2022/11/15
臨床研究セミナー基礎編

疾患と臨床試験シリーズ
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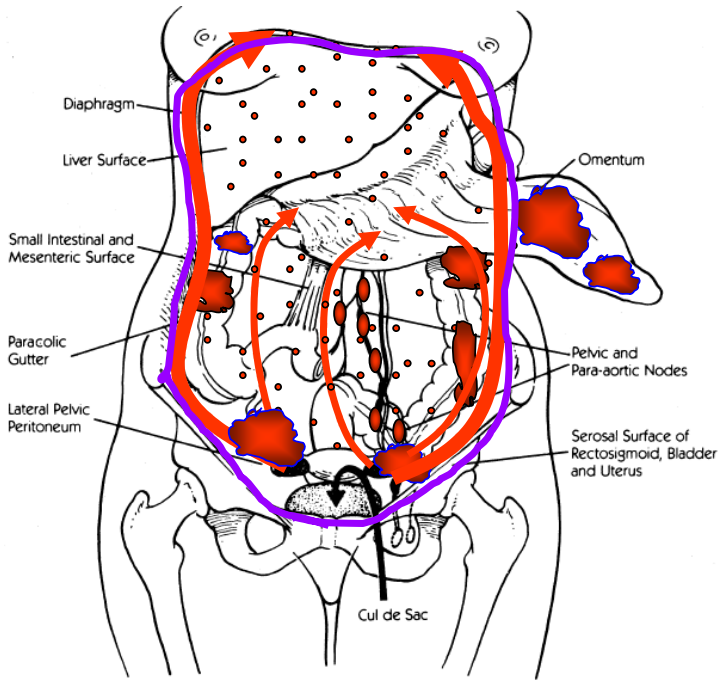
先端医療科・乳腺腫瘍内科

原野謙一

卵巣がんの診断と治療

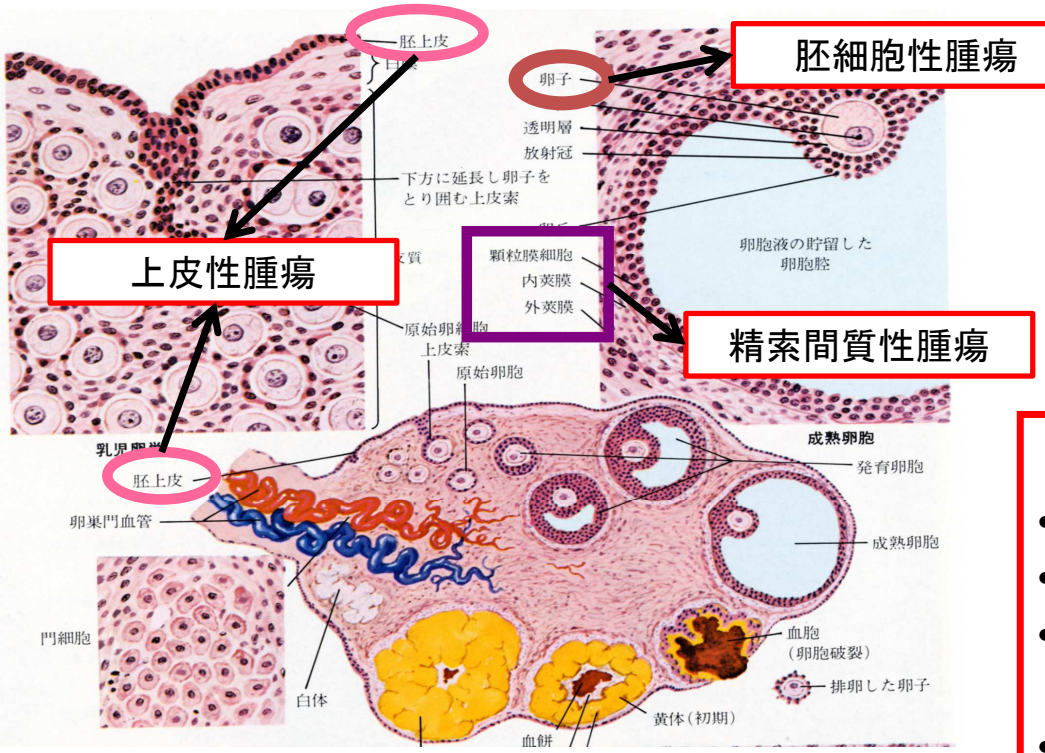
卵巣がんの疫学

- 罹患数 (2019)/死亡数 (2020)　13338人/4876人
- 卵巣がんの罹患は、40歳代から増加し、50歳代前半でピーク
- 1975年以降緩やかに増加傾向[1]
- リスクファクター：卵巣がんや乳がんの家族歴(HBOC)、不妊、初経年齢が低い、閉経年齢が高い、肥満、ホルモン補充療法、子宮内膜症
- 検診（経膣超音波＋CA-125）の有用性は示されていない[2]
- 60～70%がstage III以上の進行癌
  - 腹腔内容積が大きいため、腫瘍増大にもかかわらず無症状
  - 転移形式は腹膜播種、大網転移、骨盤・傍大動脈リンパ節転移の頻度が高い



1. 国立がん研究センターがん対策情報センター http://ganjoho.jp/reg_stat/statistics/stat/summary.html
2. JAMA 2011; 305: 2295

悪性卵巣腫瘍の組織分類



- 上皮性腺癌 (Epithelial adenocarcinoma) 90%以上
- 胚細胞性腫瘍 (Germ Cell Tumor) 5-6%
- 精索間質性腫瘍 (Sex Cord Tumor) 1%以下

上皮性腺癌

- 漿液性 serous(最も多い、35%)
- 類内膜 endometrioid(20%, 時に子宮体癌と合併)
- 明細胞 clear cell(25%、化学療法が効きにくい、日本に多い)
- 粘液性 mucinous(10%, 化学療法が効きにくい)

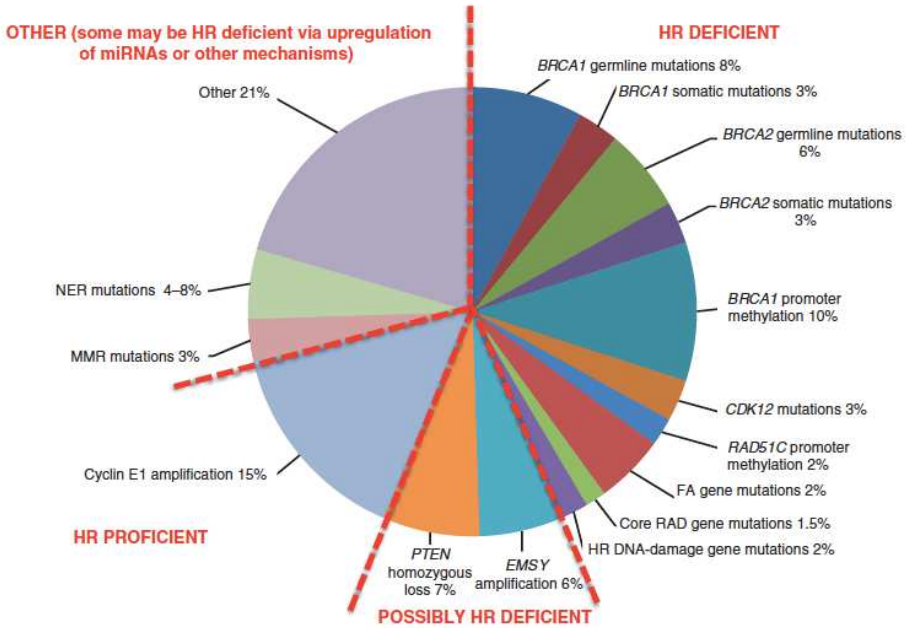
診断

- 症状：無症状が多い。他、腹部膨満、腹痛、食欲不振など
- 画像：経膣超音波（感度80～100%)、CT、MRI
- 腫瘍マーカー：CA125
  - 卵巣がん患者の80%以上で陽性。閉経後で骨盤内腫瘤を呈する患者を対象とし、65IU/dLをカットオフとすると、感度97%、特異度78%[1]。
  - CA125/CEA比が25倍以上だと卵巣がんの可能性が高い[2]。
  - 他のCA125が上昇する疾患（子宮内膜症、子宮筋腫、腹水貯留）との鑑別が必要。
  - 治療によるCA125の推移が治療効果と相関する、臨床試験の治療効果判定に用いられる[3]。

1.N Engl J Med 2004; 351(24): 2519-29
2.Tumour Biol 1992; 13(1-2): 18-26.
3.J Natl Cancer Inst 2004; 96(6): 487-8.

BRCA遺伝子異常

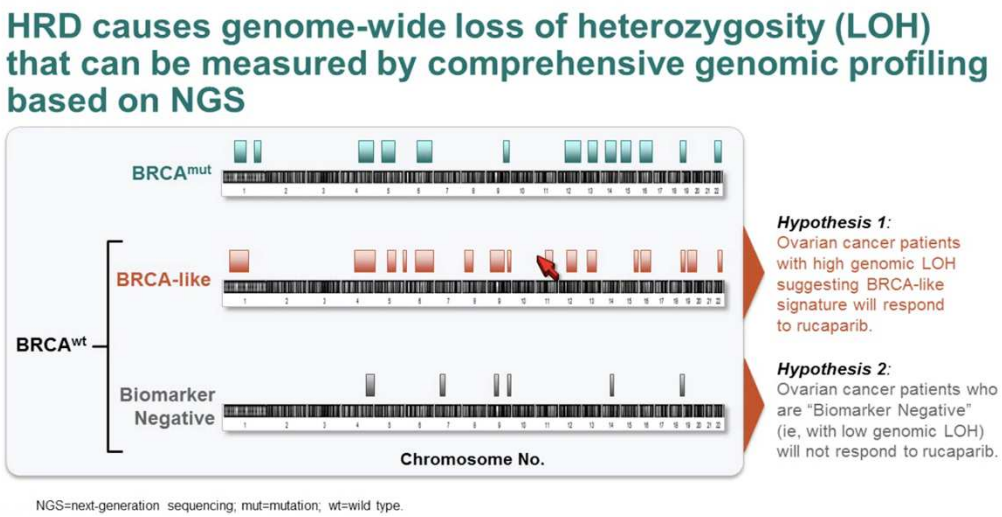
- BRCA1/2は、遺伝子修復機構の一つである、2本鎖DNA切断を修復する遺伝子相同組み換え（homologous recombination, HR) に関与する遺伝子である[1]。
- 上皮性卵巣がんの約10-15%において、germline BRCA1/2 gene mutation (gBRCAmt) を有する。
- 約50%の卵巣癌において“BRCA-ness”または”HRD-ness” を有する[2,3]。
  - BRCA1/2の体細胞性(somatic) 変異
  - BRCA1のDNAプロモーター領域のメチル化による機能喪失
  - HRに関与する他の遺伝子変異（RAD51C, PTEN, ATM, ATR, FANCD2)



1. Cancer Treat Rev 2018; 68: 62
2. Cancer Discov 2015; 5: 1137
3. Nat Rev Clin Oncol 2019; 16: 81

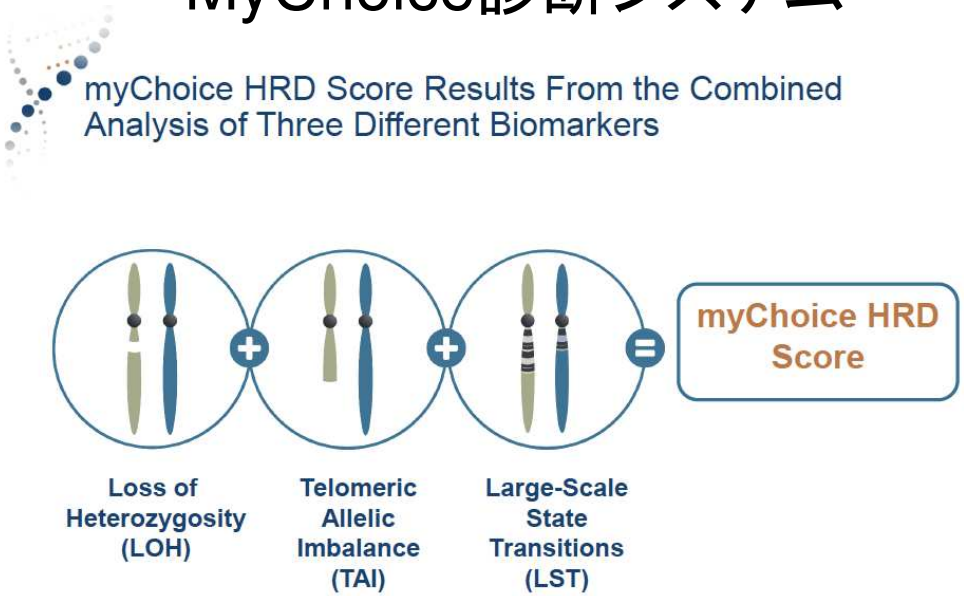
HRD testing

パネル検査



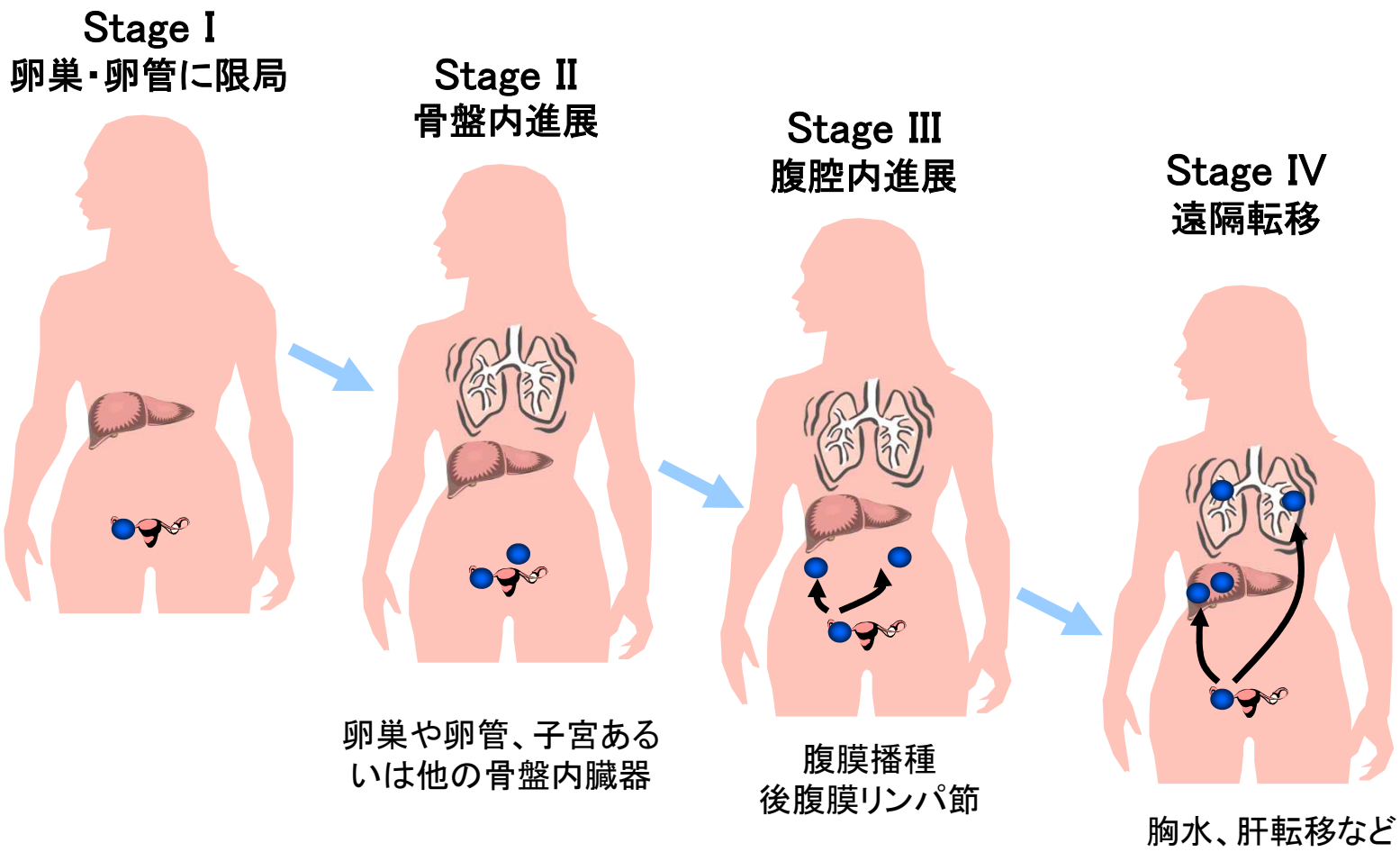
Foundation Medicine T5 next generation sequencing assay
LOH cut-off: 16%

MyChoice診断システム

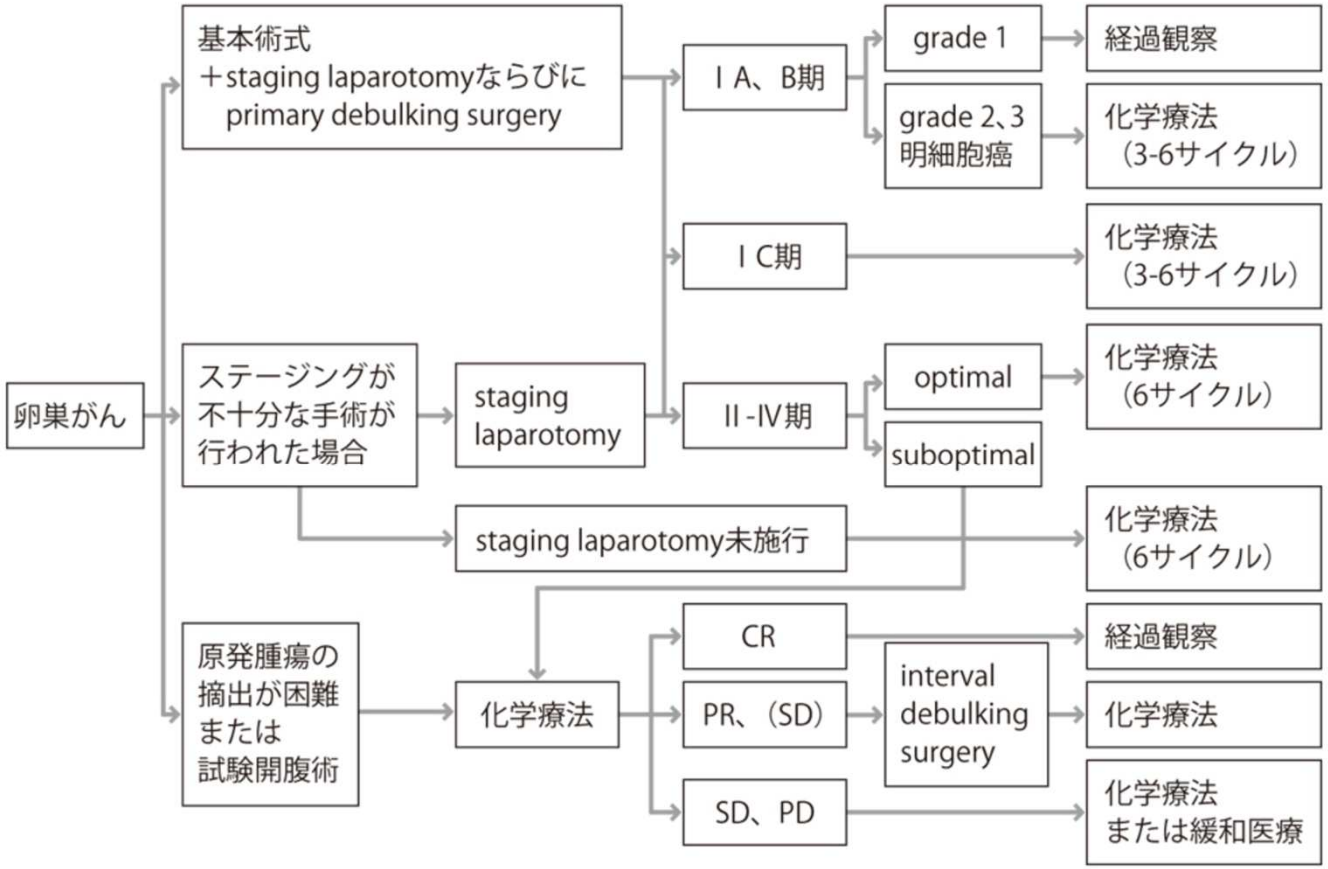


myChoice CDx
Cut-off ≧ 42

臨床進行期分類 (FIGO2014)



初回治療方針



CR：完全奏効　PR：部分奏効　SD：安定　PD：進行

卵巣がんガイドライン2015

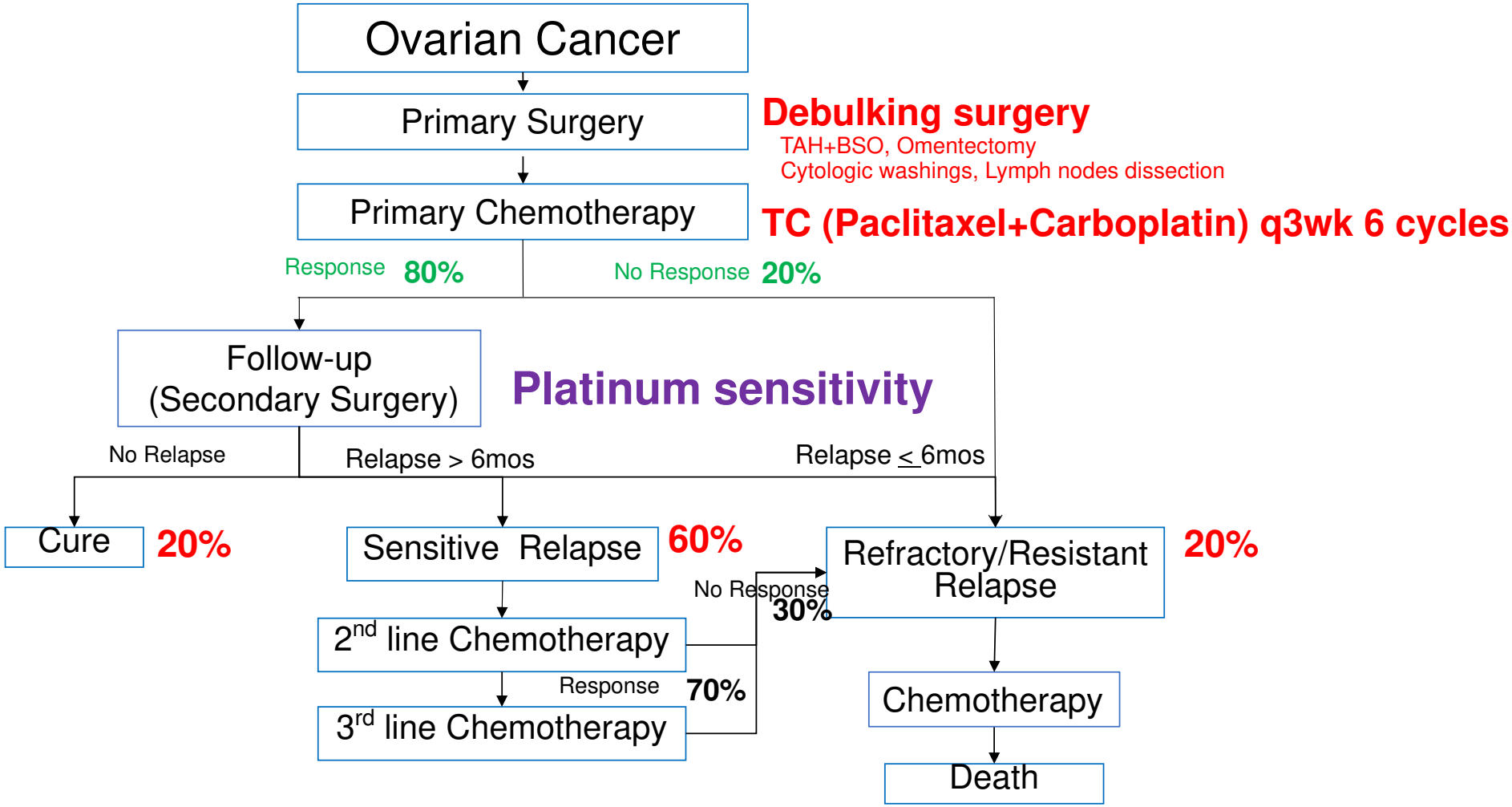
手術による肉眼的残存腫瘍の有無が予後に影響する

手術時に肉眼的残存腫瘍がない＝Complete resection
腫瘍径1cm以下＝Optimal surgery
腫瘍径1cmを超える＝Suboptimal surgery

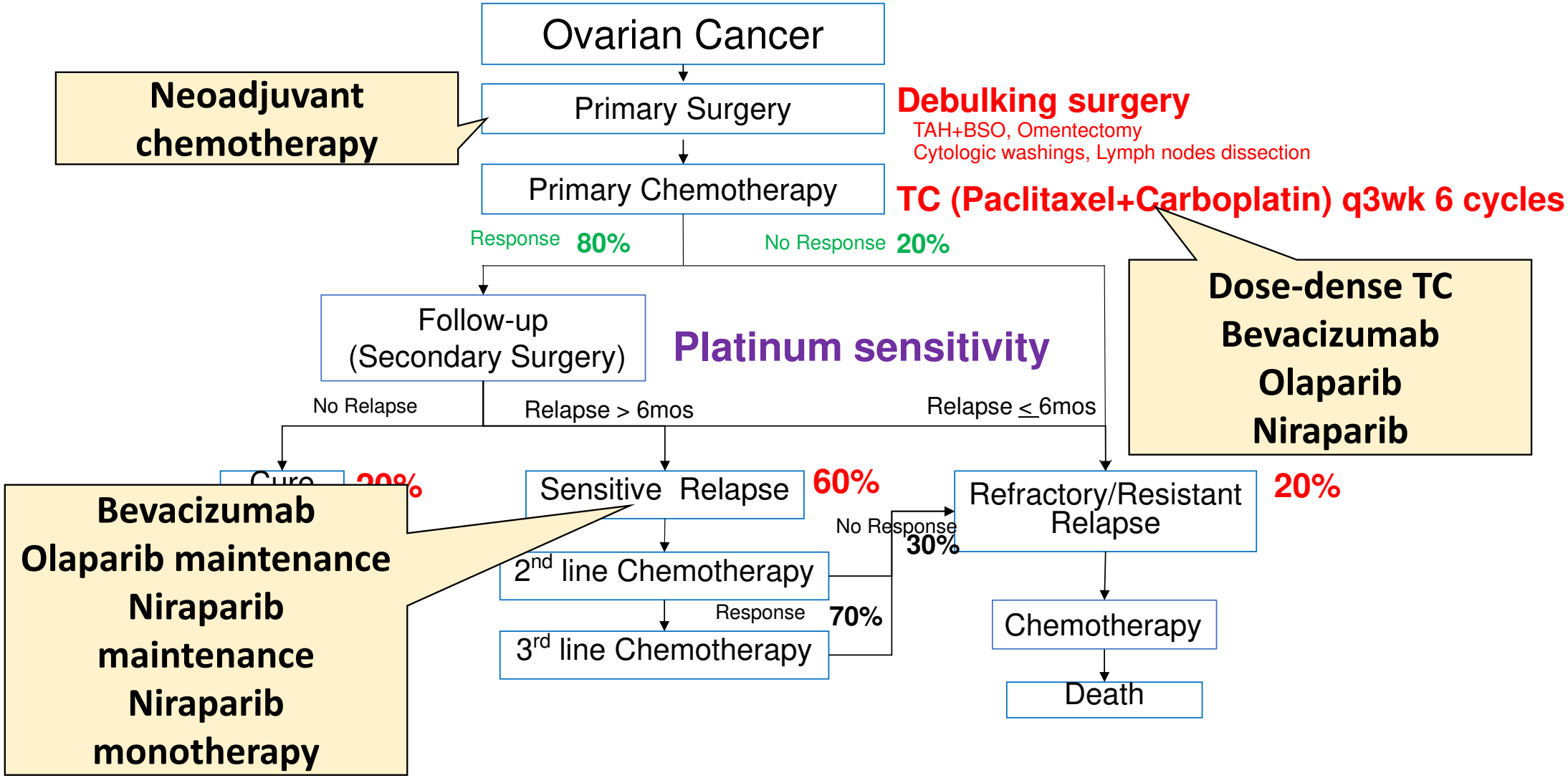
	Univariate Analysis			Multivariate Analysis		
Parameter	HR	95% CI	*P*	HR	95% CI	*P*
Overall Survival						
Age [10 y]	1.23	(1.17, 1.29)	<.0001	1.13	(1.08, 1.18)	<.0001
ECOG 2 vs 0-1	1.76	(1.54, 2.01)	<.0001	1.36	(1.18, 1.56)	<.0001
FIGO IIIC-IV vs IIB-IIIB	2.24	(1.99, 2.53)	<.0001	1.45	(1.28, 1.65)	<.0001
Grading G2/3 vs G1	2.50	(1.99, 3.13)	<.0001	1.74	(1.37, 2.21)	<.0001
Endometrioid vs serous histology	0.77	(0.64, 0.91)	.0029	0.94	(0.79, 1.13)	.5030
Mucinous vs serous histology	1.76	(1.43, 2.15)	<.0001	2.38	(1.94, 2.92)	<.0001
Tumor residuals 1-10 mm vs 0 mm	2.70	(2.37, 3.07)	<.0001	2.12	(1.85, 2.43)	<.0001
Tumor residuals > 10 mm vs 1-10 mm	1.34	(1.21; 1.49)	<.0001	1.20	(1.08, 1.33)	.0006
Ascites > 500 mL (intraop.) yes vs no	1.95	(1.76, 2.16)	<.0001	1.36	(1.22, 1.51)	<.0001
Progression-Free Survival						
Age [10 y]	1.17	(1.12, 1.22)	<.0001	1.07	(1.02, 1.11)	.0019
ECOG 2 vs 0-1	1.51	(1.33, 1.71)	<.0001	1.15	(1.02, 1.31)	.0280
FIGO IIIC-IV vs IIB-IIIB	2.18	(1.97, 2.42)	<.0001	1.46	(1.31, 1.63)	<.0001
Grading G2/3 vs G1	2.33	(1.93, 2.81)	<.0001	1.66	(1.36, 2.01)	<.0001
Endometrioid vs serous histology	0.76	(0.65, 0.89)	.0004	0.91	(0.78, 1.06)	.2165
Mucinous vs serous histology	1.53	(1.27, 1.84)	<.0001	2.02	(1.67, 2.44)	<.0001
Tumor residuals 1-10 mm vs 0 mm	2.52	(2.26, 2.81)	<.0001	2.03	(1.81, 2.27)	<.0001
Tumor residuals >10 mm vs 1-10 mm	1.36	(1.24, 1.50)	<.0001	1.25	(1.14, 1.37)	<.0001
Ascites > 500 mL (intraop.) yes vs no	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Cancer 2009; 115: 1234-44

