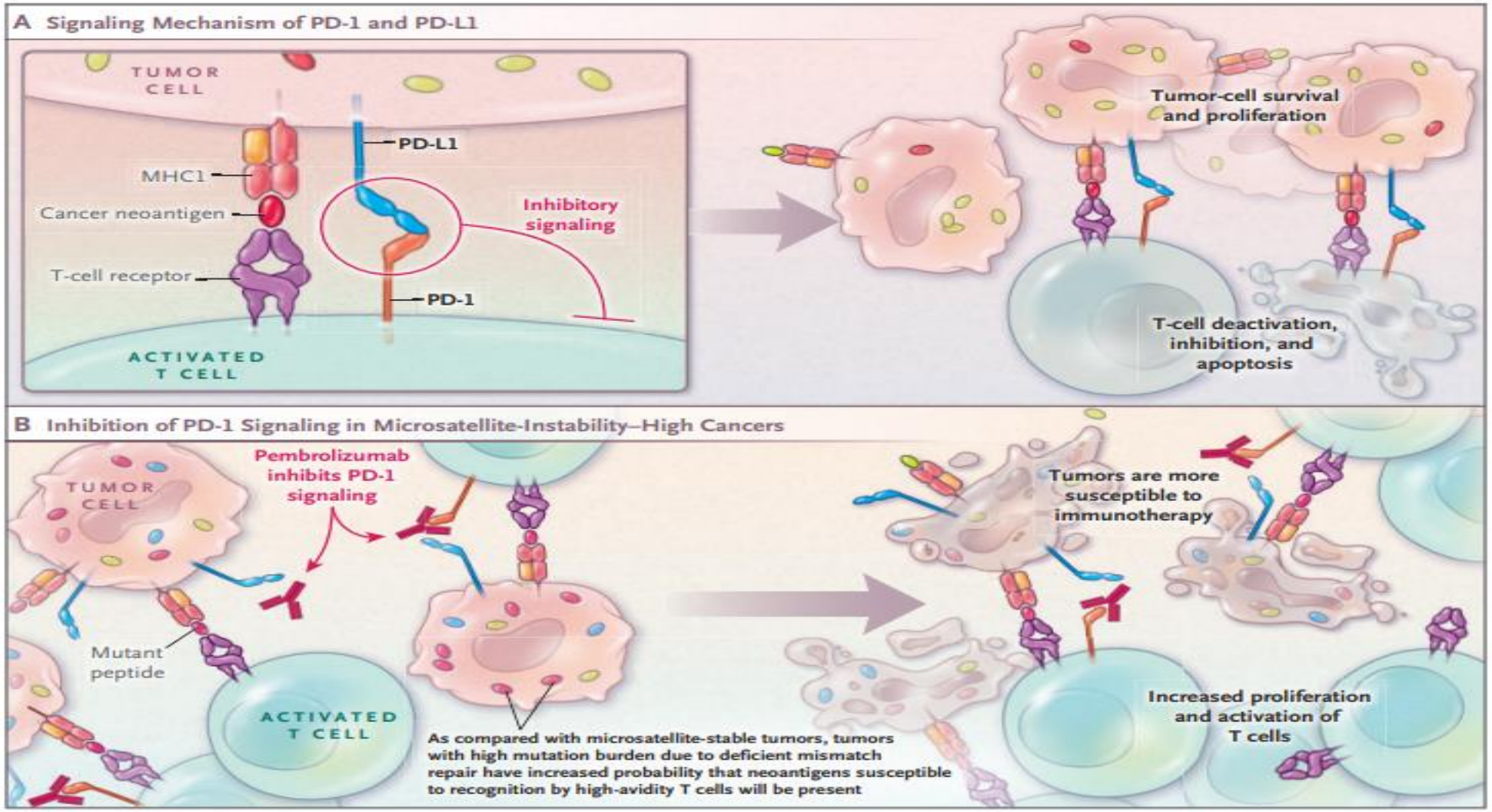
- BRCA mutasyonu olanlarda PSK 21 aya karşı 5.5 ay, mutasyonu olmayanlarda 9.3 aya karşı 3.9 ay olduğu bulunmuştur($p<.001$)

- Niraparib grubunda trombositopeni(%33.8), anemi(%25.3), nötropeni (%19.6) en sık görülen yan etki,

Mirza MR, et al.N Engl J Med. 2016;375(22):2154-64.

Over kanserinde immunoterapi

- Pembrolizumab,
- Nivolumab,



Signaling Mechanism of PD-1 and PD-L1 and Inhibition of PD-1 Signaling in Microsatellite-Instability–High Cancers.
MHC1 denotes major histocompatibility complex 1.

Lemery S,et al.First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication.N Engl J Med 2017; 377:1409-1412.

KEYNOTE-100 Çalışması

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1080–1087, 2019
doi:10.1093/annonc/mdz135
Published online 2 May 2019

ORIGINAL ARTICLE

Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study

U. A. Matulonis[1*], R. Shapira-Frommer[2], A. D. Santin[3], A. S. Lisyanskaya[4], S. Pignata[5], I. Vergote[6], F. Raspagliesi[7], G. S. Sonke[8], M. Birrer[9], D. M. Provencher[10], J. Sehouli[11], N. Colombo[12], A. González-Martín[13], A. Oaknin[14], P. B. Ottevanger[15], V. Rudaitis[16], K. Katchar[17], H. Wu[18], S. Keefe[19], J. Ruman[19] & J. A. Ledermann[20]

- Kohort A: Daha öcesinde 1-3 sıra tedavi almış, platinsiz süresi 3 veya 12 ay olan grup(285)
- Kohort B:Daha öncesinde 4-6 sıra tedavi alan platinsiz süre ≥3 ay (91)
- Pembrolizumab 200 mg/gün 3 haftada bir progresyona kabul edilemez toksisite ve 2 yıla kadar

- Primer sonlanım noktası genel cevap oranı,
- Sekonder sonlanım noktası;
- Cevap süresi,
- Hastalık kontol oranları,
- Progresyonsuz sağkalım oranları,
- Genel sağkalım oranları ve
- Güvenlik

- PDL 1 düzeyi kombine pozitif skor olarak ölçüldü.

E

Subgroup	N	ORR, % (95% CI)
Overall	376	8.0 (5.4 – 11.2)
Age		
<65	236	6.8 (3.9 – 10.8)
≥65	140	10.0 (5.6 – 16.2)
Prior Lines of Therapy		
1	85	10.6 (5.0 – 19.2)
2	121	7.4 (3.5 – 13.7)
3	79	3.8 (0.8 – 10.7)
4	42	4.8 (0.6 – 16.2)
5+	49	14.3 (5.9 – 27.2)
PFI/TFI		
<6 months	207	8.2 (4.9 – 12.8)
≥6 months	169	7.7 (4.2 – 12.8)
Platinum Sensitivity		
Platinum refractory	4	0.0 (0.0 – 60.2)
Platinum resistant-recurrent	141	7.8 (4.0 – 13.5)
Partial platinum-sensitive recurrent	128	7.8 (3.8 – 13.9)
Platinum sensitive recurrent	18	5.6 (0.1 – 27.3)
PD-L1 Status		
CPS ≥10	82	17.1 (9.7 – 27.0)
≥1 CPS <10	115	5.2 (1.9 – 11.0)
CPS <1	141	5.0 (2.0 – 10.0)
Unknown	38	7.9 (1.7 – 21.4)
Histology		
High-grade serous	283	8.5 (5.5 – 12.4)
Endometrioid carcinoma	28	0.0 (0.0 – 12.3)
Low-grade serous	21	0.0 (0.0 – 16.1)
Clear cell carcinoma	19	15.8 (3.4 – 39.6)
Other*	25	12.0 (2.5 – 31.2)