Disease Status Model of Ovarian Cancer



Disease Status Model of Ovarian Cancer



卵巣癌治療

1. 初回治療
   - Dose-dense TC療法
   - Bevacizumab
   - PARP阻害薬
2. プラチナ感受性再発
3. プラチナ抵抗性再発

卵巣癌治療

1. 初回治療
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2. プラチナ感受性再発
3. プラチナ抵抗性再発

Dose-dense TC

JGOG3016

- Ovarian Epithelial, Primary Peritoneal, or Fallopian Tube cancer
- FIGO Stage **II-IV**
- Stratified: residual disease, stage, and histology

R

Conventional TC (c-TC)

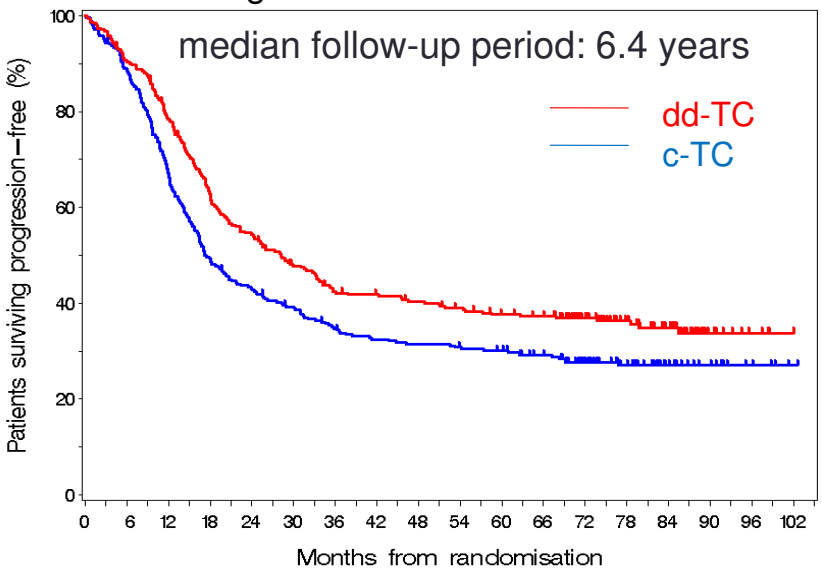
Paclitaxel 180mg/m^2, day 1
Carboplatin AUC 6.0, day 1
every 21 days for 6-9 cycles

Dose-dense TC (dd-TC)

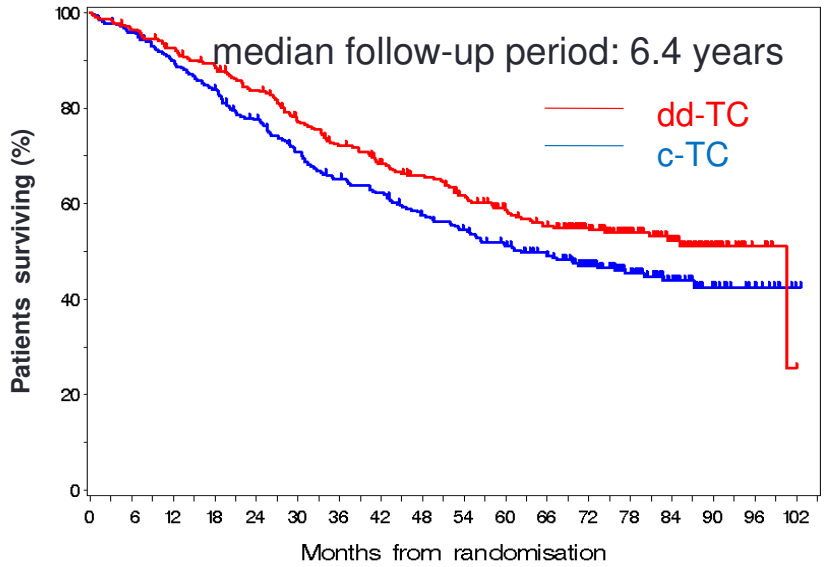
Paclitaxel 80mg/m^2, days 1,8,15
Carboplatin AUC 6.0, day 1
every 21 days for 6-9 cycles

- Primary endpoint: PFS
- Secondary endpoint: OS

Progression-free Survival



Overall Survival



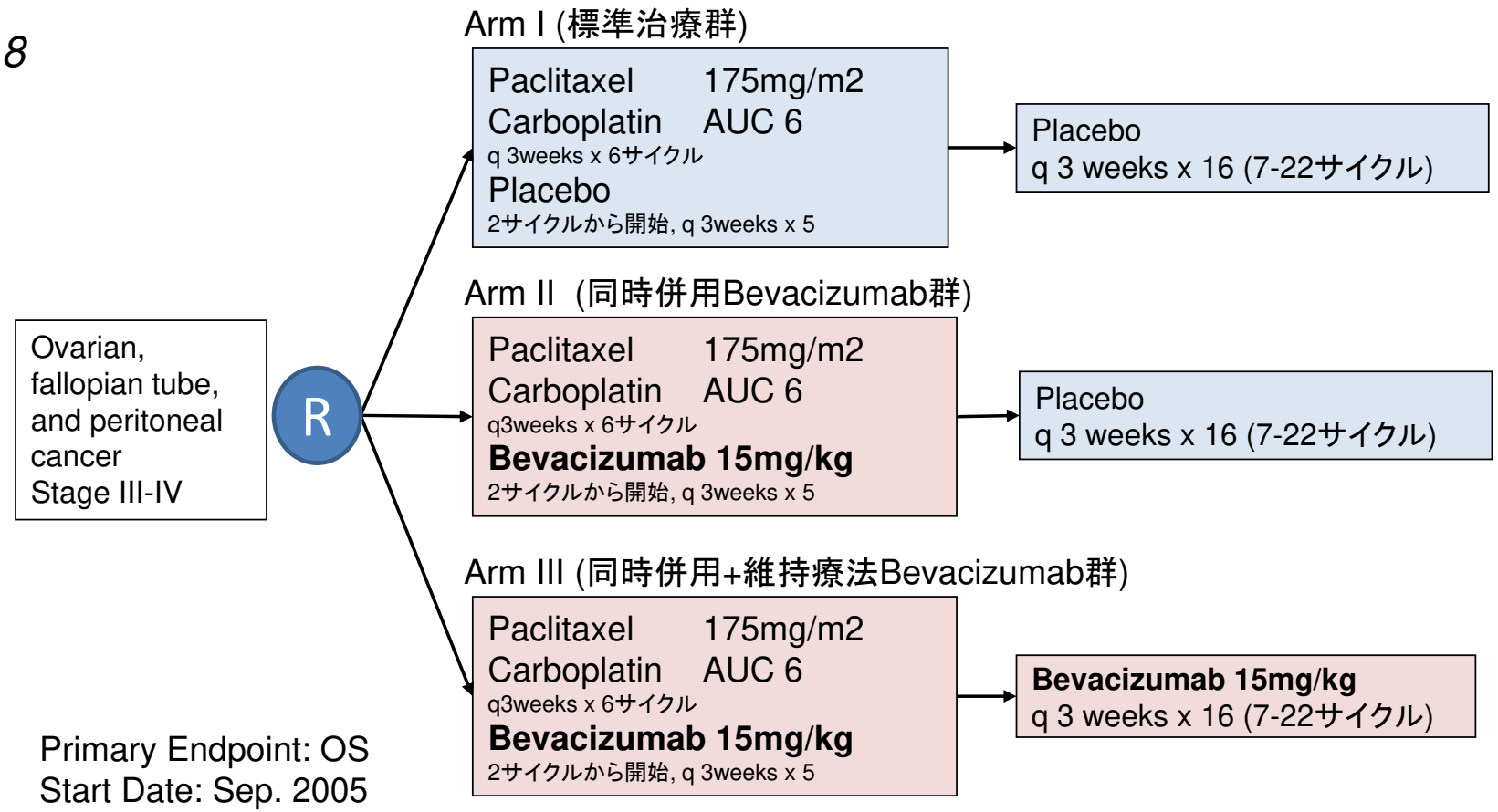
Treatment	n	Event, n (%)	Median PFS	*P* value	HR	95%CI
dd-TC	312	197 (63)	28.2 mos.	0.0037	0.76	0.62-0.91
c-TC	319	229 (72)	17.5 mos.			

Lancet Oncol 2013; 14: 1020-6

Treatment	n	Deaths, n (%)	Median OS	5-yr survival	*P* value	HR	95%CI
dd-TC	312	139 (45)	100.5 mos.	58.7%	0.039	0.79	0.63-0.99
c-TC	319	168 (53)	62.2 mos.	51.1%			

TC + Bevacizumab

GOG218



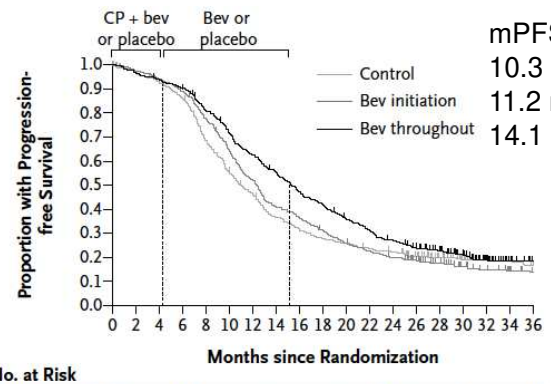
Primary Endpoint: OS
Start Date: Sep. 2005
Estimated Enrollment: 2000

N Engl J Med 2011; 365(26): 2473-83

GOG218

TC + Bevacizumab

Progression-free Survival[1]

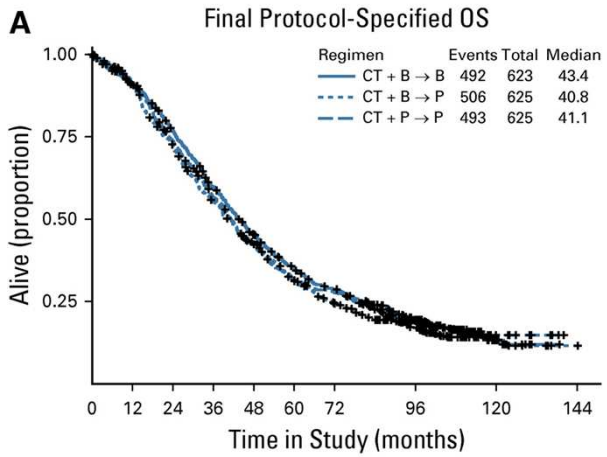


mPFS
10.3 months
11.2 months
14.1 monhts

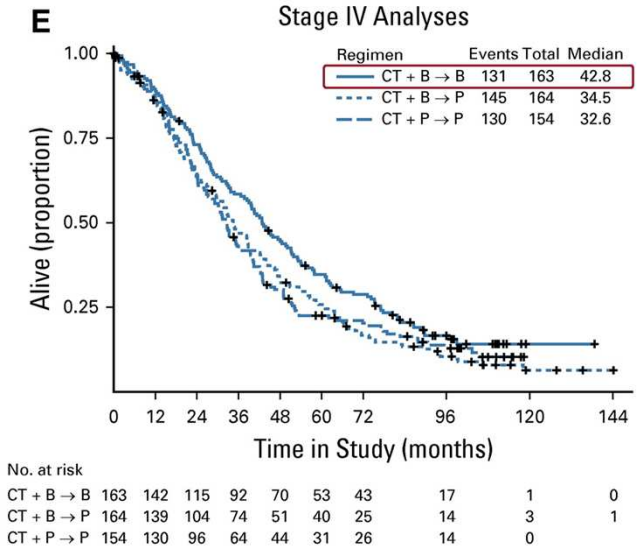
No. at Risk							
Control	625	535	283	169	133	78	49
Bev initiation	625	552	319	190	121	67	40
Bev through-out	623	559	386	256	162	97	56

CT+Bev→Bev vs. CT
PFS 14.1 months vs. 10.3 months
(HR 0.717; 95% CI, 0.625-0.824, P<0.001)

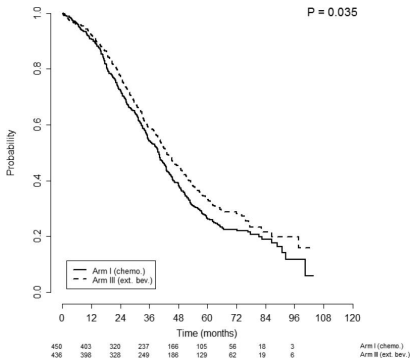
Overall Survival[2]



Stage IV[2]



CT+Bev→Bev vs. CT
OS 42.8 months vs. 32.6 months
(HR 0.75; 95% CI, 0.59-0.95)



Patients with Ascites[3]

CT+Bev→Bev vs. CT
OS 42.8 months vs. 32.6 months
(AHR 0.82; 95% CI, 0.70-0.94, P=0.014)

1. N Engl J Med 2011; 365(26): 2473-83
2. J Clin Oncol 2019; 37: 2317-28
3. Gynecol Oncol 2015; 139: 17-22

TC vs. dose-dense TC

GOG262

- Stage II-IV Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer (n=692)

R

Carboplatin AUC=6 d1
Paclitaxel 80mg/m2 d1, 8, 15
+/- Bevacizumab (C2-6)
Q3wk 6 cycles

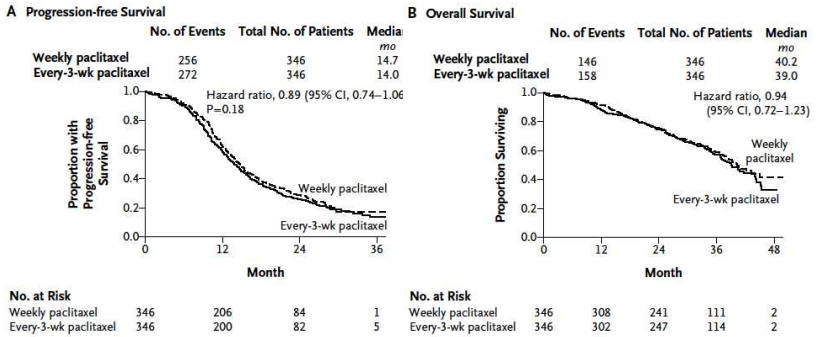
→ +/- Bevacizumab (C7-22) Q3wk

Carboplatin AUC=6 d1
Paclitaxel 175mg/m2 d1
+/- Bevacizumab (C2-6)
Q3wk 6 cycles

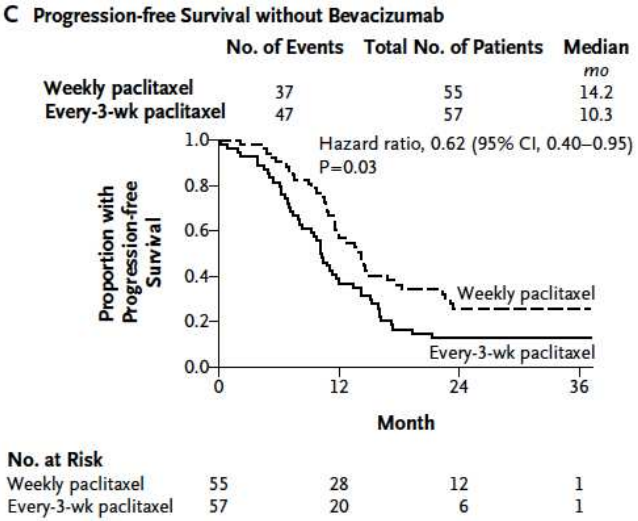
→ +/- Bevacizumab (C7-22)Q3wk

- Primary endpoint: PFS
- Bevacizumab use was permitted and was included as a stratification factor.
- Number of pts who received bevacizumab.
  weekly paclitaxel, n=291 (84%)
  every 3-wk paclitaxel, n=289 (84%)

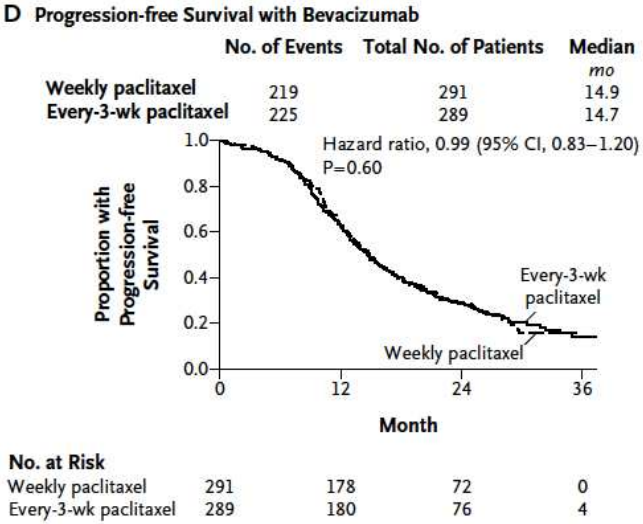
全体集団



Bevなし



Bevあり



N Engl J Med 2016; 374: 738-48

TC vs. dose-dense TC

ICON8

- Stage IC-IV Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer (n=1566)

R

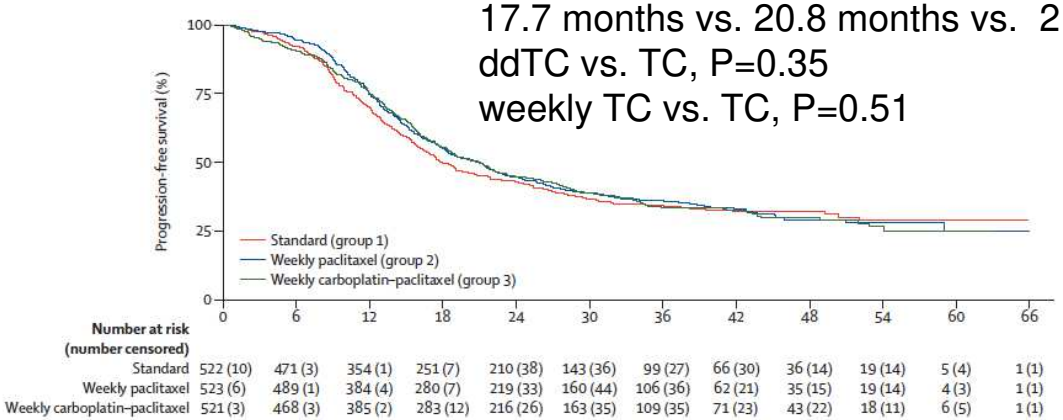
Group 1: TC
Carboplatin AUC=5 or 6 d1
Paclitaxel 175mg/m2 d1 Q3wk 6 cycles

Group 2: dose-dense TC
Carboplatin AUC=5 or 6 d1
Paclitaxel 80mg/m2 d1,8,15 Q3wk 6 cycles

Group 3: weekly TC
Carboplatin AUC=2 d1,8,15
Paclitaxel 80mg/m2 d1,8,15 Q3wk 6 cycles

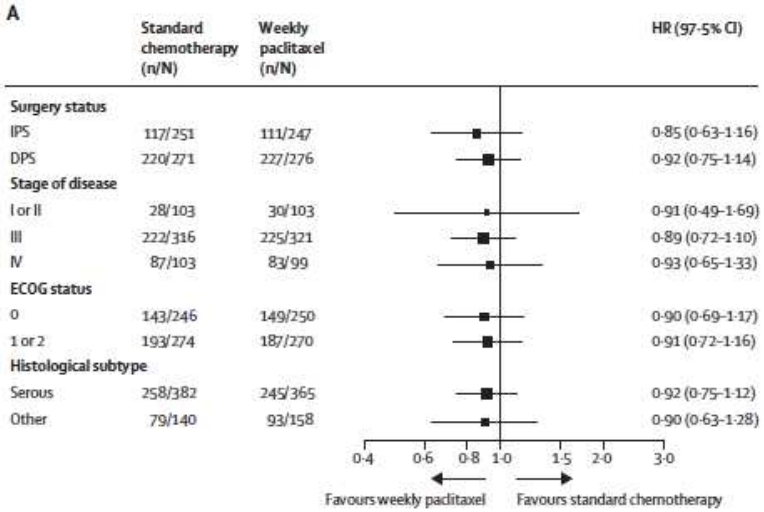
Progression-free Survival

17.7 months vs. 20.8 months vs. 21.0months
ddTC vs. TC, P=0.35
weekly TC vs. TC, P=0.51

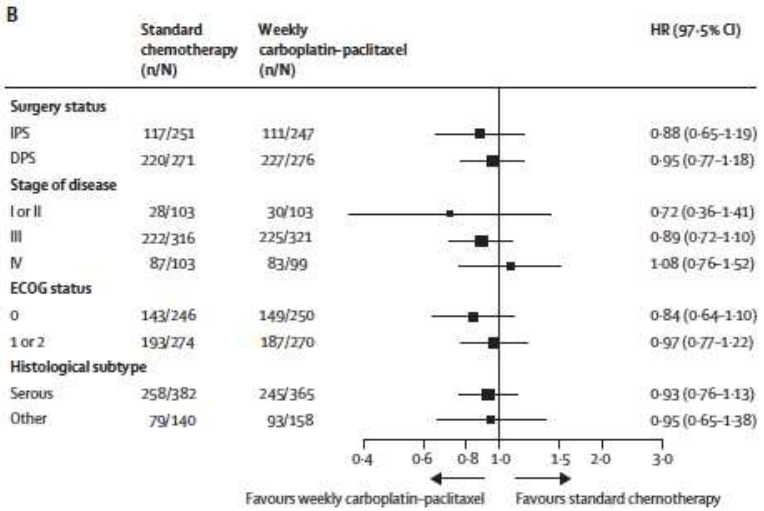


Lancet 2019; 394: 2084-95

ddTC vs. TC



Weekly TC vs. TC

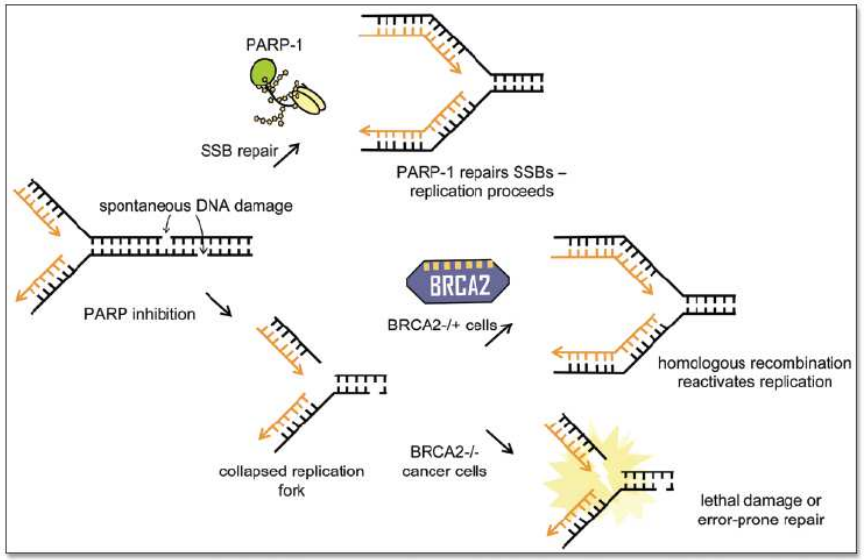


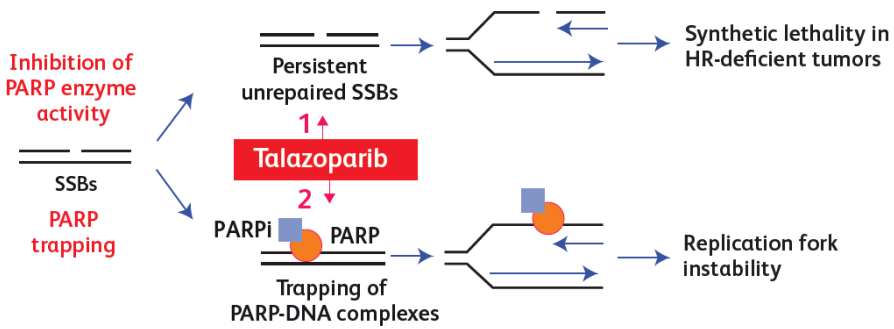
Dose-dense TCか？TC + Bevacizumabか？

- Dose-dense TCは、stage II-IVを対象としたJGOG3016試験において、TCに比較してPFS (HR 0.76), OS (HR 0.79)を改善する結果を示したが、GOG262試験、ICON8試験での追試ではnegativeだった。
- Bevacizumab療法の上乗せは、特にstage IV (GOG218, HR 0.75)や腹水貯留例(GOG218, HR 0.82)、残存腫瘍例(ICON7, HR 0.78)においてOS改善効果が示されている。
- 進行癌において、dose-dense TC療法、TC+Bevacizumab療法いずれもが標準治療であるが、残存腫瘍例やstage IVにおいてはTC+Bevacizumab療法がpreferred regimenか。

Poly(ADP-Ribose) Polymerase-1 (PARP-1)　阻害剤

- PARPは、DNA修復機構の一つである塩基除去修復(Base excision repair, BER)を通じてDNA1本鎖損傷(Single strand break, SSB)の修復に作用する。
- “合成致死”:HR異常を有するがん細胞に対し、PARP阻害剤を投与すると、遺伝子修復機構が働かず、がん細胞が細胞死に至る。
- “PARP trap”: PARP阻害剤によりPARP-DNA複合体をトラップし、複製フォークの失速、不安定化をきたし細胞死に至る。





Nat Biotech 2011; 29: 373

BRCA1/2遺伝子変異陽性の進行卵巣がん
初回治療におけるOlaparib維持療法

SOLO1

- Newly diagnosed Stage III-IV high grade serous or endometrioid ovarian, FT, and primary peritoneal cancer
- **BRCA mutation positive (blood or tumor)**

N=295

→

- Surgery
- Platinum-based chemotherapy

→ R

CR or PR

Maintenance treatment

Olaparib 300mg bid

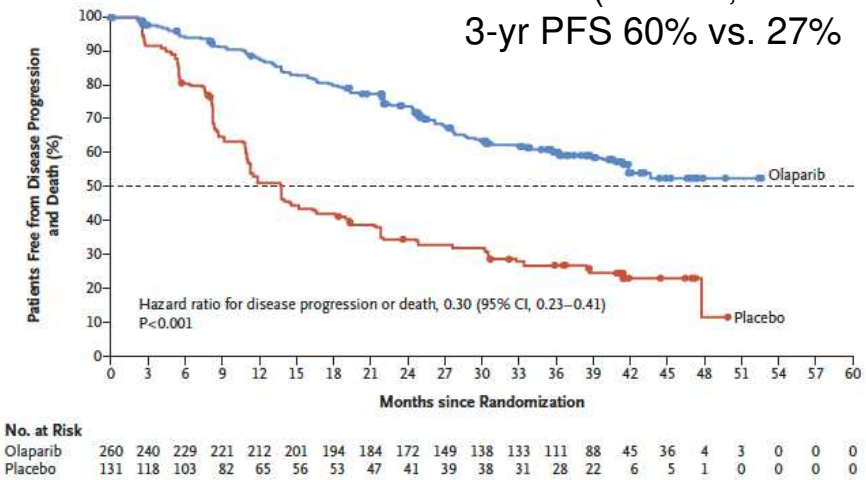
2:1

Placebo bid

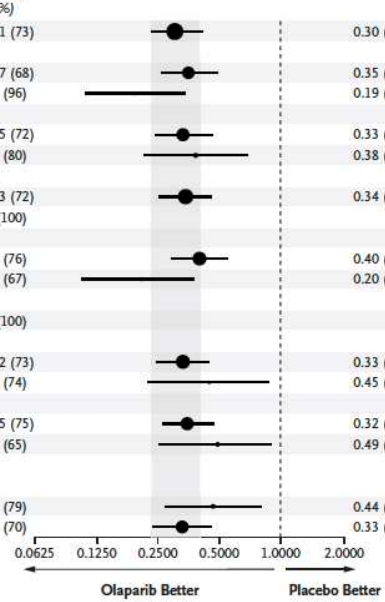
2 years

Primary endpoint: PFS

HR 0.3 (95% CI, 0.23-41)
3-yr PFS 60% vs. 27%



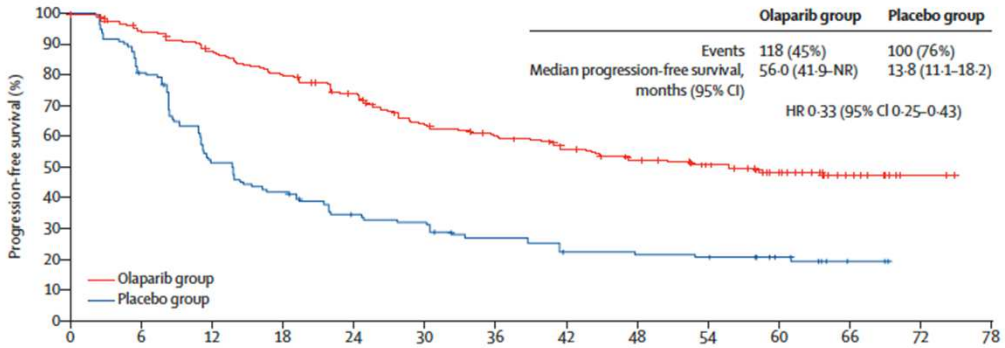
Subgroup	Olaparib	Placebo	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients with disease progression or death/total no. (%)		
All patients	102/260 (39)	96/131 (73)	0.30 (0.23–0.41)
Clinical response after chemotherapy			
Complete response	73/213 (34)	73/107 (68)	0.35 (0.26–0.49)
Partial response	29/47 (62)	23/24 (96)	0.19 (0.11–0.34)
ECOG performance status at baseline			
Normal activity	75/200 (38)	76/105 (72)	0.33 (0.24–0.46)
Restricted activity	27/60 (45)	20/25 (80)	0.38 (0.21–0.68)
CA-125 level at baseline			
≤ULN	92/247 (37)	89/123 (72)	0.34 (0.25–0.46)
>ULN	10/13 (77)	7/7 (100)	NC
Germline *BRCA* mutation according to testing at Myriad			
BRCA1	84/188 (45)	69/91 (76)	0.40 (0.29–0.56)
BRCA2	15/62 (24)	26/39 (67)	0.20 (0.10–0.38)
BRCA1 and *BRCA2*	0/3	0/0	NC
None	3/7 (43)	1/1 (100)	NC
Age at baseline			
<65 yr	85/225 (38)	82/112 (73)	0.33 (0.24–0.45)
≥65 yr	17/35 (49)	14/19 (74)	0.45 (0.22–0.92)
International FIGO stage at initial diagnosis			
Stage III	83/220 (38)	79/105 (75)	0.32 (0.24–0.44)
Stage IV	19/40 (48)	17/26 (65)	0.49 (0.25–0.94)
Presence of residual macroscopic disease after debulking surgery performed before trial entry			
Yes	29/55 (53)	23/29 (79)	0.44 (0.25–0.77)
No	70/200 (35)	69/98 (70)	0.33 (0.23–0.46)



N Engl J Med 2018; 379: 2495-2505

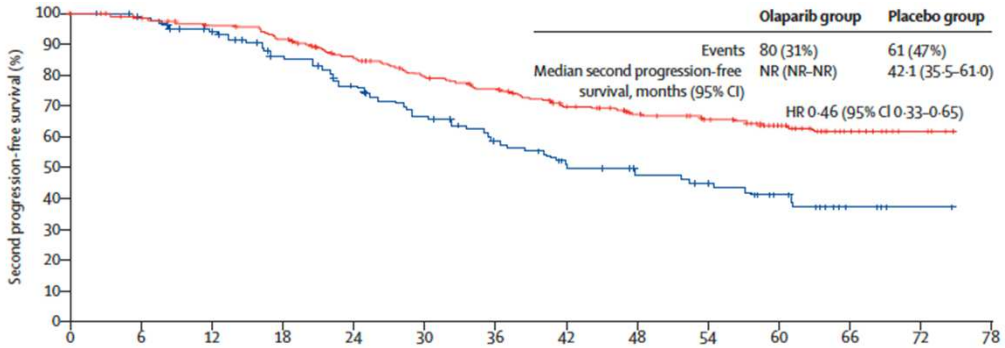
５年フォローアップ結果でもOlaparib維持療法により良好なProgression-free survivalが得られた

Progression-free survival



Number at risk (number censored)	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Olaparib group	260 (0)	229 (16)	212 (18)	194 (18)	173 (23)	140 (34)	129 (37)	115 (42)	101 (49)	91 (56)	58 (85)	30 (112)	2 (140)	0 (142)
Placebo group	131 (0)	103 (3)	65 (4)	53 (4)	41 (7)	38 (7)	30 (9)	24 (10)	23 (10)	22 (10)	16 (16)	3 (28)	0 (31)	..

Time to secondary progression or death

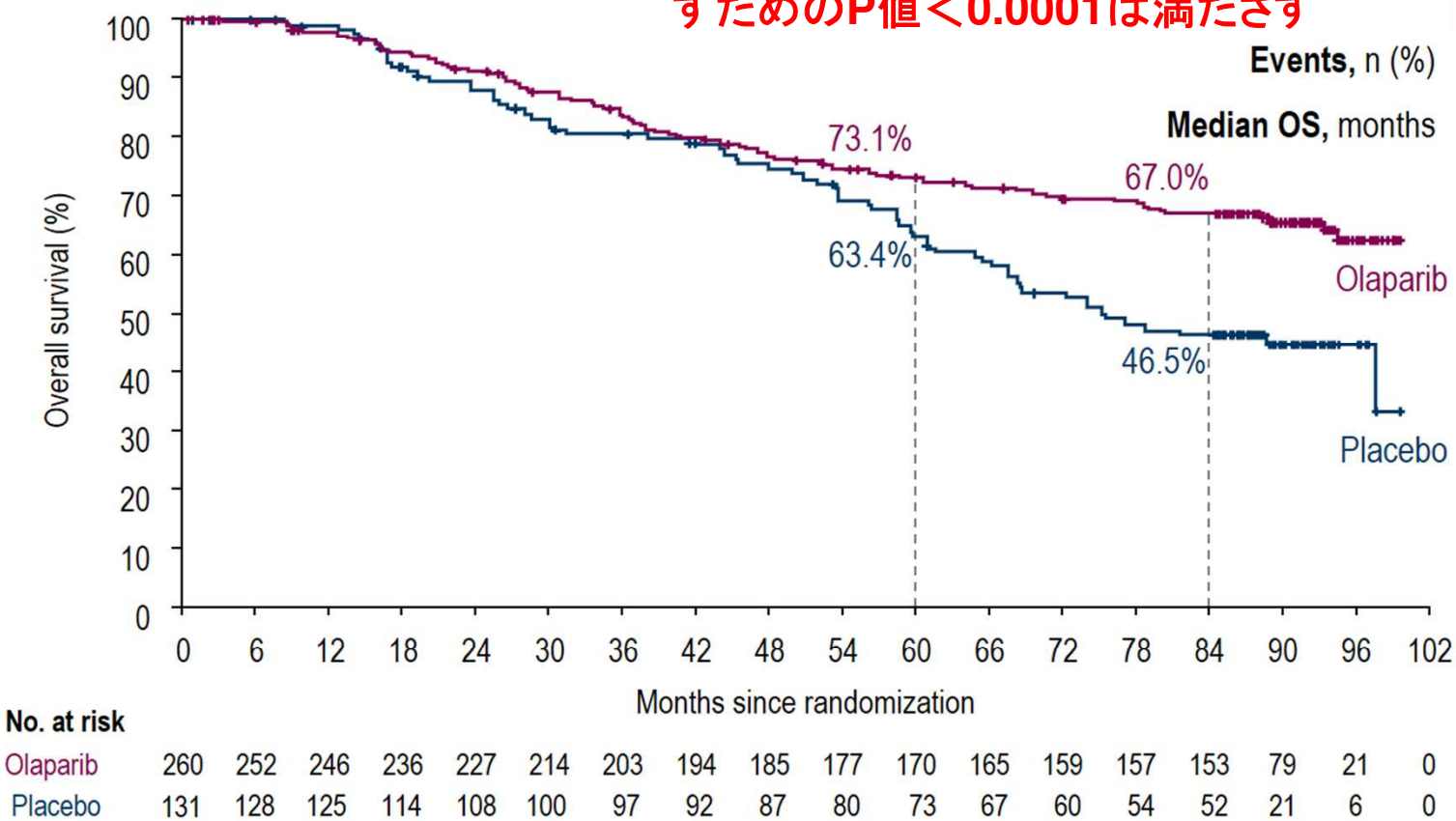


Number at risk (number censored)	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Olaparib group	260 (0)	239 (18)	229 (22)	216 (24)	195 (32)	170 (43)	159 (45)	141 (52)	125 (63)	115 (70)	78 (104)	37 (143)	4 (176)	0 (180)
Placebo group	131 (0)	122 (7)	107 (17)	92 (23)	79 (26)	68 (27)	56 (31)	44 (36)	38 (39)	35 (40)	23 (49)	6 (64)	1 (69)	0 (70)

Lancet Oncol 2021: 22:1721-31

Maintenance olaparib provided a clinically meaningful OS benefit

OSにおける統計学的な有意差を示すためのP値＜0.0001は満たさず



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**
HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*		

44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

*$P<0.0001$ required to declare statistical significance

PARIS 2022 ESMO congress

No new safety signals observed after 7 years of follow-up

	Primary PFS analysis (DCO 17 May 2018)		7-year descriptive OS analysis (DCO 7 March 2022)	
	Olaparib (N=260)	Placebo (N=130)	Olaparib (N=260)	Placebo (N=130)
Median (range) duration of treatment, months	24.6 (0.0–52.0)	13.9 (0.2–45.5)	24.6 (0.0–97.5)	13.9 (0.2–60.9)
Any TEAE, n (%)	256 (98.5)	120 (92.3)	256 (98.5)	120 (92.3)
Grade ≥3 TEAEs, n (%)	102 (39.2)	24 (18.5)	103 (39.6)	26 (20.0)
Serious TEAEs, n (%)	54 (20.8)	16 (12.3)	55 (21.2)	18 (13.8)
TEAE leading to dose interruption, n (%)	135 (51.9)	22 (16.9)	137 (52.7)	22 (16.9)
TEAE leading to dose reduction, n (%)	74 (28.5)	4 (3.1)	75 (28.8)	4 (3.1)
TEAE leading to treatment discontinuation, n (%)	30 (11.5)	3 (2.3)	31 (11.9)	4 (3.1)
AEs of special interest, n (%)				
MDS/AML*	3 (1.2)	0	4 (1.5)	1 (0.8)
New primary malignancies*	5 (1.9)	3 (2.3)	14 (5.4)†	8 (6.2)‡
Pneumonitis/ILD	5 (1.9)	0	5 (1.9)	0

*Proactively followed up until death due to any cause; †Breast cancer (n=10), lip and/or oral cavity cancer (n=1), thyroid cancer (n=1), pancreatic adenocarcinoma (n=1) and gall bladder adenocarcinoma (n=1); ‡Breast cancer (n=5), lung adenocarcinoma (n=1), squamous cell carcinoma of the tongue (n=1) and chronic myeloid leukaemia (n=1)

AE, adverse event; AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event

進行卵巣がん初回治療におけるOlaparib+Bevacizumab維持療法

PAOLA-1

- Newly diagnosed Stage III-IV high grade serous or endometrioid ovarian cancer
- **Surgery (upfront or interval)**
- **>/=3 cycles of bevacizumab**

NED, CR or PR

R

2:1

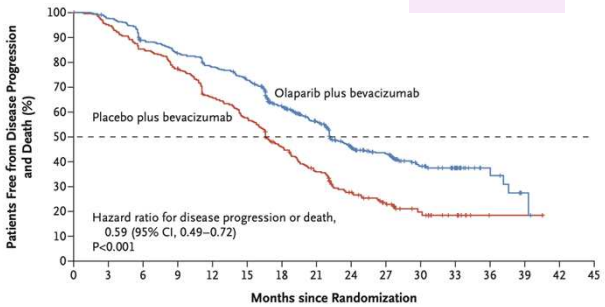
Maintenance treatment

Olaparib 300mg bid x 2 years
Bevacizumab 15 mg/kg Q3w for 15 months

Placebo x 2 years
Bevacizumab 15 mg/kg Q3w for 15 months

ITT population

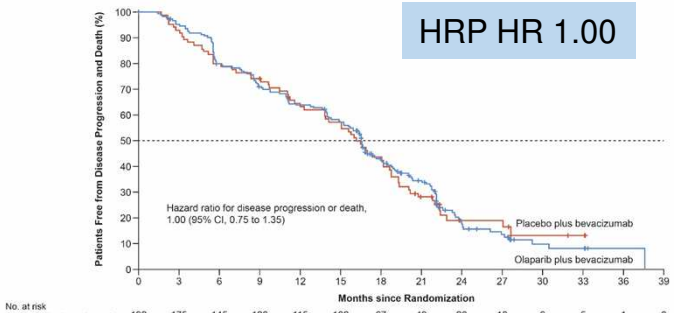
HR 0.59



No. at Risk

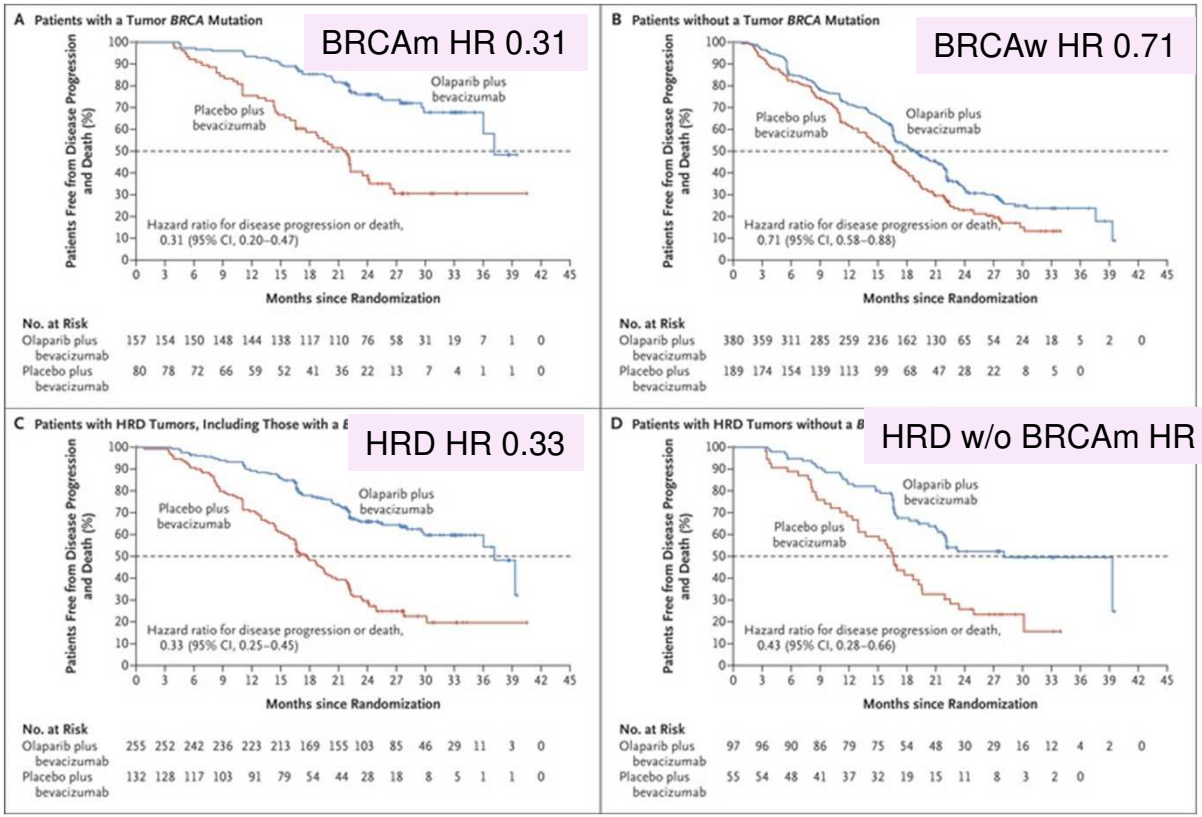
Olaparib plus bevacizumab	537	513	461	433	403	374	279	240	141	112	55	37	12	3	0
Placebo plus bevacizumab	269	252	226	205	172	151	109	83	50	35	15	9	1	1	0

HRP HR 1.00



No. at risk

Olaparib plus bevacizumab	192	175	145	128	115	102	67	49	20	13	6	5	1	0	
Placebo plus bevacizumab	85	79	68	63	52	47	34	20	8	8	3	2	0		



No. at Risk

Olaparib plus bevacizumab	157	154	150	148	144	138	117	110	76	58	31	19	7	1	0
Placebo plus bevacizumab	80	78	72	66	59	52	41	36	22	13	7	4	1	1	0

No. at Risk

Olaparib plus bevacizumab	380	359	311	285	259	236	162	130	65	54	24	18	5	2	0
Placebo plus bevacizumab	189	174	154	139	113	99	68	47	28	22	8	5	0		

No. at Risk

Olaparib plus bevacizumab	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo plus bevacizumab	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

No. at Risk

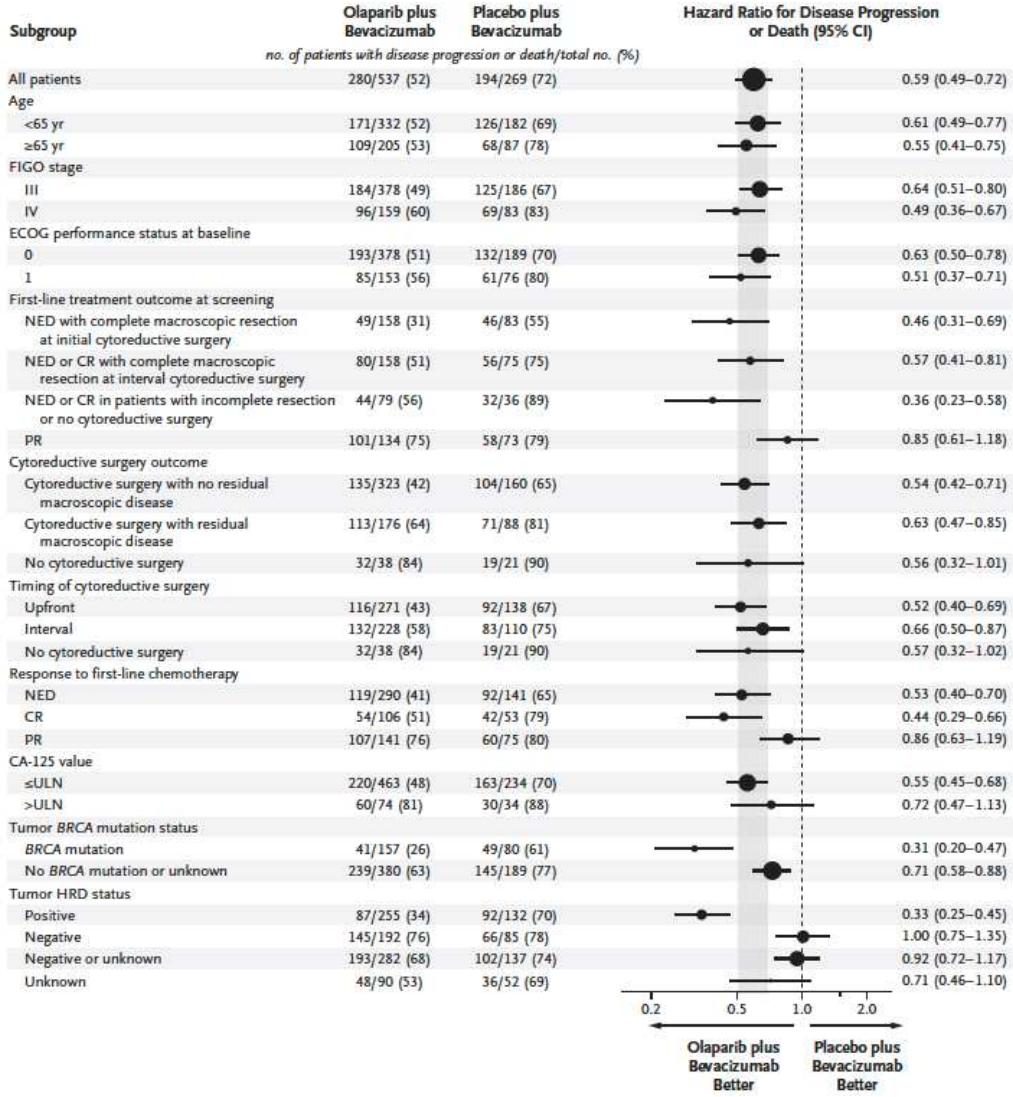
Olaparib plus bevacizumab	97	96	90	86	79	75	54	48	30	29	16	12	4	2	0
Placebo plus bevacizumab	55	54	48	41	37	32	19	15	11	8	3	2	0		

N Engl J Med 2019; 381: 2416-28

※本邦未承認情報を含む

進行卵巣がん初回治療におけるOlaparib+Bevacizumab維持療法

・Stage III vs IV
・術後残存腫瘍の有無
・PDS vs. IDS　　に関わらず、Olaparib+Bevacizumab維持療法はBevacizumab単剤維持療法に比較してPFSを改善する



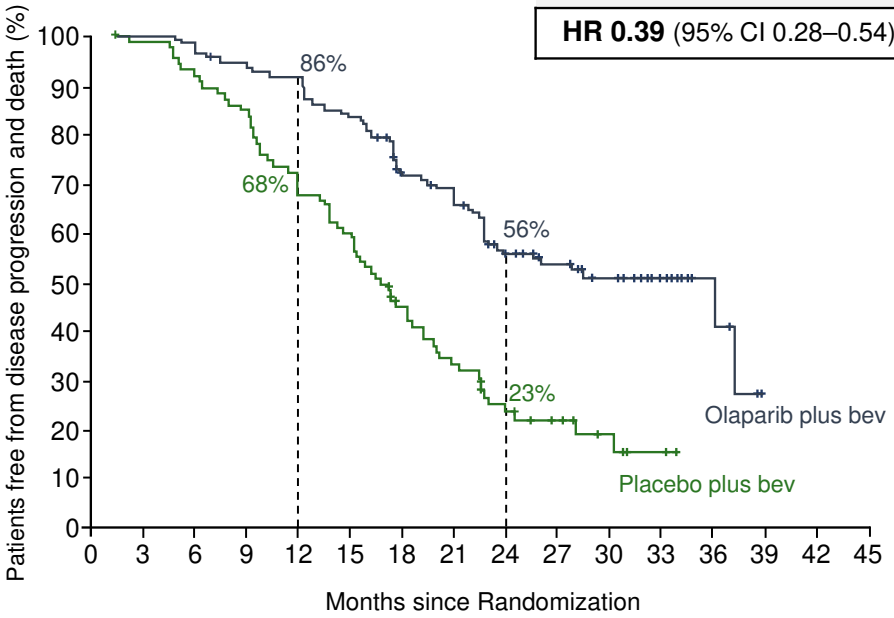
N Engl J Med 2019; 381: 2416-28

PFS by clinical risk in HRD-positive patients

Higher risk, HRD positive

	Olaparib + bev (n=177)	Placebo + bev (n=89)
Events, n (%)	77 (44)	67 (75)
Median PFS, months	**36.0***	**16.0**

HR 0.39 (95% CI 0.28–0.54)



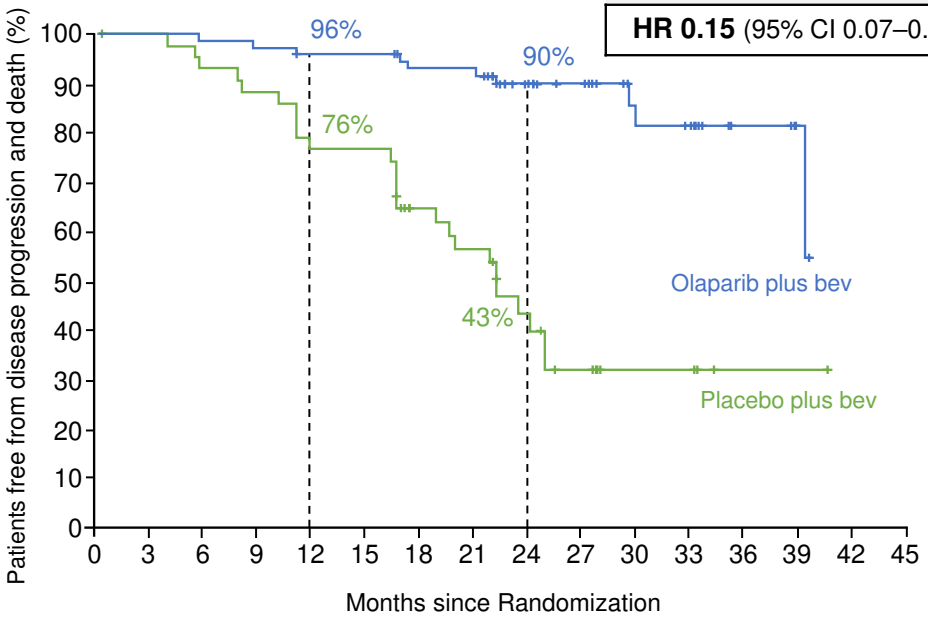
Number of patients at risk:

Olaparib plus bev	177	175	166	161	150	140	109	95	63	50	27	15	5	0	0
Placebo plus bev	89	86	78	66	59	47	31	24	16	11	5	2	0	0	0

Lower risk, HRD positive

	Olaparib + bev (n=78)	Placebo + bev (n=43)
Events, n (%)	10 (13)	25 (58)
Median PFS, months	**NR**	**22.1**

HR 0.15 (95% CI 0.07–0.30)

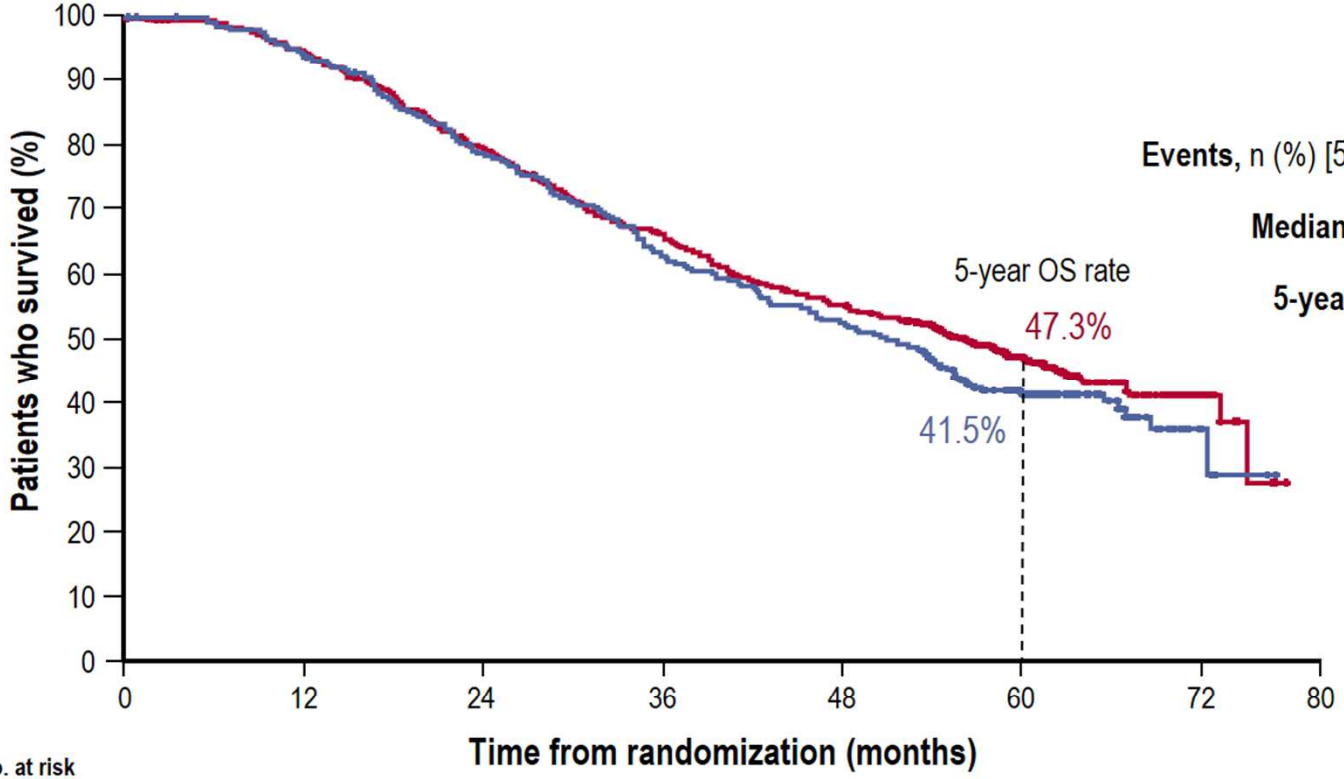


Number of patients at risk:

Olaparib plus bev	78	77	76	75	73	73	60	60	40	35	19	14	6	3	0
Placebo plus bev	43	42	39	37	32	32	23	20	12	7	3	3	1	1	0

Higher-risk patients: Stage III patients with upfront surgery and residual disease or NACT, stage IV patients
Lower-risk patients: Stage III patients with upfront surgery and complete resection

OS analysis: ITT population



No. at risk																										
Olaparib + bevacizumab	537	530	528	517	503	480	463	440	420	398	376	357	347	329	308	295	286	276	262	217	169	113	82	40	19	4	0
Placebo + bevacizumab	269	267	264	261	250	242	229	220	208	199	188	179	166	160	154	146	139	132	121	96	76	51	37	20	5	2	0

	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [55% maturity]	288 (53.6)	158 (58.7)
Median OS, months	**56.5**	**51.6**
5-year OS rate, %	**47.3**	**41.5**

HR 0.92 (95% CI 0.76–1.12); ***P*=0.4118**

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **19.6%** (105/537)
Placebo + bevacizumab: **45.7%** (123/269)

Median time from first cycle of chemotherapy to randomization = 6 months

PARP, poly(ADP-ribose) polymerase.