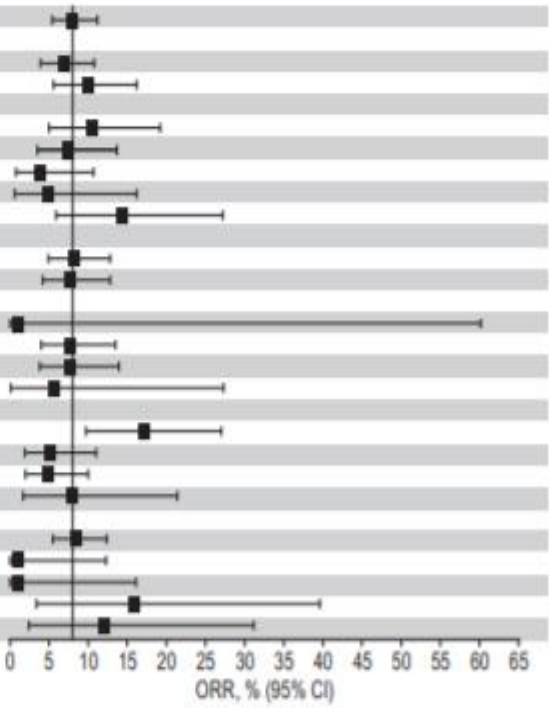
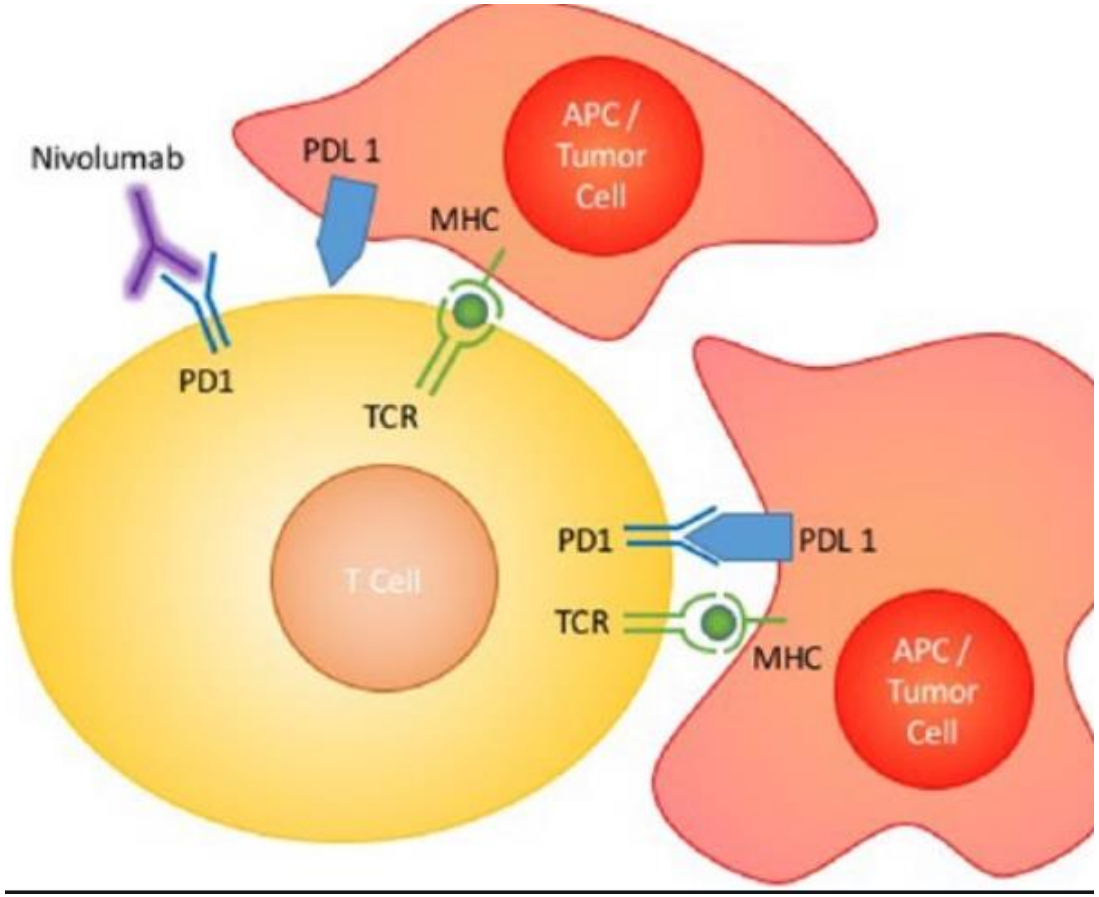