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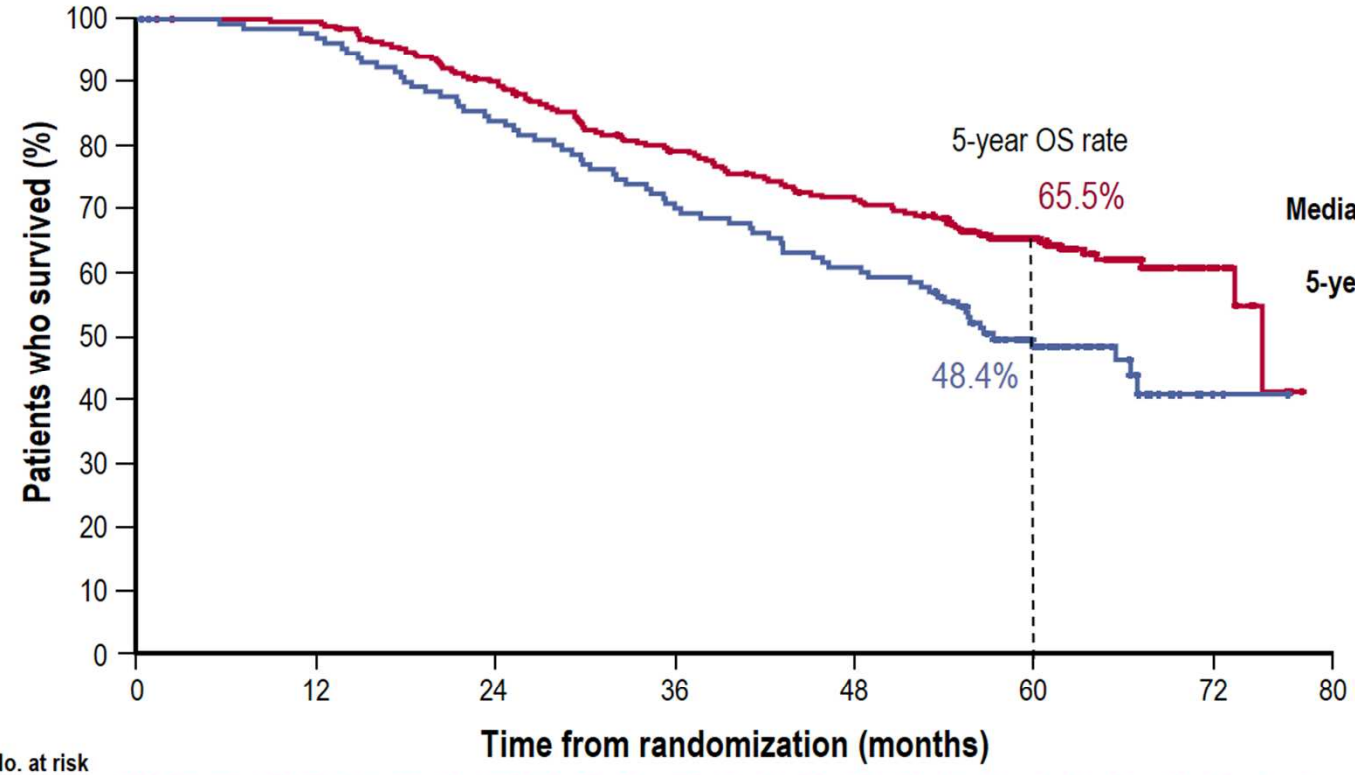
OS was prolonged in the HRD-positive subgroup



No. at risk																										
Olaparib + bevacizumab	255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0
Placebo + bevacizumab	132	130	129	128	126	121	117	114	109	105	100	96	91	89	86	82	79	77	70	59	44	29	21	9	2	1	0

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)*	**57.3**
5-year OS rate, %	**65.5**	**48.4**

HR 0.62 (95% CI 0.45–0.85)

38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **17.3%** (44/255)
Placebo + bevacizumab: **50.8%** (67/132)

*Median unstable; <50% data maturity.
HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay.

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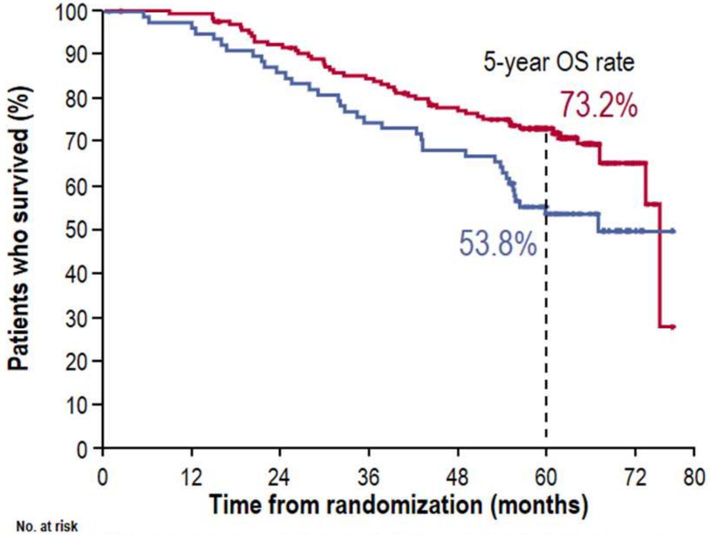
OS subgroup analysis by BRCAm and HRD status

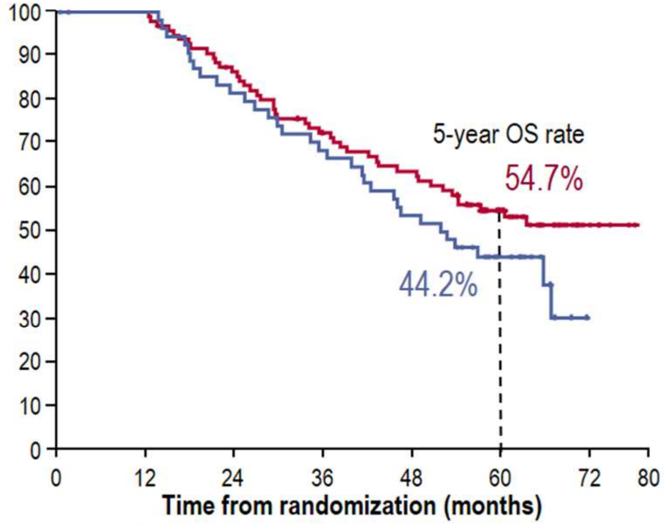
BRCAm*



No. at risk																											
Olaparib + bevacizumab	157	156	156	155	155	152	150	144	143	139	134	131	130	127	123	118	117	115	112	99	80	55	42	21	11	2	0
Placebo + bevacizumab	80	79	78	77	76	74	72	71	68	66	64	61	59	58	58	54	54	53	50	40	33	22	17	10	3	1	0

	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
	HR 0.60 (95% CI 0.39–0.93)	

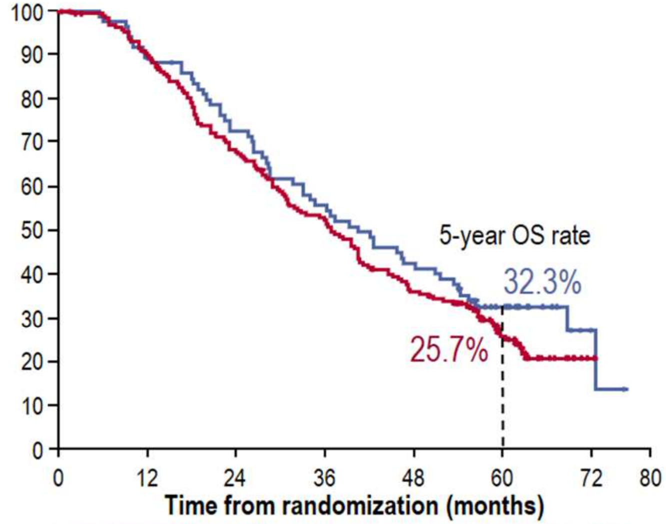
HRD positive‡ excluding BRCAm



97	96	96	96	96	91	87	86	81	76	71	70	66	63	61	59	58	55	52	45	37	29	22	12	5	2	0
55	54	54	54	54	51	48	46	44	42	40	39	37	36	33	32	29	28	24	21	15	9	6	2	0		

	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
Events, n (%)	44 (45.4)	32 (58.2)
Median OS, months	NR	52.0
5-year OS rate, %	**54.7**	**44.2**
PARPi as subsequent treatment, n (%)	9 (9.3)	23 (41.8)
	HR 0.71 (95% CI 0.45–1.13)	

HRD negative†



192	187	186	179	169	157	146	135	126	119	109	100	97	89	77	72	66	62	57	43	30	16	11	5	1	0	
85	85	84	83	76	74	71	65	60	56	51	48	46	43	41	38	35	33	31	21	17	11	8	5	2	1	0

	Olaparib + bevacizumab (N=192)	Placebo + bevacizumab (N=85)
Events, n (%)	140 (72.9)	58 (68.2)
Median OS, months	36.8	40.4
5-year OS rate, %	**25.7**	**32.3**
PARPi as subsequent treatment, n (%)	46 (24.0)	34 (40.0)
	HR 1.19 (95% CI 0.88–1.63)	

本試験はアストラゼネカ社の支援により行われた

*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

AEs of special interest

	Primary PFS analysis (DCO: 22 March 2019)		Final PFS2 analysis (DCO: 22 March 2020)		Final OS analysis (DCO: 22 March 2022)	
	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)	7 (1.3)	4 (1.5)	9 (1.7)	6 (2.2)
New primary malignancies, n (%)*	7 (1.3)	3 (1.1)	13 (2.4)	5 (1.9)	22 (4.1)	8 (3.0)
Pneumonitis/ILD/bronchiolitis, n (%)†	6 (1.1)	0 (0.0)	6 (1.1)	0 (0.0)	7 (1.3)	2 (0.7)

- All patients had discontinued treatment at PFS2 DCO
- TEAEs have been reported previously[1,2] and the olaparib safety profile has been well characterized

*New primary malignancies were: 1 plasma cell myeloma, 2 basal cell carcinoma, 11 breast cancer, 1 bronchial carcinoma, 1 colon cancer, 1 glioblastoma, 1 malignant neoplasm, 1 pancreatic carcinoma, 2 squamous cell carcinoma, and 1 ureteric cancer in the olaparib arm; and 1 papillary thyroid cancer, 4 breast cancer, 1 diffuse large B-cell lymphoma, 1 malignant lung neoplasm, and 1 malignant neoplasm in the placebo arm;
†Pneumonitis/ILD/bronchiolitis events were: 1 bronchiolitis, 1 pneumonia, 1 acute respiratory distress syndrome, 2 interstitial lung disease, and 2 pneumonitis in the olaparib arm; and 1 corona virus infection and 1 pneumonitis case in the placebo arm.
AA, aplastic anaemia; AE, adverse event; AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome.

1. Ray-Coquard I *et al. N Engl J Med* 2019;381:2416–28; 2. González-Martín A *et al. Eur J Cancer* 2022;174:221–31.

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進行卵巣がん初回治療におけるNiraparib維持療法

PRIMA/ENGOT-OV26/GOG3012

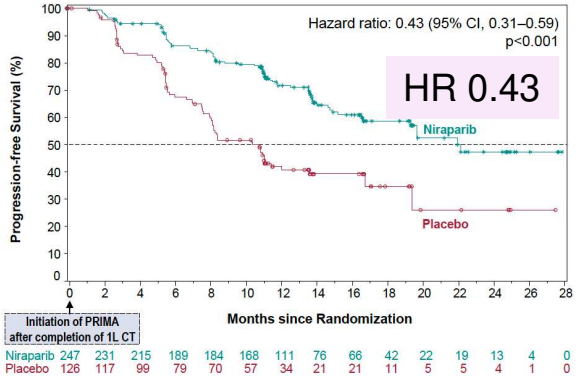
- Newly diagnosed Stage III-IV high grade serous or endometrioid ovarian cancer
- **Must have visible residual disease after primary surgery**
- Stage III with NACT are eligible regardless of residual disease after IDS
- **Surgery (upfront or interval)**
- **Must NOT receive bevacizumab**

CR or PR → R (2:1)

Maintenance treatment

- Niraparib 300mg qd x 3 years
  *BW <77kg, Plt<150,000では200mg qd
- Placebo x 3 years

HRD



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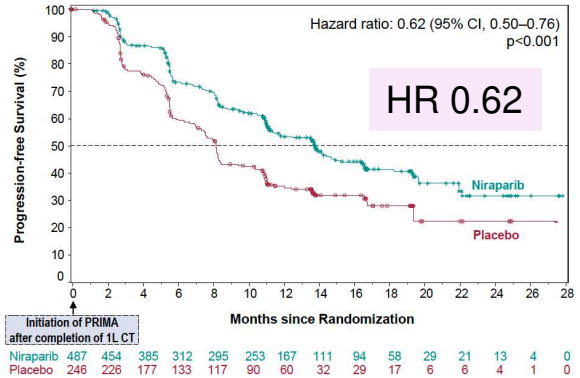
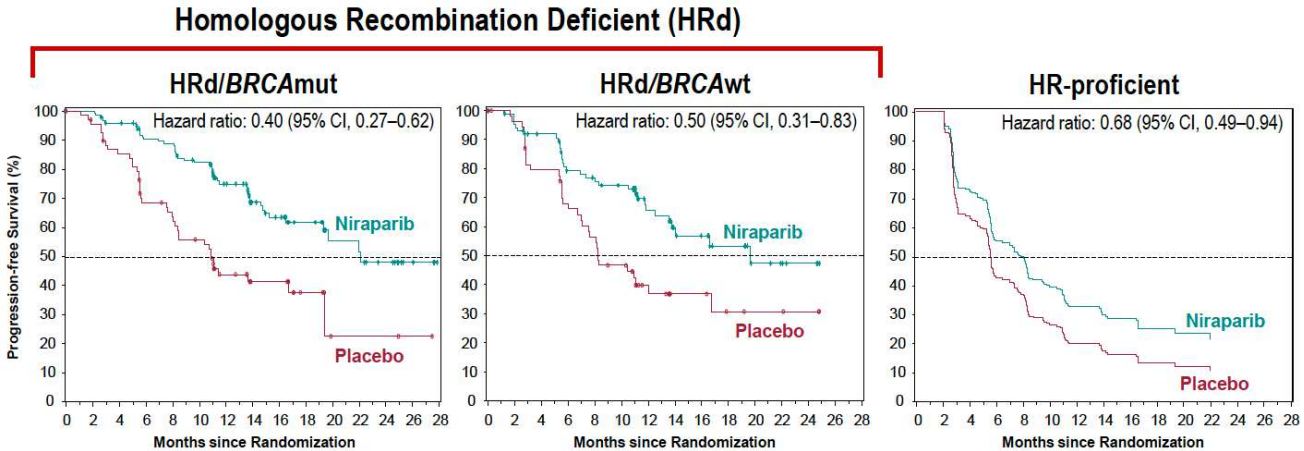




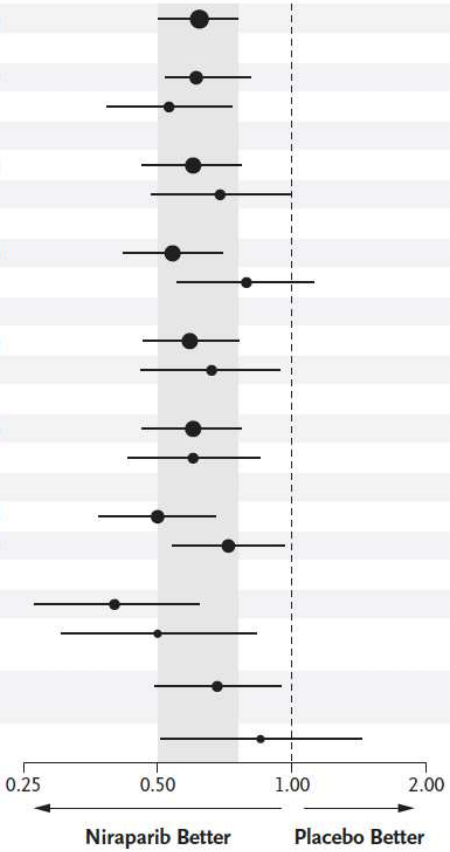
HR 0.40 HR 0.50 HR 0.68

N Engl J Med 2019; 381: 2391-402

進行卵巣がん初回治療におけるNiraparib維持療法

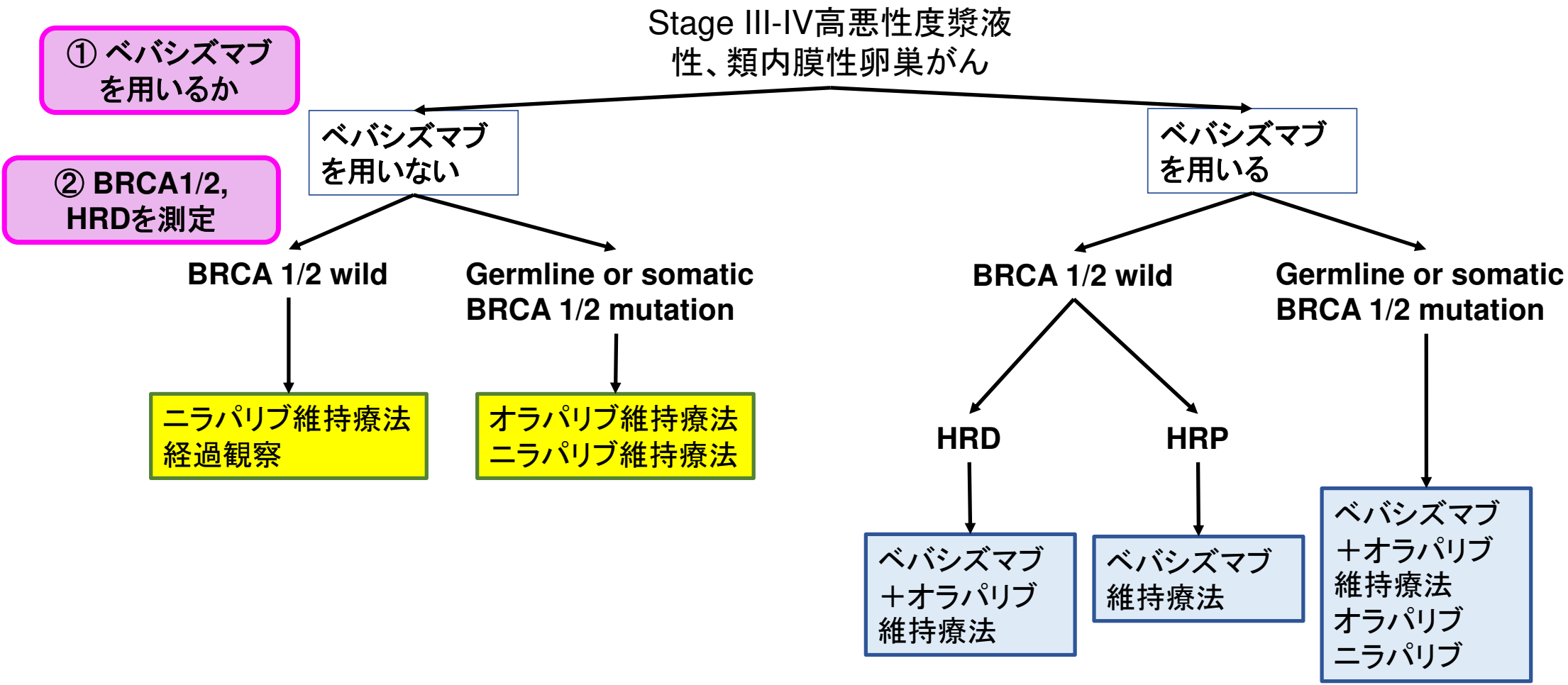
・Stage III vs IV
・PDS vs. IDS
・HRの状況 に関わらず、
Niraparib維持療法はプラセボ群に
比較してPDSを改善する

Subgroup	Niraparib	Placebo	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients with disease progression or death/total no. (%)		
All patients	232/487 (47.6)	155/246 (63.0)	0.62 (0.50–0.76)
Age			
<65 yr	136/297 (45.8)	86/147 (58.5)	0.61 (0.47–0.81)
≥65 yr	96/190 (50.5)	69/99 (69.7)	0.53 (0.38–0.74)
ECOG score			
0	146/337 (43.3)	107/174 (61.5)	0.60 (0.46–0.77)
1	86/150 (57.3)	48/72 (66.7)	0.69 (0.48–1.00)
Stage of disease at initial diagnosis			
III	143/318 (45.0)	103/158 (65.2)	0.54 (0.42–0.70)
IV	89/169 (52.7)	52/88 (59.1)	0.79 (0.55–1.12)
Neoadjuvant chemotherapy			
Yes	151/322 (46.9)	107/167 (64.1)	0.59 (0.46–0.76)
No	81/165 (49.1)	48/79 (60.8)	0.66 (0.46–0.94)
Best response to platinum therapy			
Complete response	146/337 (43.3)	100/172 (58.1)	0.60 (0.46–0.77)
Partial response	86/150 (57.3)	55/74 (74.3)	0.60 (0.43–0.85)
Geographic region			
North America	104/218 (47.7)	82/115 (71.3)	0.50 (0.37–0.68)
All other regions	128/269 (47.6)	73/131 (55.7)	0.72 (0.54–0.96)
Homologous-recombination status			
BRCA mutation	49/152 (32.2)	40/71 (56.3)	0.40 (0.27–0.62)
No *BRCA* mutation, homologous-recombination deficiency	32/95 (33.7)	33/55 (60.0)	0.50 (0.31–0.83)
Homologous-recombination proficiency	111/169 (65.7)	56/80 (70.0)	0.68 (0.49–0.94)
Not determined	40/71 (56.3)	26/40 (65.0)	0.85 (0.51–1.43)



N Engl J Med 2019; 381: 2391-402

進行卵巣癌の治療指針



NCCN® guidelines 2022より作図

初回治療における課題

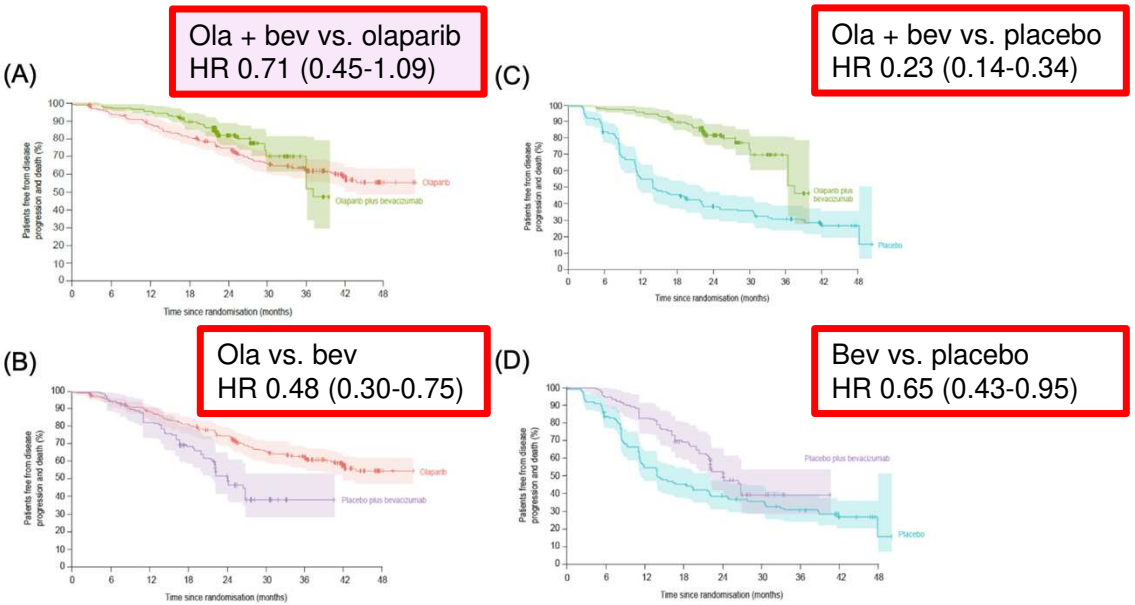
- BRCAmtの集団において、PARP阻害剤にBevを加えることのメリットは？
- HRPの集団において、Niraparibメンテナンス？Bevメンテナンス？
- 化学療法レジメンをどうするか？TC+Bev? Dose-dense TC?　リスクを考慮したBevacizumab投与の選択は必要なのか？
- 漿液性癌、類内膜癌以外の組織型にHRD検査/BRCA遺伝子検査を行うべきか？

BRCAmutの患者に対しOlaparibにBevacizumabを加えるべきか？

- 現在の標準治療である、BRCAmに対するオラパリブ療法、HRDに対するオラパリブ＋ベバシズマブ療法のOS改善効果が示された。オラパリブ＋ベバシズマブ療法のOS改善効果はBRCAm集団に顕著だった。
- SOLO-1試験におけるOS改善については統計学的な有意差はなかったものの、7年OS 67% vs 46.5%、プラセボ群の44%がその後PARP阻害薬を投与した上での結果であることから、臨床的には評価できる。
- BRCAm患者に対しオラパリブ単独で良いのか、ベバシズマブを併用すべきなのかは明らかでない。

SOLO-1、PAOLA-1 BRCAmut cohort の統合解析

- Population-adjusted indirect treatment comparison (PA-ITC)
- SOLO1とPAOLA-1試験のBRCAm患者を対象に、両試験患者間のbaseline characteristicsをpropensity score weighting techniqueを用いて調整
- 調整項目：tumor location、ECOG PS、FIGO stage、timing of surgery、postoperative residual disease status、response to first-line chemotherapy、age、histological type



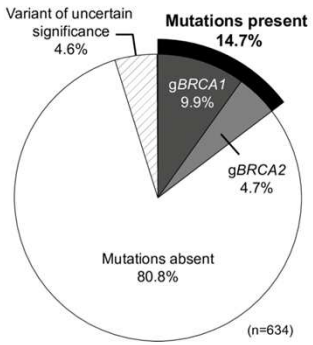
Eur J Cancer. 2021; 157: 415-423.

TC+Bev→Olaparib+BevとddTC→PARPiの使い分け

- Dose-dense TC療法とTC+Bev療法いずれも選択可能。
- 腹水貯留、stage IVといった高リスク例でBevが有効と言われているが、PAOLA-1の結果からは、HRD症例においてはリスクに関わらずolaparib+bevが有効。
- HRD症例には積極的にTC+Bev→Bev+olaparibを選択することが勧められる。
- HRP症例においてはdose-dense TC→ニラパリブ療法が勧められる。

漿液性癌、類内膜癌以外の組織型に
HRD検査/BRCA遺伝子検査を行うべきか？

CHARLOTTE study



*gBRCA**	n=634 n (%) [95% CI]
Mutations present	93 (14.7) [12.0–17.7]
gBRCA1 only	63 (9.9)
gBRCA2 only	30 (4.7)
gBRCA1/2	0
Mutations absent	512 (80.8)
Variant of uncertain significance	29 (4.6)

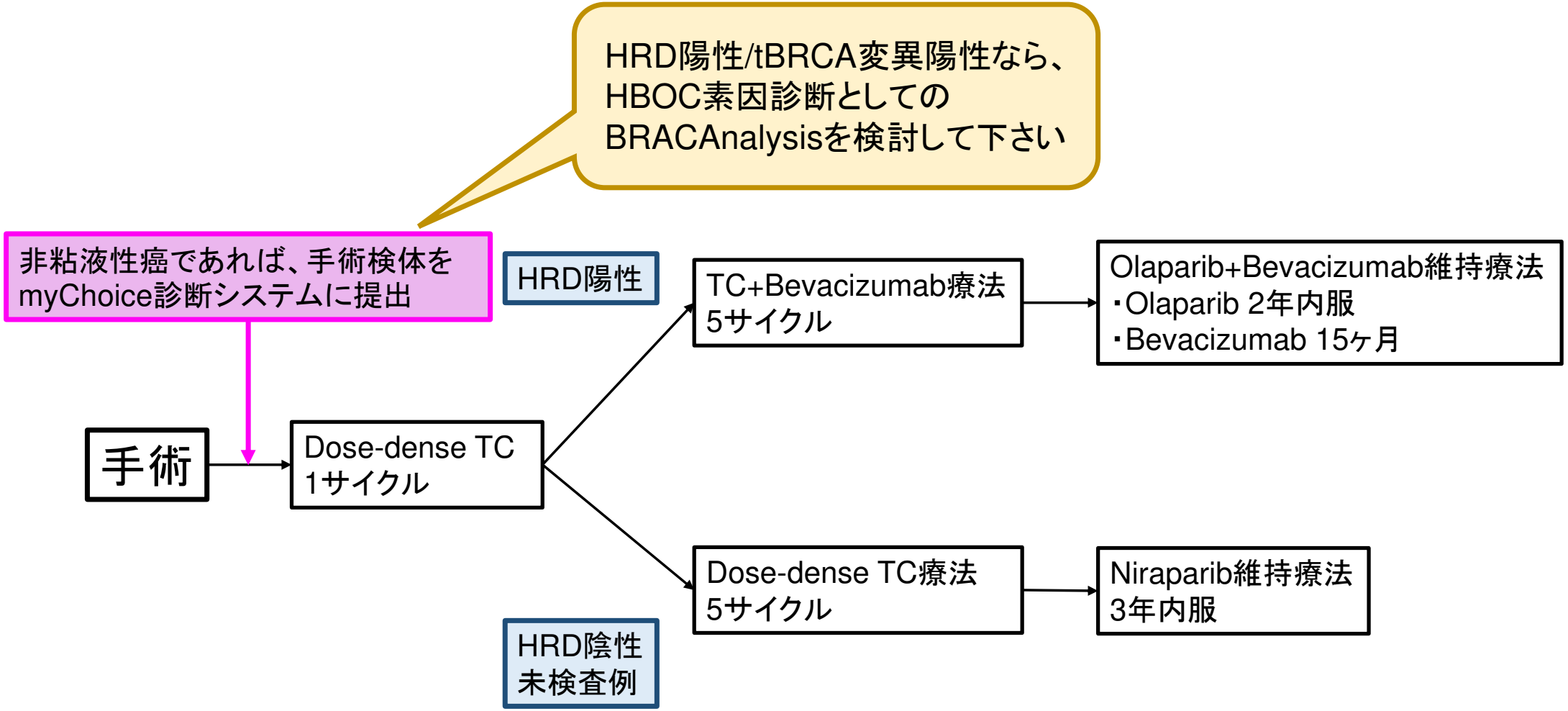
Figure 1 Prevalence of g*BRCA1/2* mutations. *g*BRCA* mutations were interpreted using the Myriad Database. CI, confidence interval; g*BRCA*, germline *BRCA*.

Table 1 Prevalence of germline *BRCA1/2* (*gBRCA1/2*) mutation classified by patient background and ovarian factors

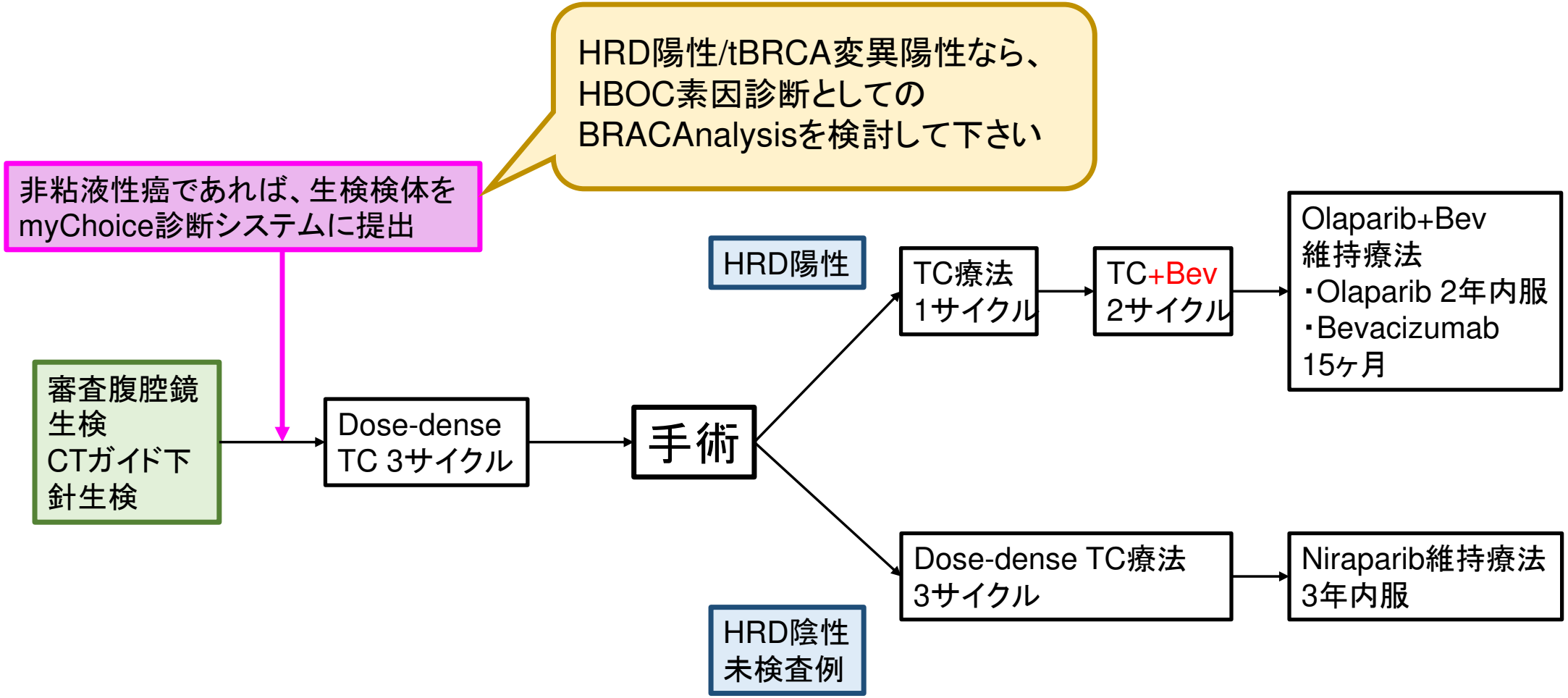
		gBRCA mutation prevalence					
Classification factors	**n**	**Present**	***gBRCA1* mutation only**	***gBRCA2* mutation only**	***gBRCA1* and *gBRCA2* mutations**	**Absent**	**Variant of uncertain significance**
Patient factors pathological diagnosis)							
All serous cancers	279	79 (28.3)	54 (19.4)	25 (9.0)	0 (0.0)	185 (66.3)	15 (5.4)
High-grade serous cancer	274	78 (28.5)	53 (19.3)	25 (9.1)	0 (0.0)	181 (66.1)	15 (5.5)
Low-grade serous cancer	5	1 (20.0)	1 (20.0)	0 (0.0)	0 (0.0)	4 (80.0)	0 (0.0)
All mucinous cancers	19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (100.0)	0 (0.0)
All endometrioid cancers	120	8 (6.7)	7 (5.8)	1 (0.8)	0 (0.0)	104 (86.7)	8 (6.7)
Clear-cell carcinoma	187	4 (2.1)	2 (1.1)	2 (1.1)	0 (0.0)	178 (95.2)	5 (2.7)
Seromucinous cancer	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)
Other	25	2 (8.0)	0 (0.0)	2 (8.0)	0 (0.0)	22 (88.0)	1 (4.0)

Int J Gynecol Cancer 2019; 29:1043-49より改変

Advanced stage: PDS症例



Advanced stage: NAC➡IDS症例

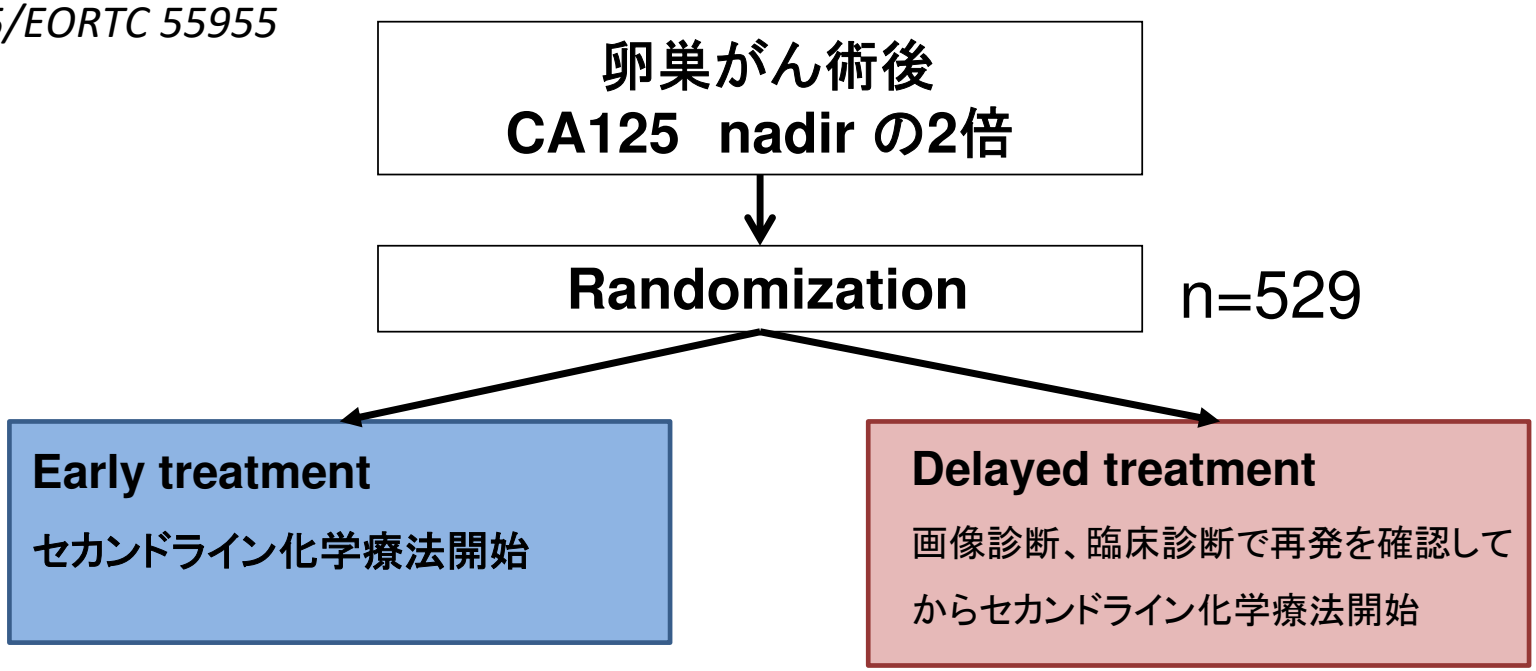


卵巣癌治療

1. 初回治療
   - Dose-dense TC療法
   - Bevacizumab
   - PARP阻害薬
2. プラチナ感受性再発
3. プラチナ抵抗性再発

再発卵巣がんの治療をいつから始めるか?

MRC OV5/EORTC 55955

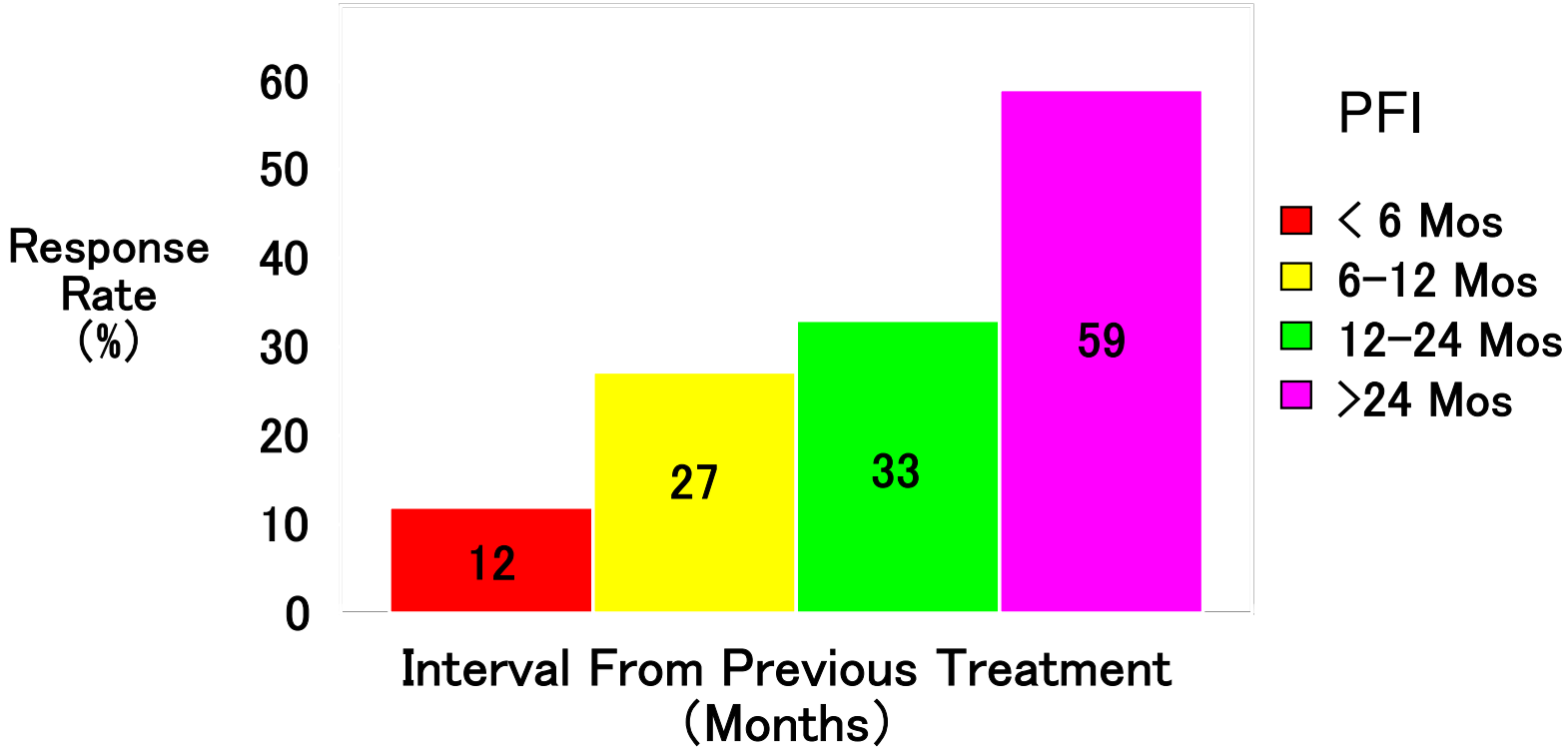


- **Early treatment群のほうが4.8か月早期に治療開始**
- **Overall Survivalに有意差なし HR＝1.00 (95% CI 0.82-1.22) P = 0.98**
- **QOLはearly treatment群で有意に不良**

Lancet 2010; 376: 1155-1163

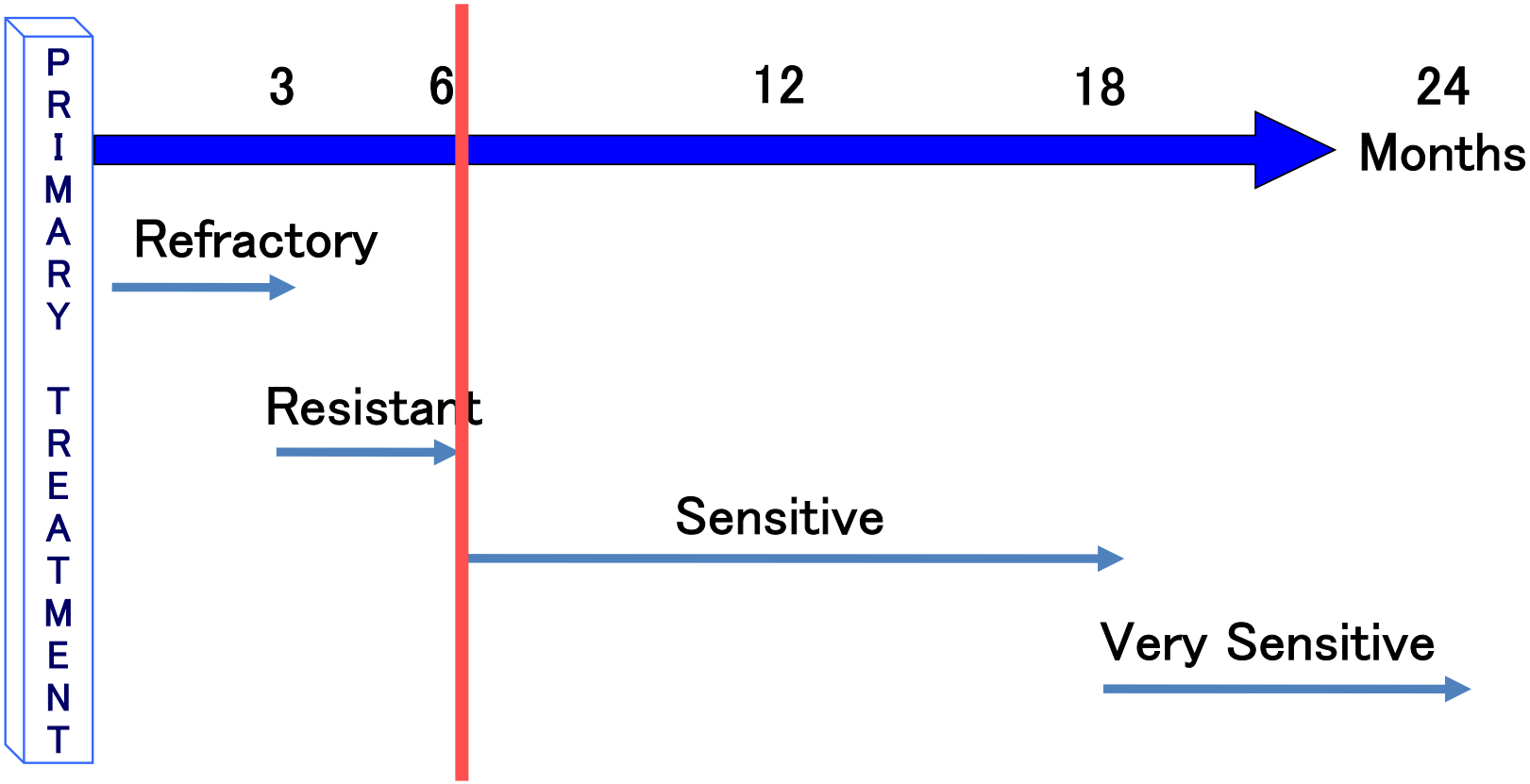
再発後化学療法の選択

前治療から再発日までのインターバル (platinum-free interval, PFI)と、再発時プラチナ系化学療法の抗腫瘍効果



Lancet Oncol 2002; 3(9): 537-45

Definition of Platinum sensitivity



Choices of 2nd line Chemotherapy

Platinum-Sensitive relapse

PFI ≥ 6 months

Platinum-containing Doublet

- **Carboplatin + Paclitaxel**
- **Carboplatin + Gemcitabine**
- **Carboplatin + Doxil**

Platinum-Resistant/Refractory relapse

PFI < 6 months

Single agent

- **Liposomal DXR (Doxil)**
- **Gemcitabine**
- **Topotecan**
- **Weekly Paclitaxel**
- **Oral Etoposide**

(PFI: Platinum-free interval)

Carbo/Gem + Bevacizumab

OCEANS

- Platinum-sensitive recurrent OC
- Measurable disease
- ECOG PS 0-1
- No prior chemo for recurrent OC
- No prior BV

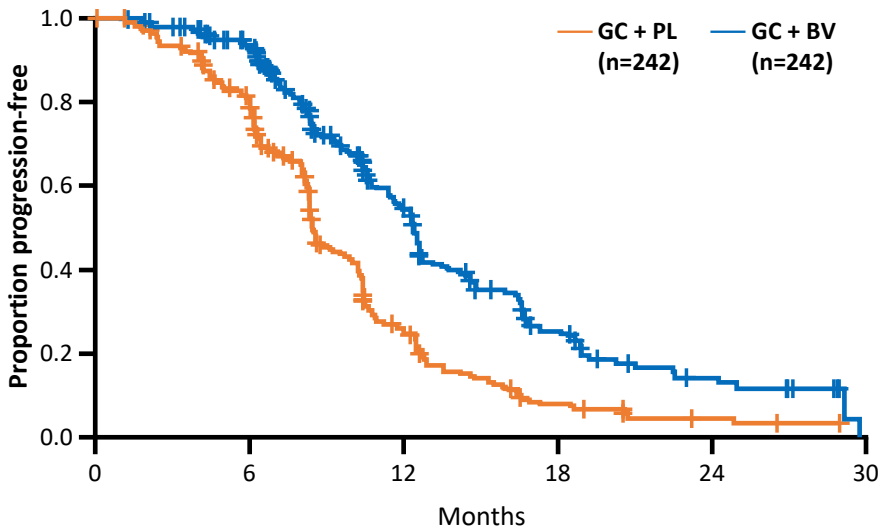
(n=484)

R

Carboplatin AUC=4 d1
Gemcitabine 1000mg/m2, day1,8
Q3wk 6 cycles

Carboplatin AUC=4 d1
Gemcitabine 1000mg/m2 d1,8
Bevacizumab 15mg/kg d1
Q3wk 6 cycles

Bevacizumab 15mg/kg
Q3wk until progression

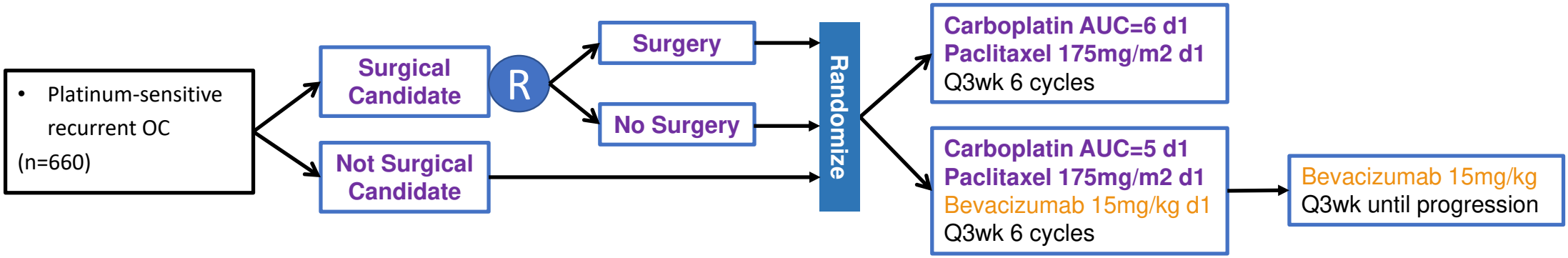


J Clin Oncol 2012; 30: 2039-45

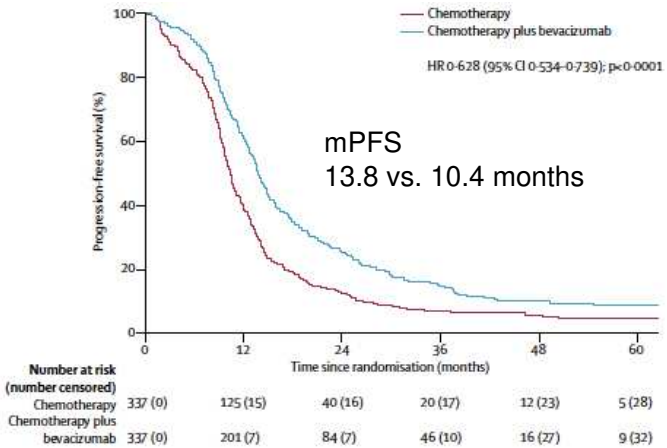
	GC + PL (n=242)	GC + BV (n=242)
PFS by INV		
Median PFS, mo	8.4	12.4
Stratified analysis, HR (95% CI)	0.484 (0.388 – 0.605)	
Log-rank *P* value	<.0001	
ORR and DOR by INV		
ORR, %	57	79
Median DOR, mo	7.4	10.4
HR (95% CI)	0.53 (0.41–0.70)	

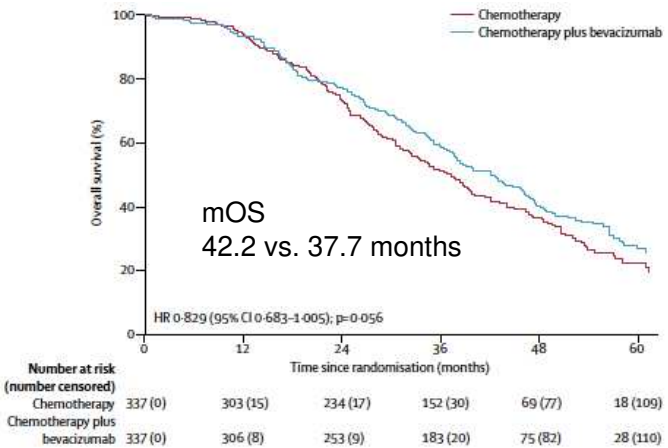
Carbo/Pacli + Bevacizumab

GOG213



	TC	TC+Bev
Response rate	59%	78%
	P<0.0001	

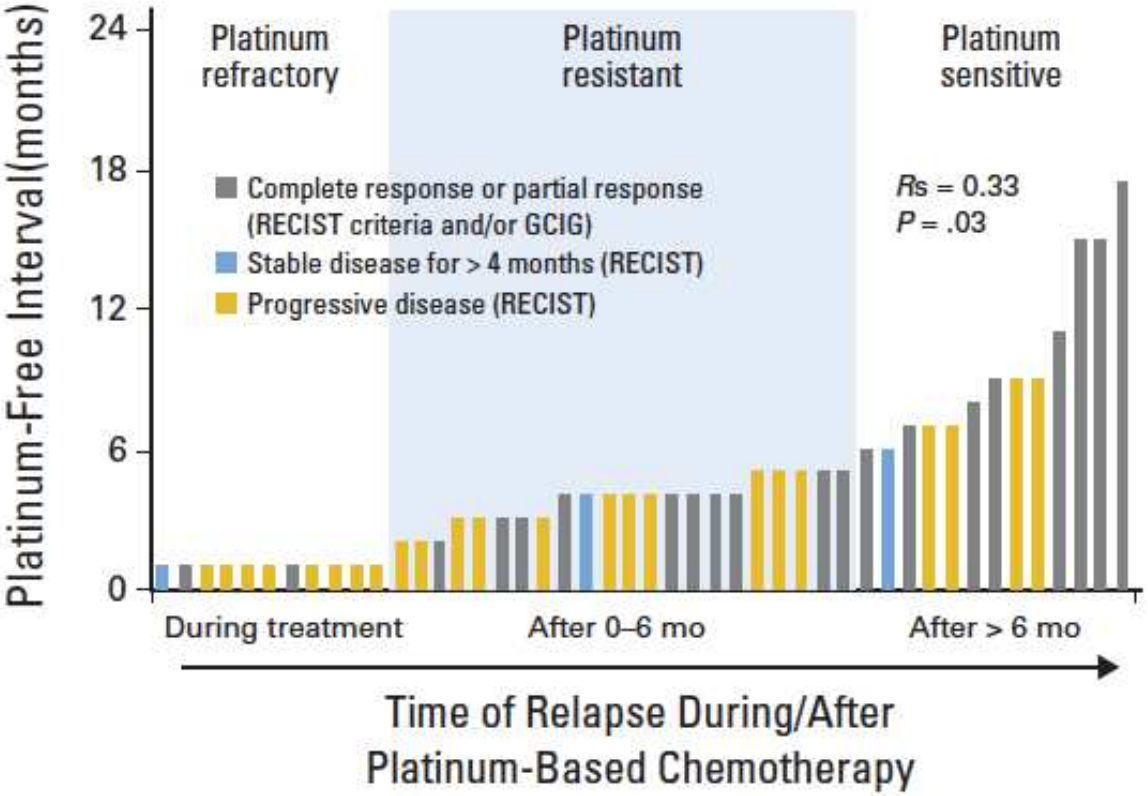




Lancet Oncol 2017; 18: 779-91

プラチナ感受性再発の高い方が Olaparibの効果が高い

Clinical benefit rate 23% 45% 69%



J Clin Oncol 2010; 28: 2512

BRCA mutationの有無に関わらずOlaparibは予後改善効果あり

Study19: randomized phase 2 study

- high grade serous ovarian, FT, and primary peritoneal cancer
- **Platinum-sensitive Relapse** (n=265)