Figure 1. Antitumor activity of pembrolizumab in the total population. (A) Best change from baseline in target lesion size assessed by RECIST1.1 per independent central review in patients with ≥1 evaluable post-baseline imaging assessment ($N = 354$). (B) Time to response and response duration assessed by RECIST1.1 per independent central review. (C) Progression-free survival assessed by RECIST1.1 per independent central review in cohort A (blue) and cohort B (red). (D) Overall survival for cohort A (blue) and cohort B (red). (E) Objective response rate assessed by RECIST1.1 per independent central review in subgroups of the efficacy population ($N = 376$).

- Cevap oranı Kohort A %7.4,Kohort B %9.9.
- Median cevap süresi Kohort A da 8.2 ayken,Kohort B de ulaşılamadı.

- Sonuç olarak:
- Tek ajan pembrolizumab,PDL1 düzeyi ile korele olarak nüks over kanserli hastalarda etkili olduğu sonucuna ulaşılmıştır.

- **Nivolumab**;
- PD-1 bloke eden anti PD-1 antikoru,



VOLUME 33 · NUMBER 34 · DECEMBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Safety and Antitumor Activity of Anti–PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer

Junzo Hamanishi, Masaki Mandai, Takafumi Ikeda, Manabu Minami, Atsushi Kawaguchi, Toshinori Murayama, Masashi Kanai, Yukiko Mori, Shigemi Matsumoto, Shunsuke Chikuma, Noriomi Matsumura, Kaoru Abiko, Tsukasa Baba, Ken Yamaguchi, Akihiko Ueda, Yuko Hosoe, Satoshi Morita, Masayuki Yokode, Akira Shimizu, Tasuku Honjo, and Ikuo Konishi

- Faz II,
- 20 platin dirençli over kanserli hasta,
- 1 mg ve 3 mg/kg 15 günde bir