BRCA status was not required

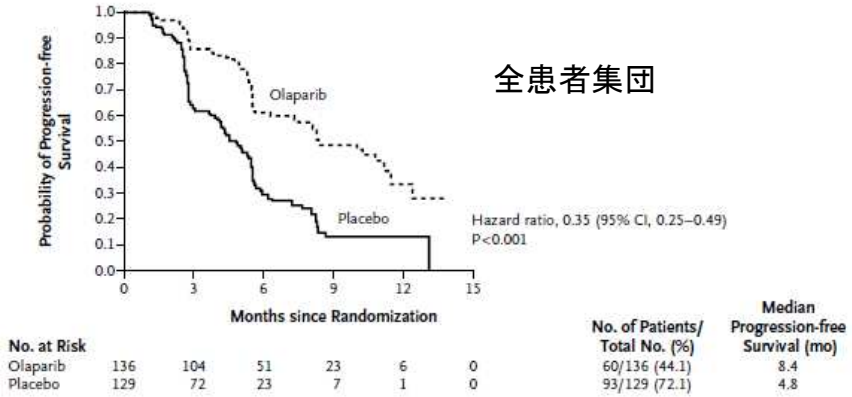
→ Platinum-based chemotherapy → R (**CR or PR**)

→ Olaparib 400mg bid

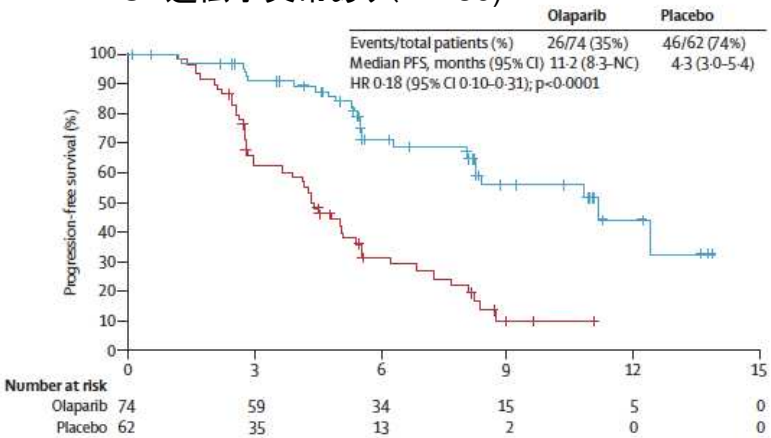
→ Placebo bid

Until PD

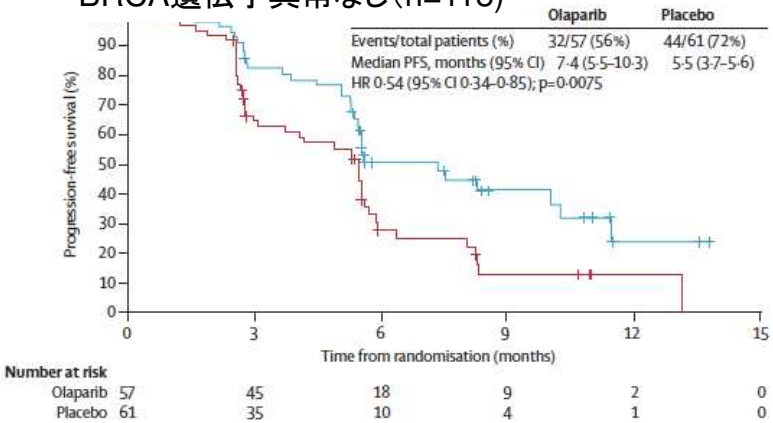
Primary endpoint: PFS
Secondary endpoints: TTP, response, OS



BRCA遺伝子異常あり（n=136）



BRCA遺伝子異常なし（n=118）



N Engl J Med 2012; 366: 1382-92
Lancet Oncol 2014; 15: 852

BRCA mutationを有するプラチナ感受性再発卵巣癌に対するOlaparib維持療法　検証性試験

SOLO2/ENGOT-Ov21: randomized phase 3 study

- Platinum-sensitive Relapse
- high grade serous ovarian, FT, and primary peritoneal cancer
- BRCA mutation positive

N=295

→ Platinum-based chemotherapy → **CR or PR** → R

2:1

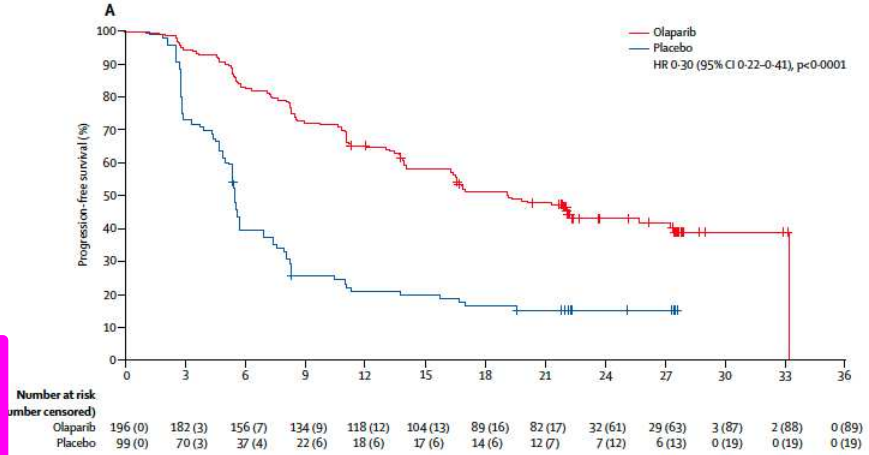
→ Olaparib 300mg bid

→ Placebo bid

Until PD

Primary endpoint: PFS
Secondary endpoints: TTP, time to first subsequent therapy or death, time to second progression or death, time to second subsequent therapy, response rate, OS

mPFS 19.1 months vs. 5.5 months
HR 0.30 (95%CI 0.22-0.41)
P<0.0001



SOLO2試験はBRCA1/2遺伝子変異陽性患者に対する第3相試験であったが、その後「プラチナ感受性再発で直近の化学療法により奏効が得られた患者」に対する維持療法としてオラパリブが保険承認された。

Lancet Oncol 2017; 18: 1274

プラチナ感受性再発卵巣がんに対するNiraparib維持療法

ENGOT-OV16/NOVA trial

- Platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer
- ≥ 2 prior platinum-based regimens
- For the last chemotherapy, patients receive at least 4 cycles of PI chemo and achieve CR/PR

N=553

Primary endpoint: PFS

Myriad HRD test

Germline BRCA mutation cohort (n = 203)

2:1

Niraparib 300 mg QD (n = 136)

Placebo QD (n = 65)

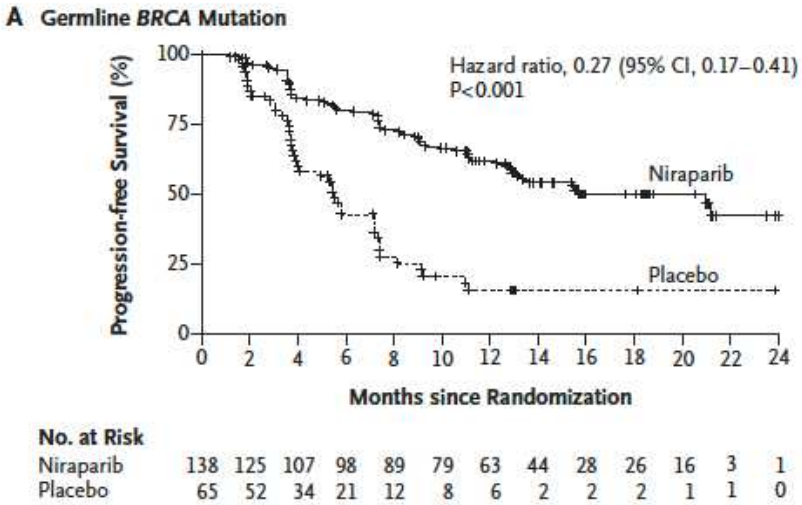
No germline BRCA mutation cohort (n = 350)

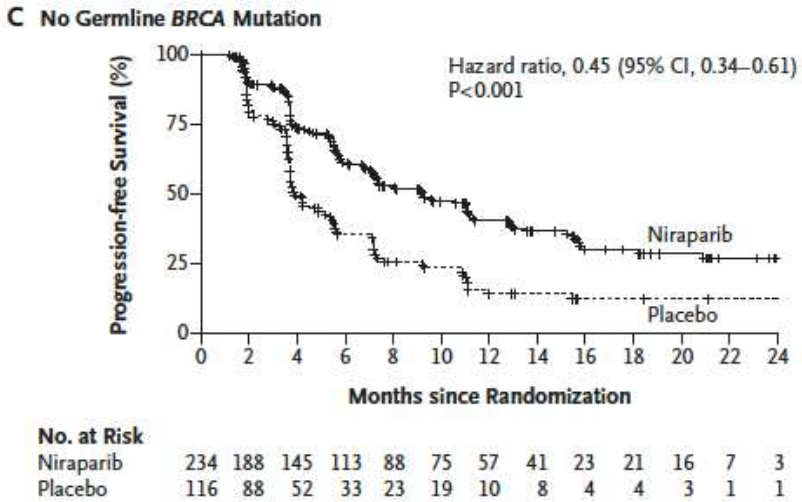
2:1

Niraparib 300 mg QD (n = 231)

Placebo QD (n = 114)

Treatment until PD with no crossover allowed





N Engl J Med 2016; 375: 2154-64

プラチナ感受性再発卵巣がんに対するNiraparib維持療法

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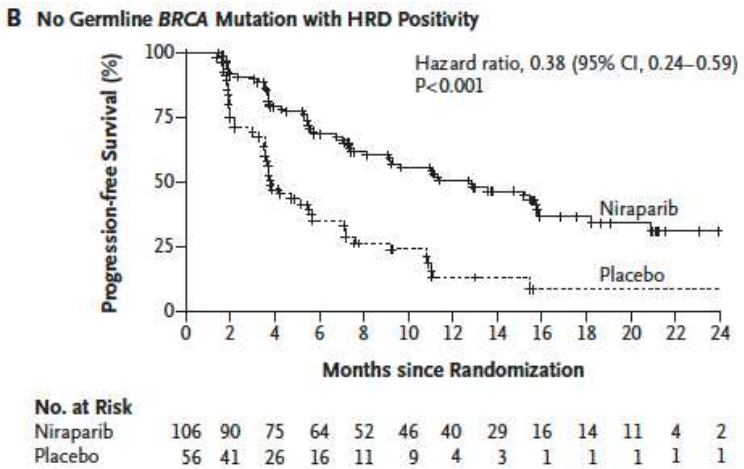
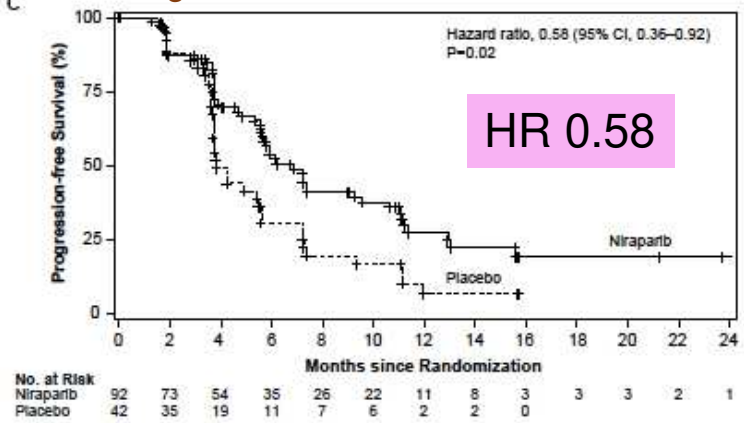


HRD negative



N Engl J Med 2016; 375: 2154-64

プラチナ感受性再発卵巣がんに対するNiraparib

QUADRA trial

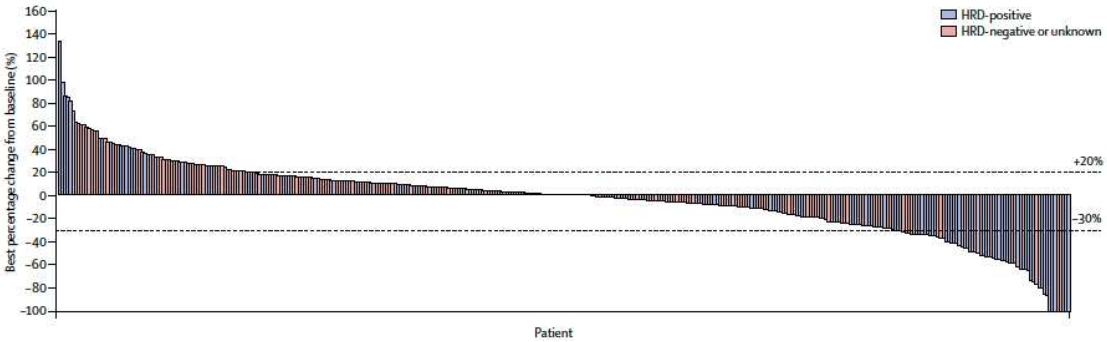
- Metastatic or relapsed high-grade serous ovarian, fallopian tube, or primary peritoneal cancer
- 3 or 4 prior chemotherapy regimens and who had a response to first-line platinum-based therapy lasting at least 6 months.
- Consented to undergo HRD test and blood germline BRCA-mutated status testing

N=463

→ **Niraparib 300 mg QD**
(n = 136)

Primary endpoint: overall response
Hierarchical testing:

1) **patients with HRD-positive tumors sensitive to the last platinum-based chemotherapy**
2) all patients with platinum-sensitive or resistance
3) all patients including HRD negative or unknown tumors.

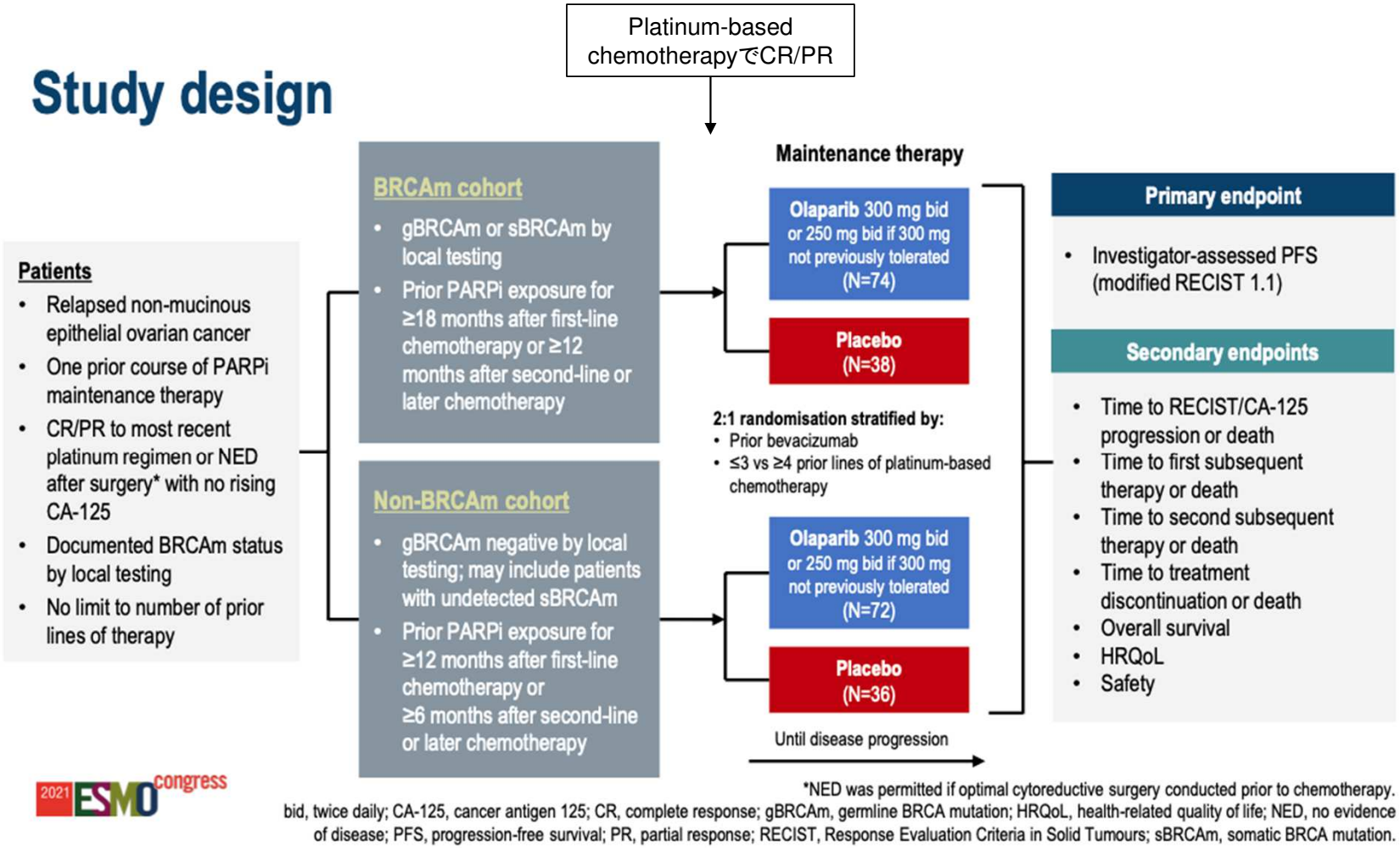


	BRCA-mutated (n=63)	HRD-positive* (n=189)	HRD-negative or unknown (n=230)
Platinum-sensitive to most recent line of platinum therapy	7/18 (39%)	14/53 (26%)	2/52 (4%)
Platinum-resistant or refractory	10/37 (27%)	12/120 (10%)	5/169 (3%)
Platinum status unknown	1/8 (13%)	3/16 (19%)	1/9 (11%)
All	18/63 (29%)	29/189 (15%)	8/230 (3%)

Lancet Oncol 2019; 20: 636-48

PARP阻害薬再投与の有効性は？

OReO/ENGOT Ov-38 trial

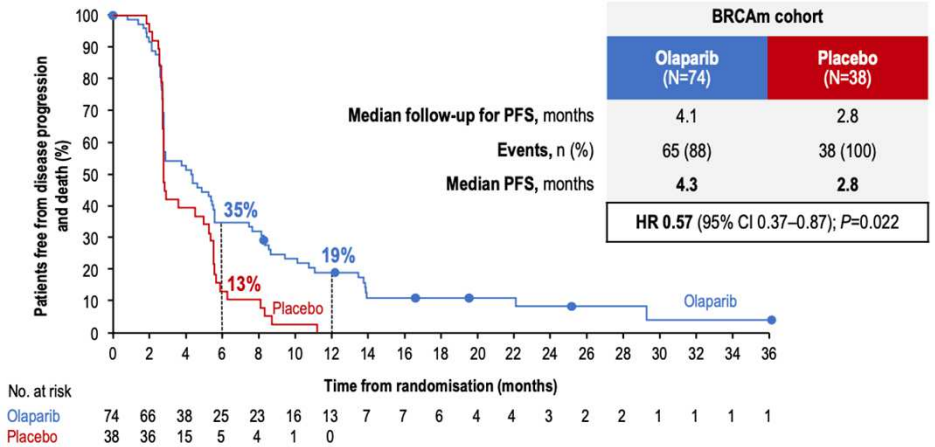


*NED was permitted if optimal cytoreductive surgery conducted prior to chemotherapy.
bid, twice daily; CA-125, cancer antigen 125; CR, complete response; gBRCAm, germline BRCA mutation; HRQoL, health-related quality of life; NED, no evidence of disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; sBRCAm, somatic BRCA mutation.

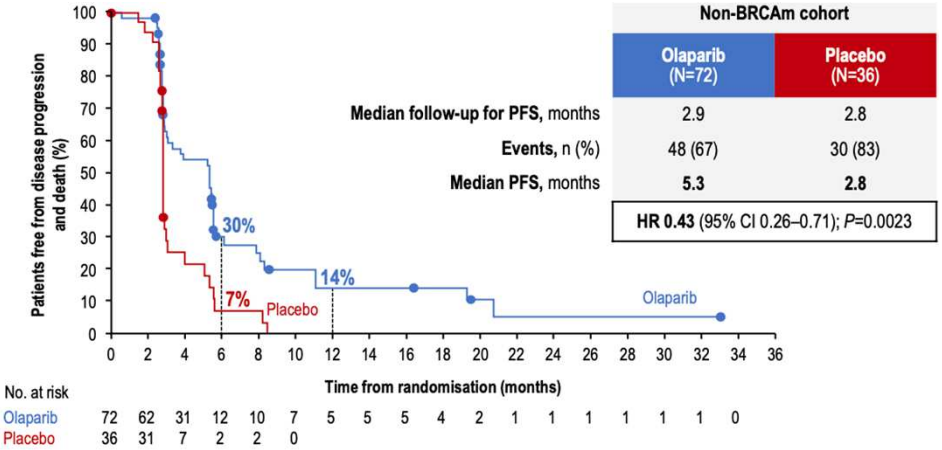
ESMO Congress 2021 LBA33

BRCA遺伝子変異の有無に関わらず、Olaparip再投与によりPFSが改善

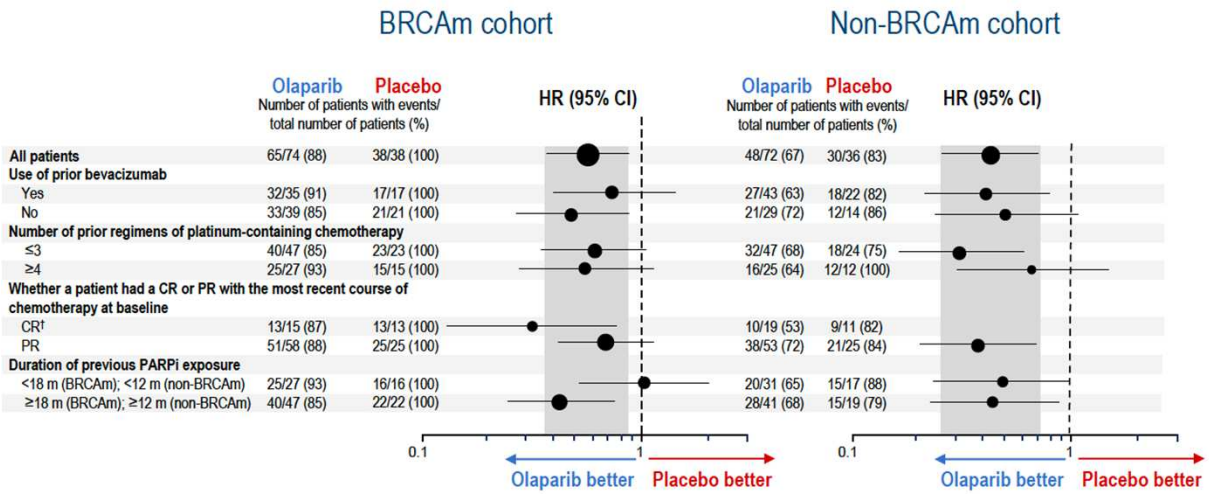
OReO/ENGOT Ov-38 trial



BRCAm cohort	Olaparib (N=74)	Placebo (N=38)
Median follow-up for PFS, months	4.1	2.8
Events, n (%)	65 (88)	38 (100)
Median PFS, months	**4.3**	**2.8**
HR 0.57 (95% CI 0.37–0.87); *P*=0.022		



Non-BRCAm cohort	Olaparib (N=72)	Placebo (N=36)
Median follow-up for PFS, months	2.9	2.8
Events, n (%)	48 (67)	30 (83)
Median PFS, months	**5.3**	**2.8**
HR 0.43 (95% CI 0.26–0.71); *P*=0.0023		



ESMO Congress 2021 LBA33

プラチナ感受性再発卵巣癌　治療方針

初回治療
TC療法、dose-dense TC療法、TC+Bevacizumab療法
維持療法　BRCAmt: Olaparib±Bev, Niraparib
HRD:　Olaparib+Bev, Niraparib
HRP:　Niraparib, Bevacizumab

初回治療でPARP阻害薬　既治療

プラチナ感受性再発
- Platinum doublet ± Bevacizumab
- BRCAmtでは18ヶ月以上、non-BRCAmtでは12ヶ月以上のPARP阻害薬治療期間を保っていた患者においては、Olaparibの再投与が検討される

初回治療でPARP阻害薬　未治療

プラチナ感受性再発
- プラチナ併用化学療法後のOlaparib維持療法、Niraparib維持療法
- 3–4前治療歴ありHRDに対するNiraparib単剤療法

卵巣癌治療

1. 初回治療
   - Dose-dense TC療法
   - Bevacizumab
   - PARP阻害薬
2. プラチナ感受性再発
3. プラチナ抵抗性再発

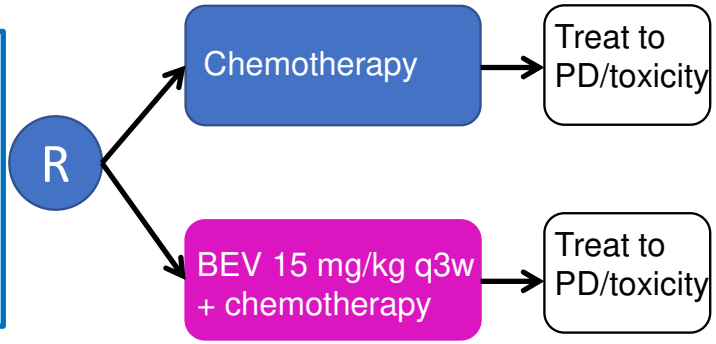
Chemotherapy for platinum-resistant relapse

Study	n	Regimens	TTP (wks)	*P*	OS (wks)	*P*
Ten Bokkel Huinink, JCO 1997	226	Topotecan Paclitaxel	23 14	*0.002	61 43	NS
Gordon, JCO 2001	474	Topotecan Doxil	17 16	NS	57 60	NS
O'Byrne, Proc ASCO 2002, abstr 808	214	Paclitaxel Doxil	22 22	NS	56 46	NS
Mutch, JCO 2007	195	Gemcitabine Doxil	13 16	NS	55 59	NS

Chemotherapy + Bevacizumab

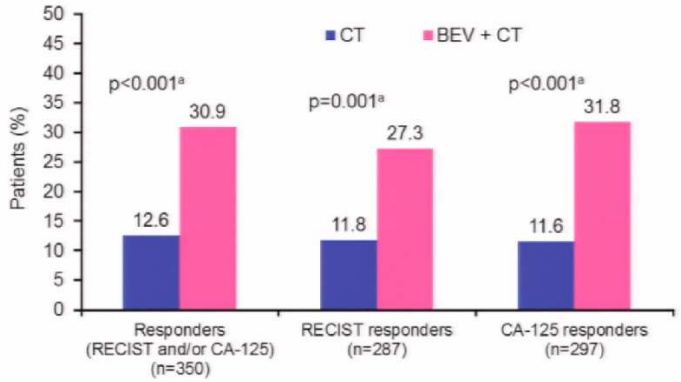
AURELIA

Platinum-resistant OC
・≤2 prior anticancer regimens
・No history of bowel obstruction/abdominal fistula

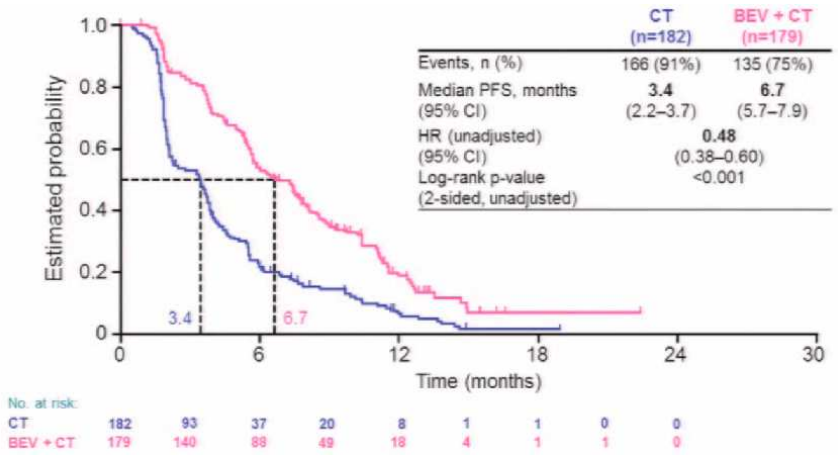


Chemotherapy options (physician's choice)
・Paclitaxel 80mg/m2 weekly
・Topotecan 4mg/m2 d1,8,15 q4w
・PLD 40mg/m2 d1 q4w

Response Rate



Progression-Free Survival



J Clin Oncol 2014; 32: 1302-1308

卵巣癌に対する治療

初回化学療法

Dose-dense TC

TC+ベバシズマブ

BRCA1/2遺伝子変異陽性に対するオラパリブ維持療法、HRD陽性に対するオラパリブ＋ベバシズマブ維持療法、初回治療後ニラパリブ維持療法

再発後化学療法

Platinum-Sensitive relapse

Platinumを含む2剤併用療法

Platinum-Resistant relapse

Non-platinum レジメン 単剤

ベバシズマブ上乗せの有効性

プラチナ感受性再発に対するオラパリブ維持療法もしくはニラパリブ維持療法

HRD陽性3~4前治療歴のあるプラチナ感受性再発に対するニラパリブ療法

今後の展望

- 卵巣がんに対する免疫チェックポイント阻害薬の有効性は、これまで単剤（Nivolumab, NINJA trial）、化学療法との併用（Avelumab, JAVELIN 100, 200）、血管新生阻害薬との併用（Atezolizumab, IMAGYN 050）で見出されていない。
- 免疫チェックポイント阻害薬とPARP阻害薬との併用療法による効果が期待される。

1st lineで現在進行中の免疫チェックポイント阻害薬とPARP阻害薬の併用試験

Trial	Study arm
ENGOT Ov43	TC + Pembrolizumab + Olaparib
ENGOT Ov44 (FIRST)	TC + TSR042 + Niraparib
ENGOT Ov45 (ATHENA)	Maintenance after TC: Rucaparib + Nivolumab
ENGOT Ov46 (DUO-O)	TC + Bev + Durvalumab + Olaparib

Mirvetuximab soravtansine (MIRV)

国内未承認・適応外

SORAYA trial
Single arm phase 3

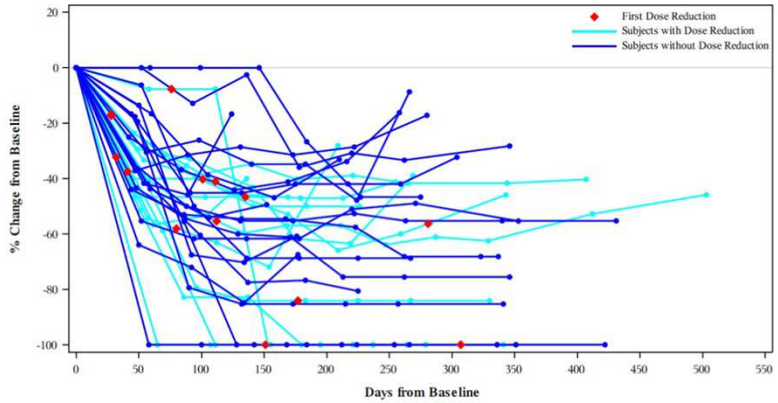
- Platinum-resistant ovarian cancer 1-3 prior therapies
- Prior bevacizumab required; prior PARP inhibitor allowed
- High FRα membrane staining with IHC-PS2+ scoring (>/= 75% of cells staining positive, with >/= 2+ staining intensity)

→ MIRV 6mg/kg, adjusted ideal body weight IV on day1 of 3-week cycle

N=60

Primary endpoint: ORR

End Point	Investigator-Assessed (N=105)	BICR-Assessed (N=96)
Response rates[a]		
ORR, n (%)[b]	**34 (32.4)**	**29 (30.2)**
95% CI[c]	[23.6-42.2]	[21.3-40.4]
Best overall response, n (%)		
Complete response	**5 (4.8)**	**6 (6.3)**
Partial response	29 (27.6)	23 (24.0)
Stable disease[d]	48 (45.7)	54 (56.3)
Progressive disease	20 (19.0)	9 (9.4)
Not evaluable	3 (2.9)	4 (4.2)
Duration of response / time to response[a]		
mDOR[e], months	**6.9**	**NR**
95% CI	[5.6, 9.7]	[5.0, NR]
Median time to response, months (range)	**1.5** (1.0-5.6)	**1.4** (1.0-5.4)



TRAEs, n (%)	All Grades	Grade 3	Grade 4
Patients with any event	**91 (86)**	**30 (29)**	**1 (1)**
Blurred vision	43 (41)	6 (6)	0 (0)
Keratopathy	31 (29)	8 (8)	1 (1)
Nausea	31 (29)	0 (0)	0 (0)
Dry eye	26 (25)	2 (2)	0 (0)
Fatigue	25 (24)	1 (1)	0 (0)
Diarrhea	23 (22)	2 (2)	0 (0)
Asthenia	16 (15)	1 (1)	0 (0)
Photophobia	14 (13)	0 (0)	0 (0)
Peripheral neuropathy	14 (13)	0 (0)	0 (0)
Decreased appetite	14 (13)	1 (1)	0 (0)
Vomiting	12 (11)	0 (0)	0 (0)
Neutropenia	14 (13)	2 (2)	0 (0)

AEs, adverse advents; TRAEs, treatment-related adverse events.

mPFS
・investigator-assessed: 4.3 months
・BICR: 5.5 months

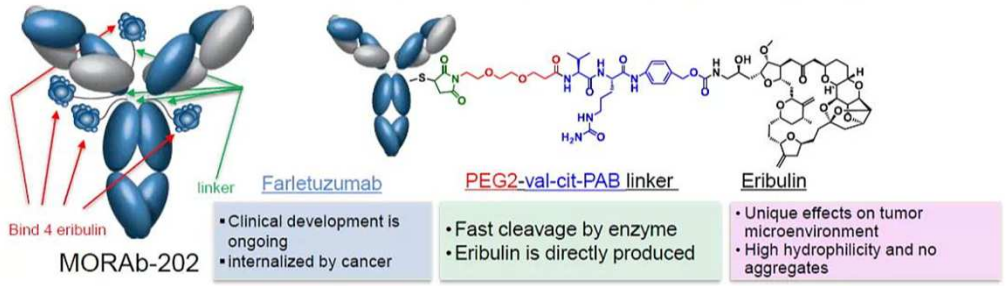
mOS 13.8 months

Ursula A. Matulonis et al. ASCO annual meeting 2022 Abstr5512

MORAb-202

国内未承認・適応外

Phase 1 trial



Key Inclusion Criteria (Ovarian cohort)

- Measureable disease by RECIST v1.1 (expansion phase only)
- ≤ 2 regimens of chemotherapy after diagnosis of PROC (expansion phase only)
- ECOG PS of 0 or 1
- Patients with HGS PROC without archival tumor samples were required to be FRα positive at the central laboratory
- Patients with other histology were required to be FRα positive confirmed at the central laboratory using tumor samples from resected specimens
- Adequate organ function

Dose escalation phase
Dosing: MORAb-202 IV Q3W (levels of 0.3, 0.45, 0.68, 0.9, 1.2 mg/kg)

1.2 mg/kg (n = 3)
0.9 mg/kg (n = 3)
0.9 mg/kg (n = 4)
0.68 mg/kg (n = 3)
0.45 mg/kg (n = 3)
0.3 mg/kg (n = 3)

PROC expansion phase[a]
2 Dosing cohorts, both IV Q3W

Cohort 1[b] (MORAb-202 0.9 mg/kg)

Safety assessment of Cohort 1
Review of pneumonitis/ILD performed by an external ILD expert committee

Cohort 2[b] (MORAb-202 1.2 mg/kg)

Primary Objective
- Determine safety and tolerability of MORAb-202

Selected Secondary Objectives
- Determine the recommended dose of MORAb-202 for future studies
- Pharmacokinetic characterization
- ORR, DCR, CBR
- DOR, PFS, OS (expansion phase only)

Study Assessments
- Tumor assessments were performed by investigator using RECIST v1.1
- All AEs and serious AEs were monitored and recorded
- Statistics for dose escalation used an accelerated mTPI method

	N	PFS (months)	ORR (%)	ORR FRα<50%)	ORR FRα>50%
Cohort 1 (0.9mg/kg)	24	6.7	25.1	2/6	4/18
Cohort 2 (1.2mg/kg)	21	8.2	52.4	1/2	10/19

Parameter, n (%)	Cohort 1: MORAb-202 0.9 mg/kg n = 24	Cohort 2: MORAb-202 1.2 mg/kg n = 21
Any ILD/Pneumonitis event	9 (37.5)	14 (66.7)
Severity: Grade 1	8 (33.3)	6 (28.6)
Grade 2	1 (4.2)	7 (33.3)
Grade 3	0	1 (4.8)
Grade 4	0	0
Grade 5	0	0
Serious respiratory event[a]	2 (8.3)	3 (14.3)
ILD/Pneumonitis event leading to MORAb-202:		
Discontinuation	1 (4.2)	5 (23.8)
Dose reduction	5 (20.8)	9 (42.9)
Dose interruption	1 (4.2)	4 (19.0)

[a]Includes pneumonitis, ILD, dyspnea.
Data cutoff date: October 31, 2021.
ILD, interstitial lung disease; TEAEs, treatment-emergent adverse events.

Nishio S et al. ASCO annual meeting 2022 Abstr5513

子宮体がんの診断と治療

子宮体がん

- 罹患数(2019)/死亡数(2020) 17880人/2644人
- 罹患数は、40歳代後半から増加し、50歳代から60歳代にピークを迎え、その後減少する
- リスクファクター：肥満、未経産、不妊傾向、更年期障害に対するエストロゲン補充療法、タモキシフェン内服など。遺伝性（リンチ症候群）
- 臨床症状：不正性器出血（90%の患者にみられ、早期発見されやすい）、過多月経

病理組織分類

- 上皮性
  類内膜腺癌 (80%)
  漿液性腺癌 (10%)
  明細胞腺癌 (4%)　など
- がん肉腫
- 肉腫
  平滑筋肉腫
  内膜間質性肉腫　など

臨床進行期分類（FIGO2008）

I期：　子宮体部に限局

A：子宮筋層浸潤1/2以内

B：子宮筋層浸潤1/2をこえる

II期：　子宮頸部間質に浸潤

III期：　癌が子宮外に広がるが、小骨盤腔をこえていないもの、 または所属リンパ節転移のあるもの

A：子宮表面の漿膜に達する、付属器に浸潤

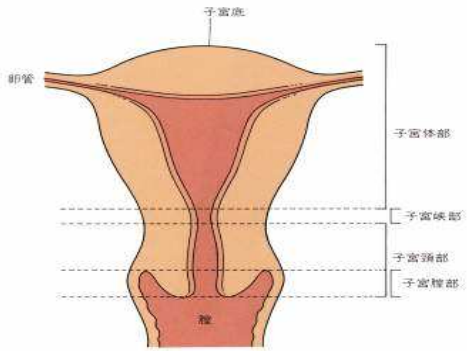
B：腟、子宮傍組織に浸潤

C：骨盤リンパ節、傍大動脈リンパ節転移節転移

IV期：　癌が小骨盤腔をこえているか、明らかに膀胱または 腸粘膜を侵すもの

A：膀胱、腸粘膜への浸潤

B：腹腔内、鼠径リンパ節転移を含む遠隔転移



再発リスクと術後療法

	リスク因子	術後治療法
低リスク群	・類内膜腺癌Grade1あるいはGrade2で筋層浸潤1/2以内 ・頚部浸潤なし ・腹腔細胞診陰性 ・脈管侵襲なし ・遠隔転移なし	なし
中リスク群	・類内膜腺癌Grade3で筋層浸潤1/2以内 ・類内膜腺癌で筋層浸潤1/2を超える ・頚部浸潤あり ・腹腔細胞診陽性 ・脈管侵襲あり ・漿液性腺癌、明細胞腺癌あるいは未分化癌 ・遠隔転移なし	No consensus
高リスク群	・付属器・漿膜・基靱帯進展あり ・膣壁浸潤あり ・骨盤あるいは傍大動脈リンパ節転移あり ・膀胱・直腸浸潤あり ・遠隔転移あり	化学療法

術後放射線治療 vs. 術後化学療法

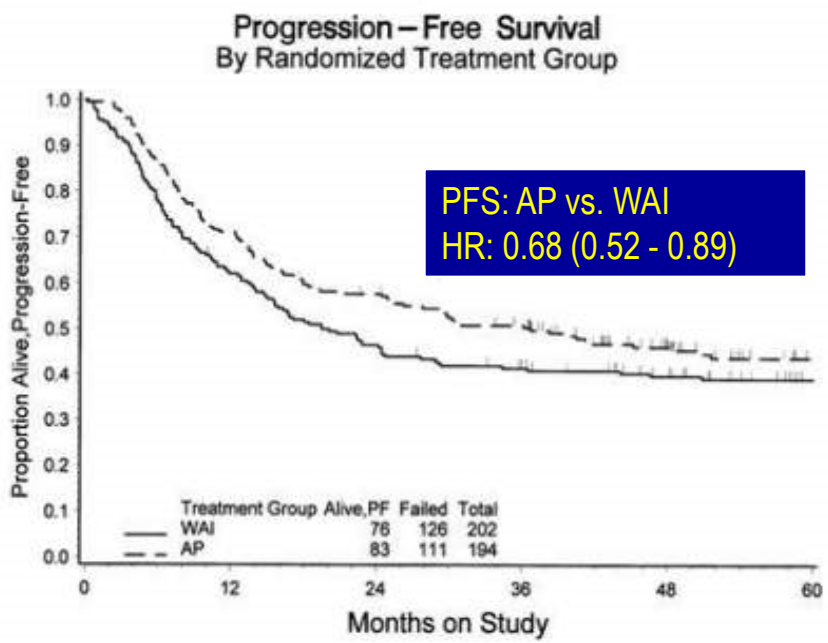
GOG122

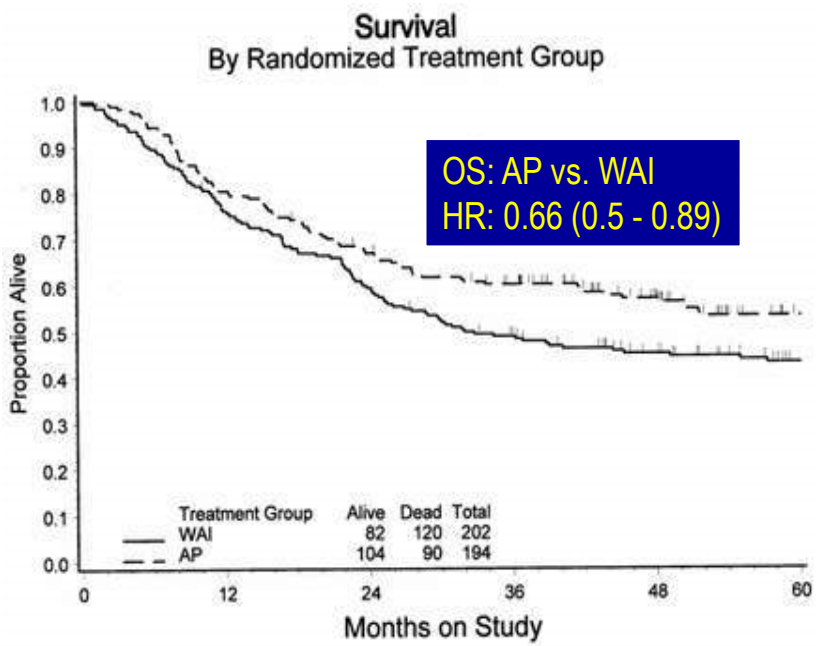
Stage III, IV
Residual disease < 2cm

R

Whole Abdominal RT (30Gy)

ADM 60mg/m2
CDDP 50mg/m2 q21d 8 cycles





J Clin Oncol 2006; 24: 36

JGOG2043

Endometrial cancer at a high risk of recurrence

- stage I, II with G2/G3 and a myometrial invasion >1/2
- stage III
- stage IV with no metastatic lesions beyond the abdominal cavity

Adjustment factors:

- FIGO surgical stage (I, II vs III, IV)
- histologic grade (G1, G2 vs G3, others)

RANDOMIZATION

Standard arm: AP

A: Doxorubicin 60 mg/m^2, I.V., day 1
P: Cisplatin 50 mg/m^2, I.V., day 1
every 21 days for 6 cycles

Experimental arm 1: DP

D: Docetaxel 70 mg/m^2, I.V., day 1
P: Cisplatin 60 mg/m^2, I.V., day 1
every 21 days for 6 cycles

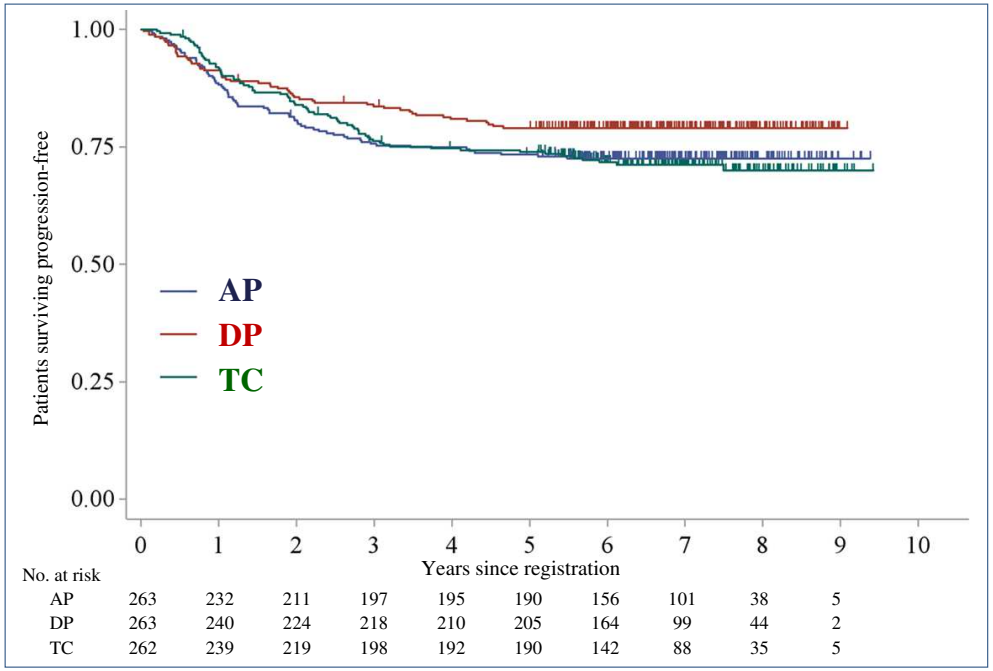
Experimental arm 2: TC

T: Paclitaxel 180 mg/m^2, I.V., day 1
C: Carboplatin AUC 6, I.V., day 1
every 21 days for 6 cycles

Primary endpoint: Progression-free survival
Secondary endpoint: Overall survival, Adverse events ,tolerability

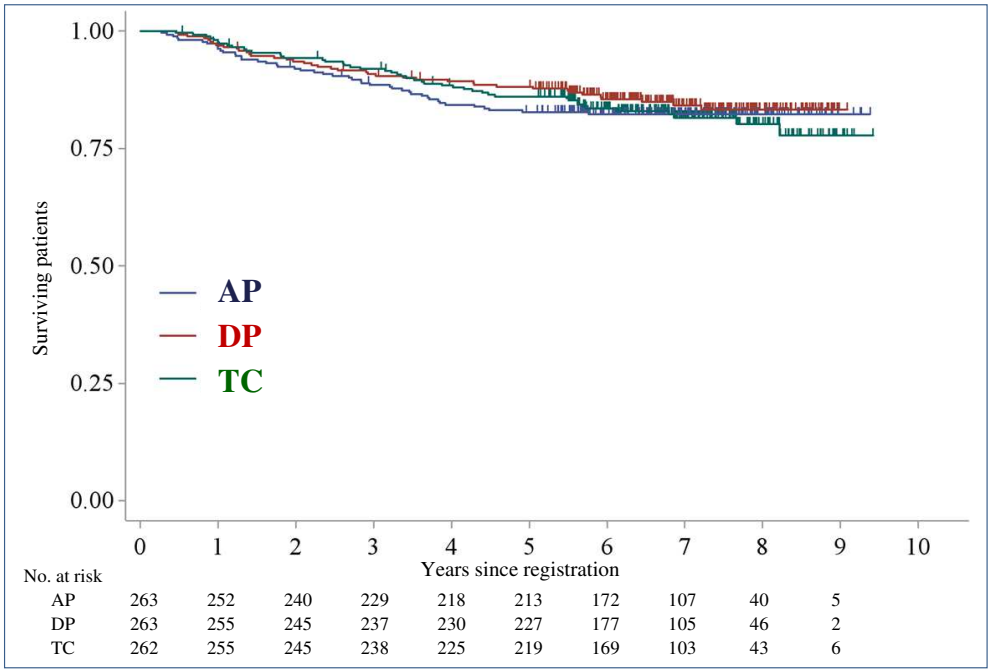
JGOG2043

Progression-free survival



Arm	N	Events	**5-yr PFS**	P value
AP	263	72	**74.5%**	
DP	263	55	**80.5%**	P=0.1246
TC	262	75	**74.3%**	

Overall survival



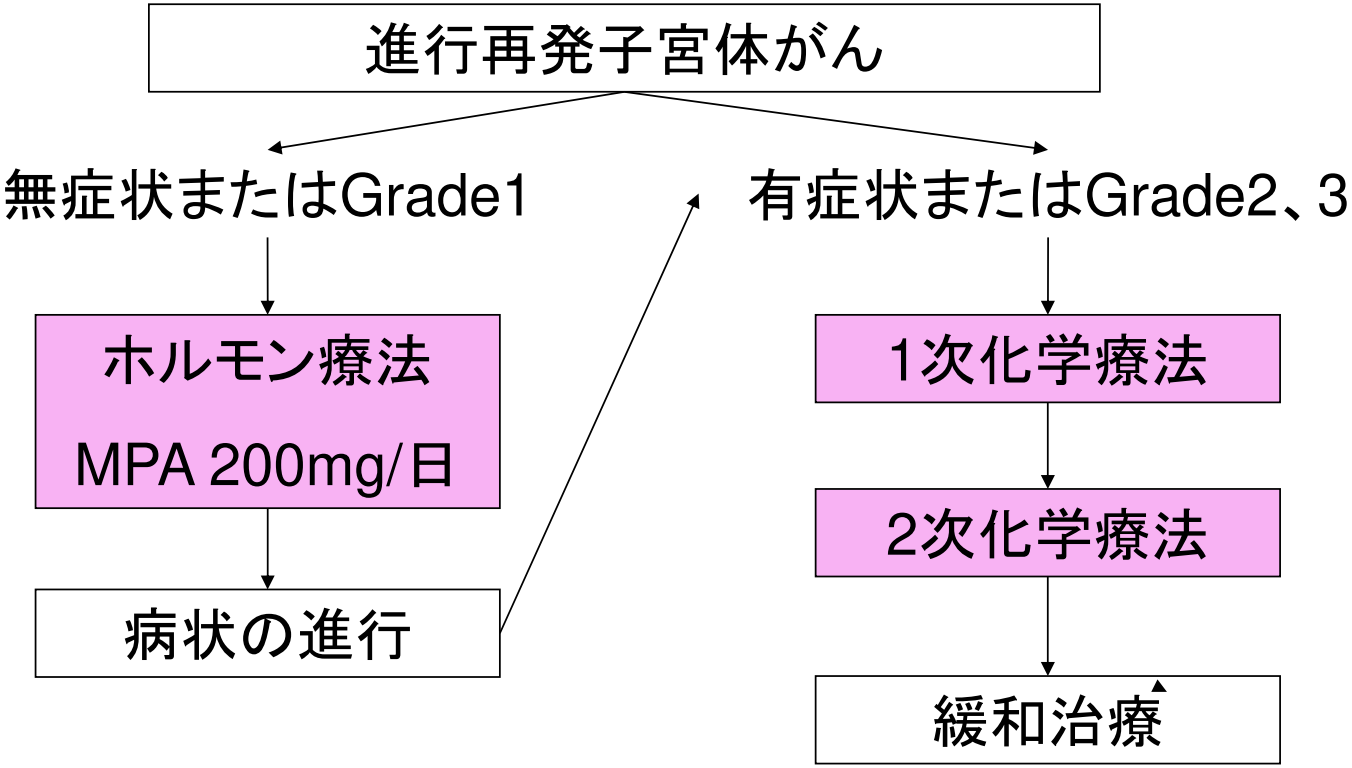
Arm	N	Events	**5-yr OS**	P value
AP	263	46	**83.9%**	
DP	263	40	**88.9%**	P=0.6734
TC	262	47	**88.0%**	

American Society of Clinical Oncology 2017 Annual Meeting

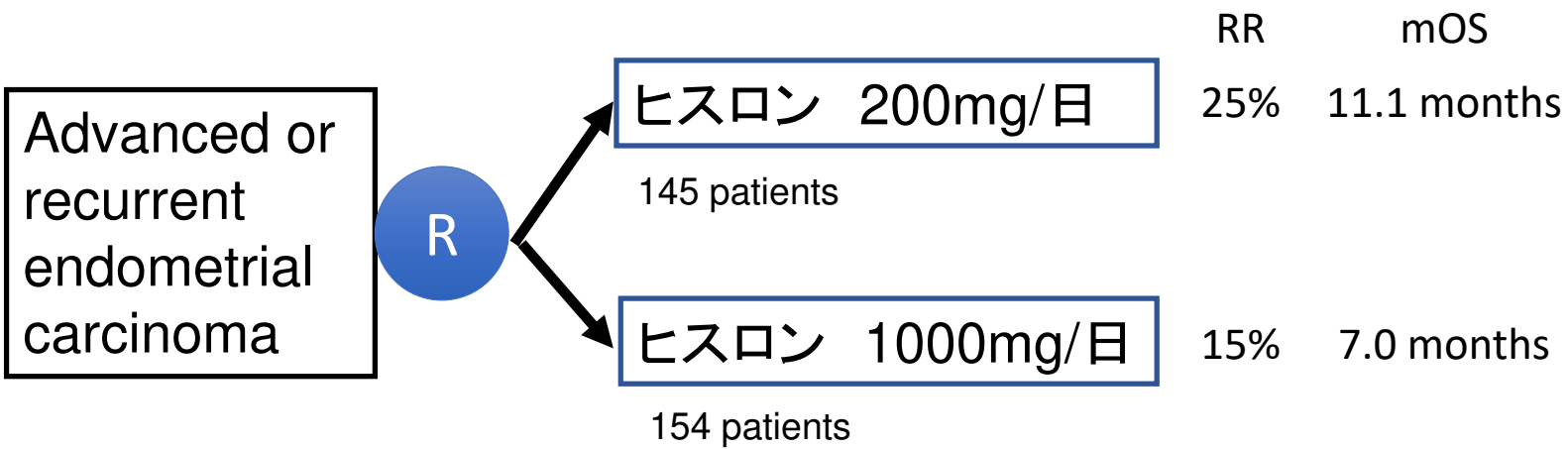
JGOG2043の解釈

- Negative study
- AP療法はDP療法、TC療法に比べ血液毒性が高く、tolerabilityも他レジメンに比べ低い。
- DP療法は毒性がマイルド（悪心嘔吐）、神経毒性も低い。しかし、全くレジメンとして受け入れがたい。
- TC療法はAP療法に比べtolerable,神経毒性はAP療法よりも高い。Globalに受け入れられている治療
- 現在、多くの施設で術補助療法の標準治療はTC療法が選択されている。

進行再発子宮体がんの治療



MPA療法　GOG81



Grade	Response		MST (mo.)
	No.	%	
1	22/59	37	18.8
2	26/113	23	7.5
3	12/127	9	6.9

J Clin Oncol 1999; 17: 1736

進行再発子宮体がん初回治療におけるTC療法

GOG209

- Surgical stage III/IV or recurrent
- Measurable disease

R

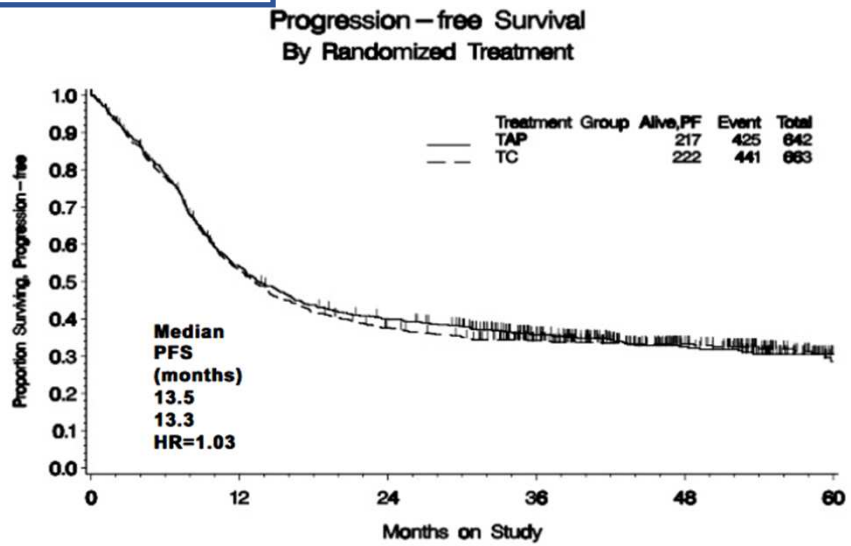
TAP療法

ADM 45mg/m^2
CDDP 50mg/m^2
Paclitaxel 160mg/m^2
q 3wk × 7 cycles

TC療法

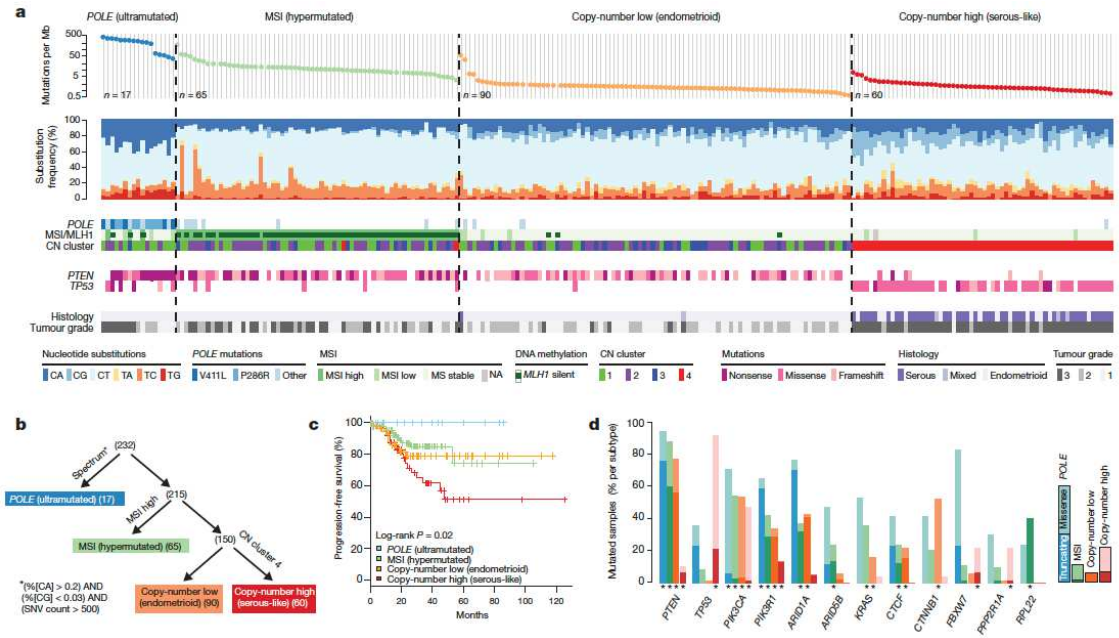
PTX 175mg/m^2
Carboplatin AUC 6
Q 3wk × 7 cycles

- Response rate 51% in each arm
- mPFS 13.5 months vs. 13.3 months (HR=1.03)
- mOS 40 months vs. 37 months
- TC is less toxic than TAP: sensory neuropathy (19 vs. 26%), thrombocytopenia (12 vs. 23%), emesis (4 vs. 7%)



LBA2. Presented at the 2012 Society of Gynecologic Oncology Annual Meeting, Austin, TX.