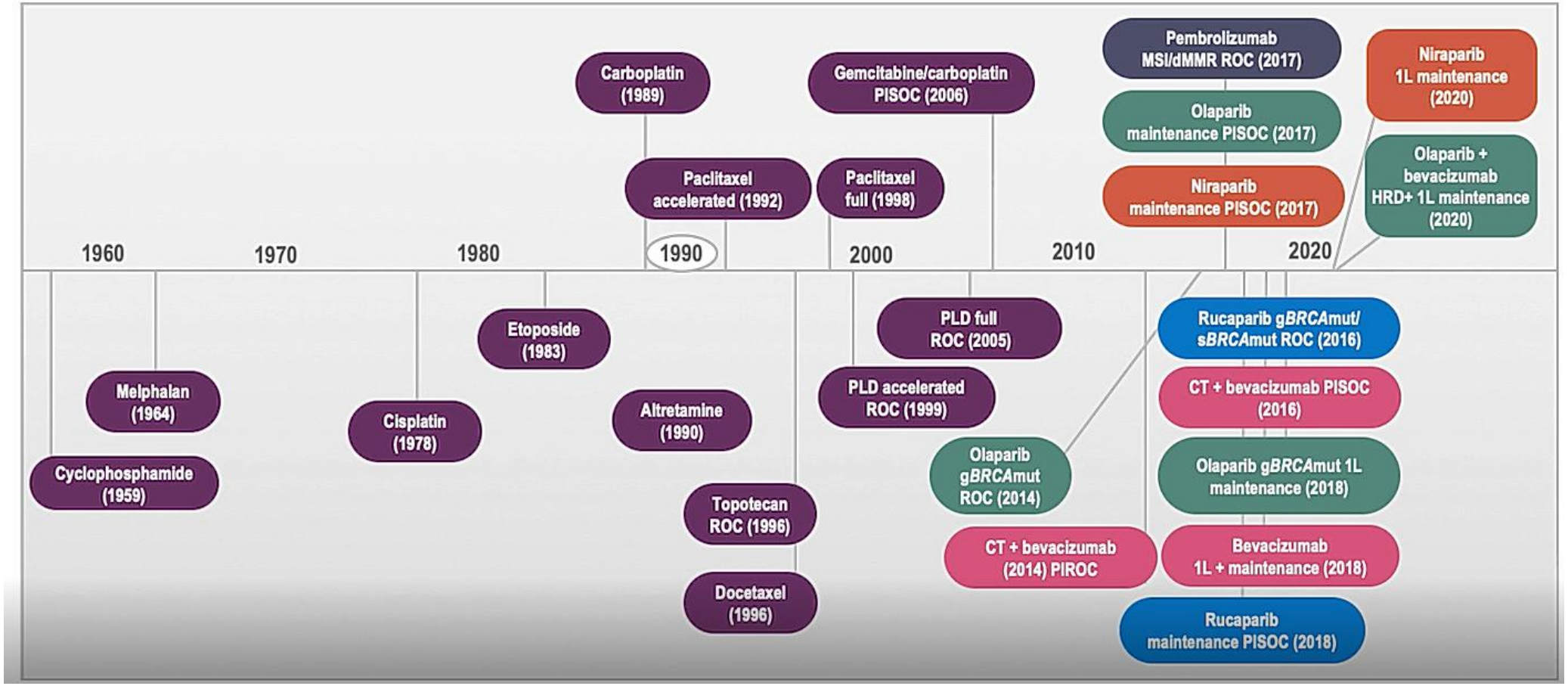
Table 3. Clinical Effect of Anti–PD-1 Antibody Treatment

Dose of Nivolumab	No. of Patients	Response					No. (%) of Patients [95% CI]*		Survival, Months (95% CI)	
		CR	PR	SD	PD	NE	RR	DCR	PFS	OS
1 mg/kg	10	0	1	4	4	1	1 (10) [0.3 to 44.5]	5 (50) [18.7 to 81.3]	3.5 (0.7 to 3.9)	16.1 (2.6 to NR)
3 mg/kg	10	2	0	2	6	0	2 (20) [2.5 to 55.6]	4 (40) [12.2 to 73.8]	3.0 (1.5 to 3.9)	NR (2.9 to NR)
Total	20	2	1	6	10	1	3/20 (15%) [3.2 to 37.9]	9/20 (45%) [23.1 to 68.5]	3.5 (1.7 to 3.9)	20.0 (7.0 to NR)

Abbreviations: CR, complete response; DCR, disease control rate (ie, CR, PR, and SD); NE, not evaluated; NR, not reached; OS, point estimate of overall survival; PD-1, programmed death-1; PFS, point estimation of progression-free survival; PR, partial response; RR, response rate (ie, CR and PR); SD, stable disease.
*No. of patients of the total listed in the same row.

Hastalık kontrol oranı %45,
PSK 3.5 ay(1.7-3.9ay),
GSK 20 ay (7-..ay)

Over Kanserinde Sistemik Tedavi



Sonuç olarak;

- Hastalık yok, hasta var..
- Her hasta bireysel olarak ele alınmalı,
- Multidisipliner bir yaklaşımla değerlendirilerek tedavi edilmelidir.

Teşekkür ederim….