子宮体がんにおけるmolecular subtype

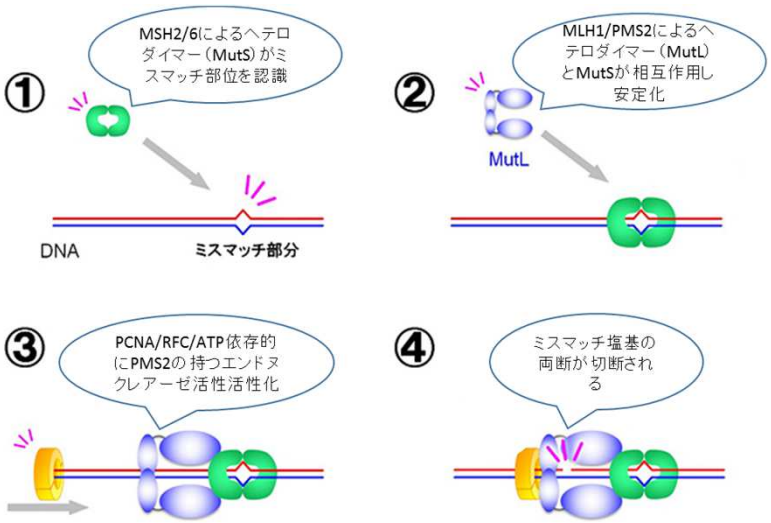


subtype	distribution	characteristics
POLE ultramutated	7%	• Endometrioid grade 3 • Somatic inactivating mutations in POLE exonuclease (POLE; a catalytic subunit of DNA polymerase epsilon involved in nuclear DNA replication and repair) • Very high mutation rates • Mutation: PTEN, PIK3CA, PIK3R1, FBXW7, ARID1A, KRAS, ARID5B
MSI hypermutated	28%	• Endometrioid carcinoma with microsatellite instability, frequently with MLH-1 promotor methylation • High mutation rate • Mutation: PTEN, RPL22, KRAS, PIK3CA, PIK3R1, ARID1A
Copy-number low	39%	• Endometrioid grade 1-3 • Low mutation rate • Mutation: PTEN, CTNNB1, PIK3CA, PIK3R1, ARID1A
Copy-number high	26%	• Serous and mixed endometrioid • Low mutation rate • TP53, PPP2R1A, PIK3CA • Showing chromosomal instability, with recurrent amplifications (MYC, ERBB2, CCNE1, FGFR3, SOX17)

Nature 2013; 497: 67-73

Microsatellite instability (MSI)

Microsatellite：DNA内で1-数塩基の塩基配列が反復される部位



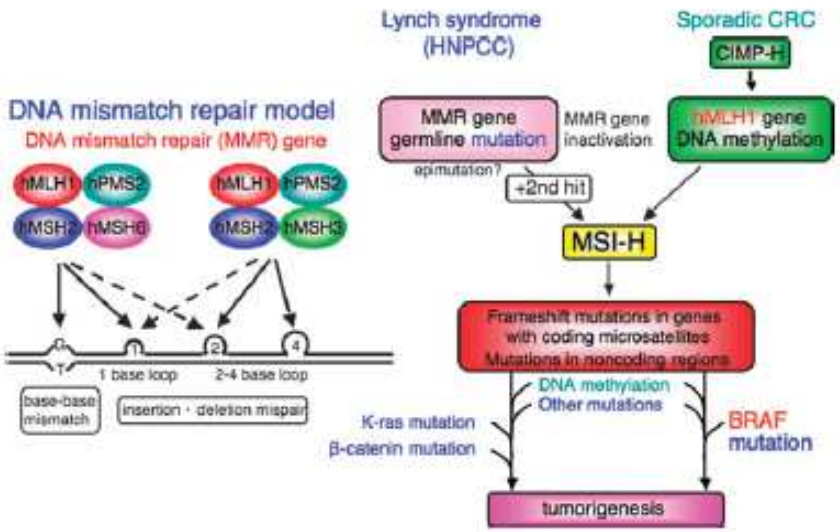
MMR遺伝子	遺伝子座	Exon数	コード蛋白のアミノ酸数
MLH1	3p21.3	19	756
MSH2	2p22-p21	16	934
PMS2	7p22	15	862
MSH6	2p16	10	1360

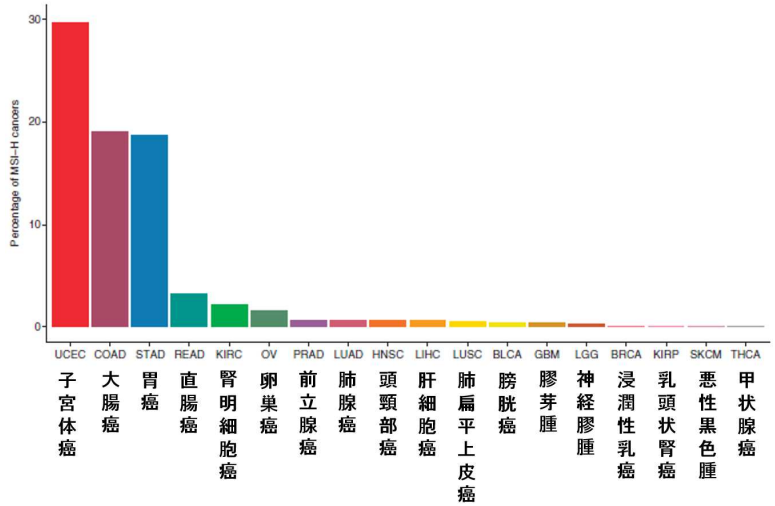
- DNA複製時に反復回数のエラーが生じやすい
- DNAミスマッチ修復(Mismatch repair; MMR)機能低下により腫瘍部位と非腫瘍部位で反復回数に違いが生じる現象を、マイクロサテライト不安定性(MSI)という
- 主なMMR遺伝子として、MLH1, MSH2, PMS2, MSH6がある

Mol Cell 2004; 15: 31-41.

MSIと発癌

- MSIは、主にMMR遺伝子の生殖細胞系列変異を原因とするLynch症候群の他、主にMLH1遺伝子のプロモータ領域の後天的なメチル化を原因とする散発性大腸がん、子宮体がん等、様々な癌種に認められる[1]。
- MSIが生じ、exon内の反復配列に異常が起こると腫瘍抑制、細胞増殖、DNA修復やアポトーシスなどに関与する遺伝子にフレームシフト変異が起こり、癌化に結びつくと考えられている。
- 子宮体癌の約5%にLynch症候群が、また約20-35%にはMMRに関連するgermline/somatic mutation, epigenetic changeが発生する[2]。





1. Carcinogenesis 2008; 29: 673
2. Nat Med 2016; 22: 1342–1350

子宮体癌に対する免疫チェックポイント阻害薬

Unselected or pMMR population

Study	Patient population	Outcome
Keynote 28: Pembrolizumab (n=28)[1]	Advanced stage or metastatic PD-L1+ endometrial cancer	ORR 13%
PHAEDRA trial: Durvalumab (pMMR, n=36)[2]	Advanced stage or metastatic endometrial cancer	ORR in pMMR 3%
GARNET study: Dostarlimab (n=94)[3]	Previously treated, recurrent advanced stage endometrial caner	ORR in pMMR 20.3%
Avelumab (pMMR, n=16)[4]	Advanced stage or metastatic endometrial cancer	ORR 6.25%

1. J Clin Oncol 2017; 35: 2535
2. ASCO Annual Meeting 2019 #5501
3. SGO Annual Meeting on women's cancer 2019
4. J Clin Oncol 2019; 37: 2786

子宮体癌に対する免疫チェックポイント阻害薬

dMMR population

Study	Patient population	Outcome
Keynote 158: Pembrolizumab (n=49)[1]	Advanced stage or metastatic dMMR endometrial cancer	ORR 57.1%
PHAEDRA trial: Durvalumab (dMMR, n=35)[2]	Advanced stage or metastatic endometrial cancer	ORR 43%
GARNET study: Dostarlimab (n=70)[3]	Previously treated, recurrent advanced stage endometrial caner	ORR 43%
Avelumab (dMMR, n=15)[4]	Advanced stage or metastatic endometrial cancer	ORR 26.7%

1. J Clin Oncol 2017; 35: 2535
2. ASCO Annual Meeting 2019 #5501
3. JAMA Oncol 2020; 6: 1
4. J Clin Oncol 2019; 37: 2786

KEYNOTE-775 Lenvatinib + Pembrolizumab vs. chemotherapy

Key eligibility criteria

- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- 1 Prior platinum-based CT[a]
- ECOG PS 0-1
- Tissue available for MMR testing

Stratification factors

MMR status (pMMR vs dMMR) and further stratification within pMMR by:

- Region (R1: Europe, USA, Canada, Australia, New Zealand, and Israel, vs R2: rest of the world)
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Y vs N)

R (1:1)

Lenvatinib
20 mg PO QD
+
Pembrolizumab[b]
200 mg IV Q3W

Treat until progression or unacceptable toxicity

Doxorubicin
60 mg/m^2 IV Q3W[c]
or
Paclitaxel
80 mg/m^2 IV QW
(3 weeks on/1 week off)

Primary endpoints

- PFS by BICR
- Overall survival

Secondary endpoints

- ORR
- HRQoL
- Pharmacokinetics
- Safety

Key exploratory endpoint

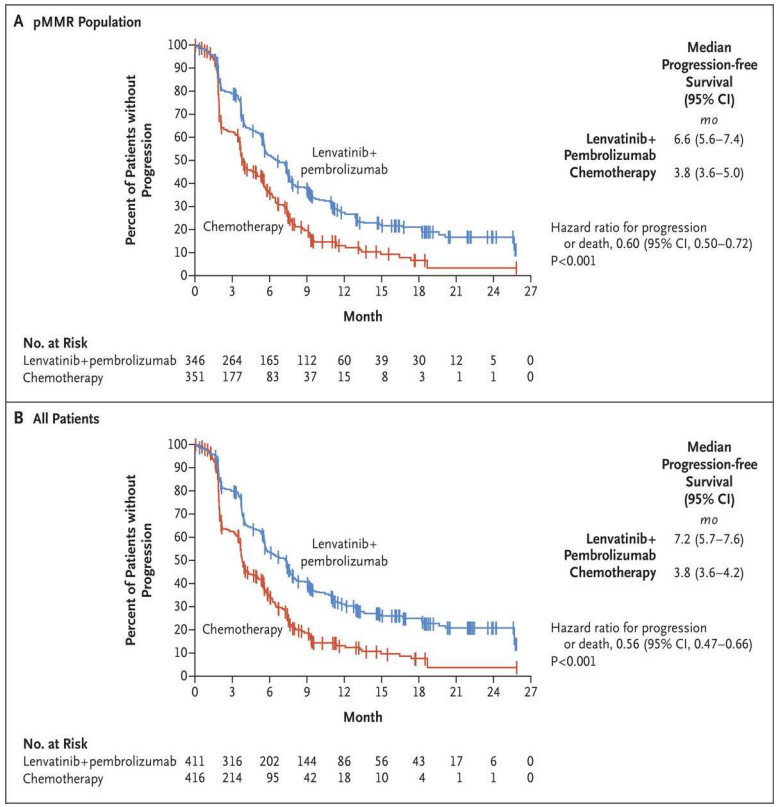
- Duration of response

N Engl J Med 2022; 386: 437-448

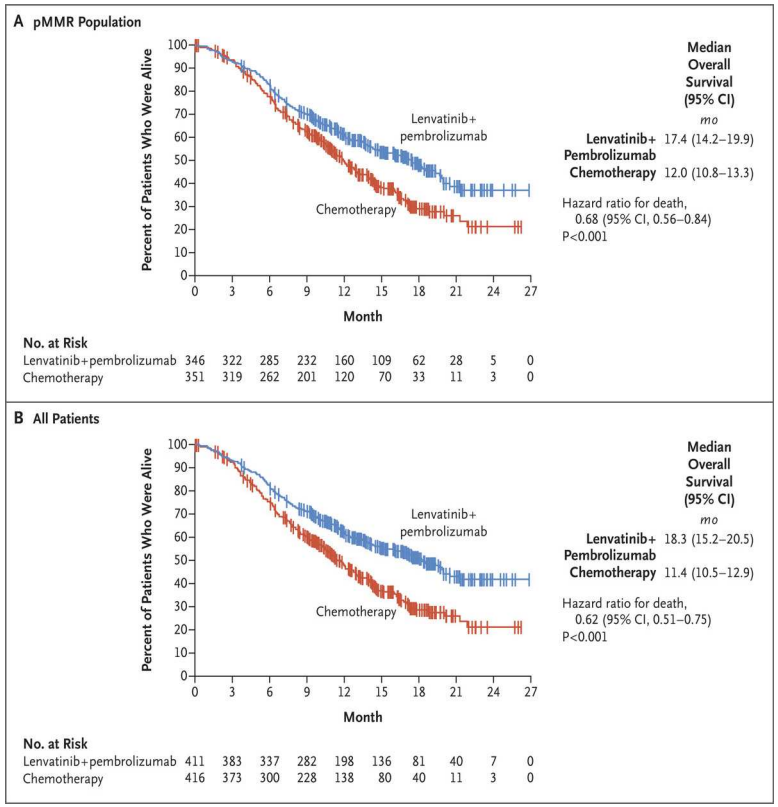
KEYNOTE-775 Lenvatinib + Pembrolizumab vs. chemotherapy

	pMMR		All-comers	
	LEN + pembro	TPC	LEN + pembro	TPC
Patients, n	346	351	411	416
Objective response rate, % (95% CI)	30.3 (25.5–35.5)	15.1 (11.5–19.3)	31.9 (27.4–36.6)	14.7 (11.4–18.4)
Difference vs TPC, %	15.2	--	17.2	--
P-value	< 0.0001		< 0.0001	

Progression-free Survival

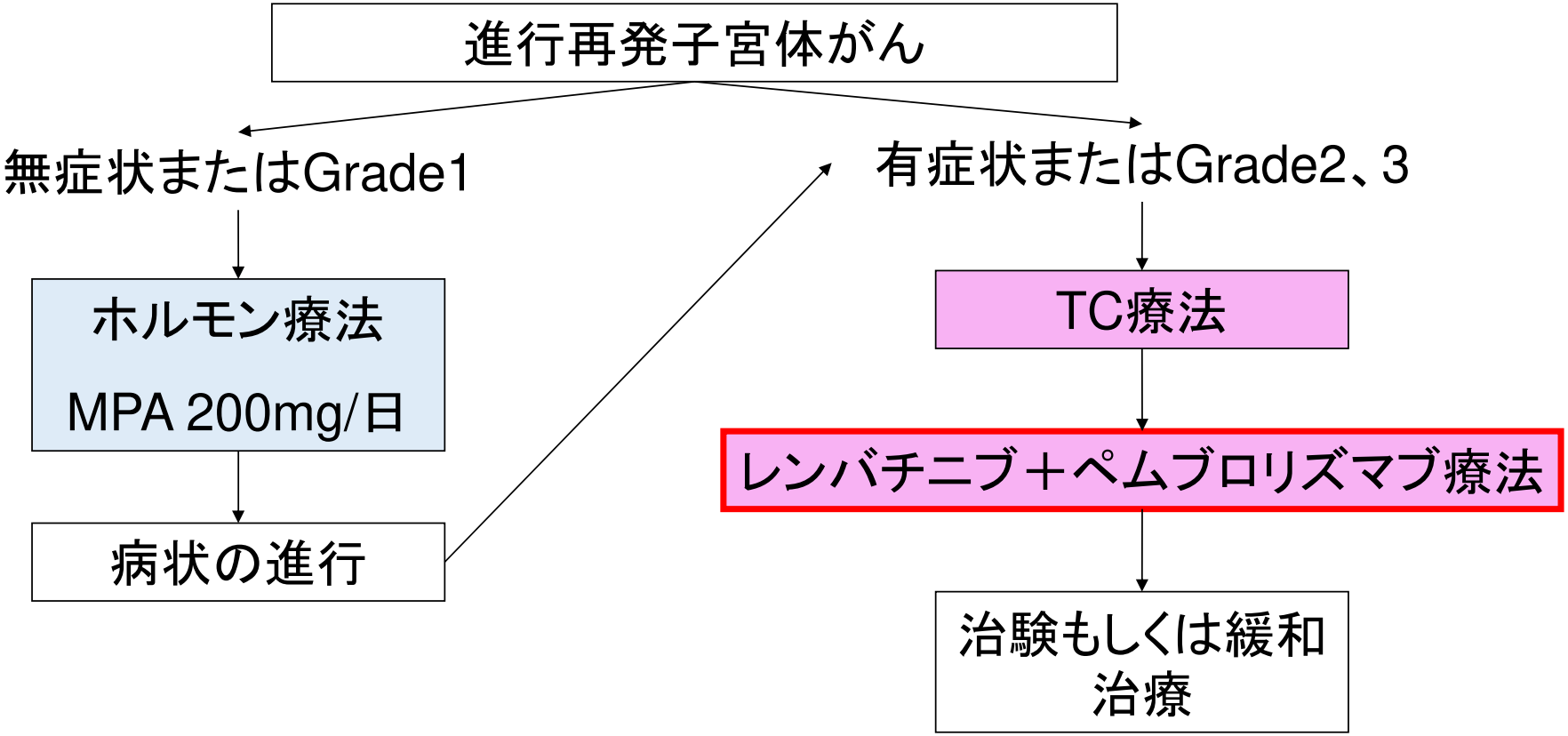


Overall Survival



N Engl J Med 2022; 386: 437-448

進行再発子宮体がんの治療



Key Clinical Studies in Advanced, Recurrent, or Metastatic Endometrial Cancer

Trial name/ID	Disease/treatment setting[a]	Brief description	Primary completion
ENGOT-En6	Recurrent Endometrial Cancer; MSI stratification	Dostarlimab vs Physician's Choice Chemotherapy with crossover	Initiating 2019
NRG-GY018	Treatment naïve for stage III–IV EC or no prior treatment for recurrent disease; MSI stratification	Pac/carbo+pembro/pembro maintenance vs Pac/carbo/placebo/placebo maintenance	Initiating 2019
KEYNOTE-775	Advanced, recurrent, or metastatic EC; after 1 prior platinum chemo	Lenvatinib + pembrolizumab vs TPC	January 2022
LEAP-001	Treatment naïve for stage III–IV EC or no prior treatment for recurrent disease	Lenvatinib + pembrolizumab vs Pac/Carbo	April 2023
AtTEnd	Treatment naïve for stage III–IV EC or no prior treatment for recurrent disease	Atezolizumab in combination with paclitaxel + carboplatin	July 2021
ROCSAN	Progressive or recurrent endometrial carcinosarcoma; failure after ≥1 prior platinum-containing regimen	Dostarlimab + niraparib or niraparib alone compared to chemo after 1L chemo	January 2023

国内未承認の情報が含まれていますが、その使用を推奨しているものではありません。
各薬剤の効能・効果、用法・用量については日本の添付文書をご参照いただき、適正使用にご留意ください。

子宮頸がんの診断と治療

子宮頸がん

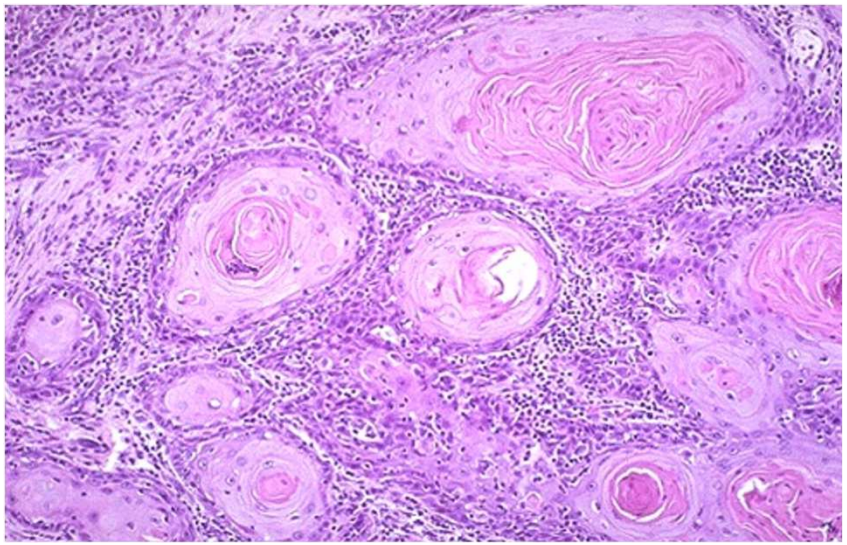
- 罹患数 (2019)/死亡数 (2020)　10879人/2887人
- 20歳代後半から30歳代後半まで罹患数が増加したのち横ばいとなり、70歳代後半から再び増加する。
- ヒトパピローマウィルス(papilloma virus, HPV)の持続感染による発症。頸がん（扁平上皮癌、腺癌）患者の90%以上からHPV-DNAが検出される。
- リスクファクター：多産、経口避妊薬、喫煙、低年齢での初性交、複数のセックスパートナーの存在、低所得層

診断

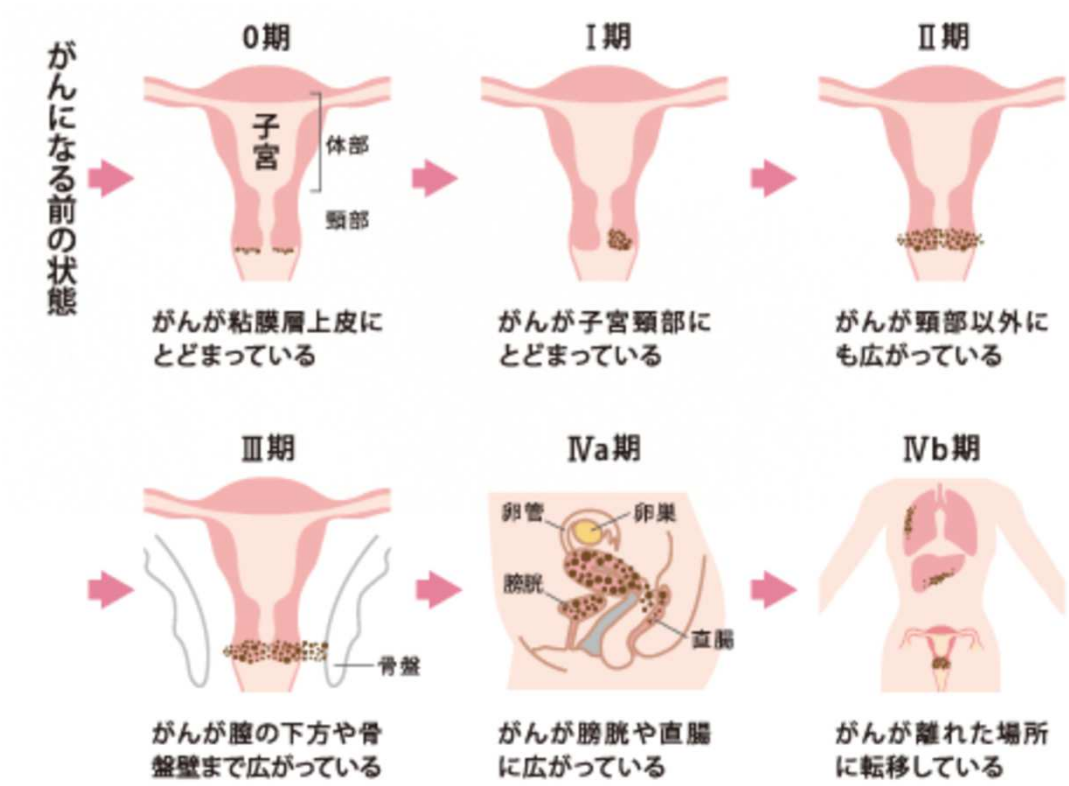
- 症状：不正性器出血、性交後出血、異常帯下
- 検査：内診、子宮鏡、CT, MRI, 超音波検査
- 腫瘍マーカー：SCC, CYFRA, CEAなどが用いられるが、腫瘍の存在診断、治療効果判定、増悪の診断ともに腫瘍マーカー単独での有用性は示されていない。
- 確定診断は生検（コルポスコピー下、診断的円錐切除術）で行われる

病理組織分類

- 扁平上皮癌　　約80%
- 腺癌　　15%
- 腺扁平上皮癌　　3-5%
- その他(小細胞癌など)



臨床進行期分類（FIGO2008）



Stage IB, II

- 日本では広汎子宮全摘出術が推奨されるが、欧米では根治的放射線療法が、無再発生存期間や全生存期間において手術療法と差がないとのエビデンスがあり、手術療法と放射線療法は並列した選択肢としている[1]。
- 術前化学療法の有用性は示されていない[2]。

1. Lancet 1997; 350: 535
2. Gynecol Oncol 2007; 106: 362

術後中間リスクに対する放射線療法

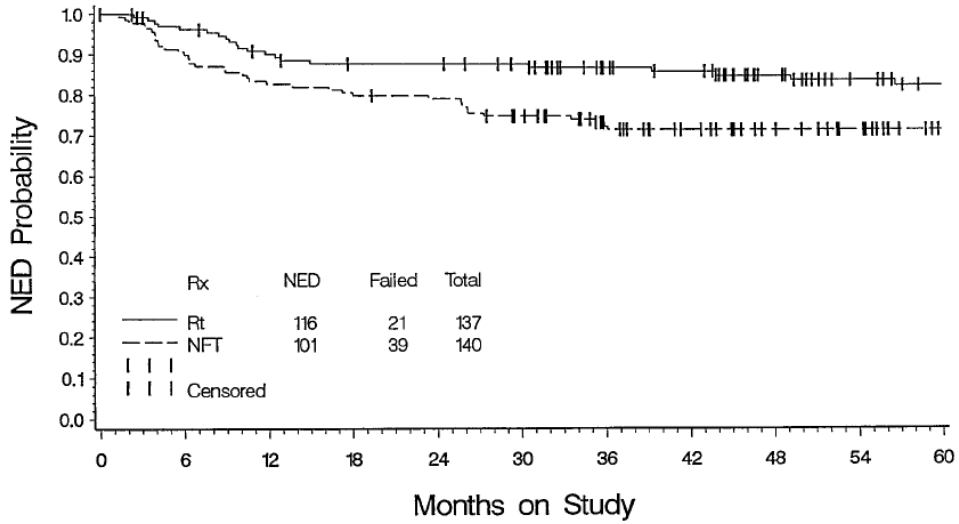
- Stage IB cervical cancer who received radical hysterectomy and lymphadenectomy
- LN mets negative
- At least 2 of 3 factors: 1) >1/3 stromal invasion, 2) lv+, 3) large tumor volume

R → Pelvic RT 46-50.4Gy
R → Observation

Eligibility Criteria

CLS[a]	Stromal invasion	Tumor size
Positive	Deep 1/3	Any
Positive	Middle 1/3	≥2 cm
Positive	Superficial 1/3	≥5 cm
Negative	Deep or middle 1/3	≥4 cm

[a] Capillary lymphatic space tumor involvement.



Gynecol Oncol 1999; 73: 177

術後高リスクに対する放射線化学療法

- Stage IA, IB and IIA cervical cancer who received radical hysterectomy and lymphadenectomy
- +pelvic lymph node mets, +parametrial involvement, or +surgical margin

R → CCRT (FP+RT49.3Gy)

R → RT 49.3Gy

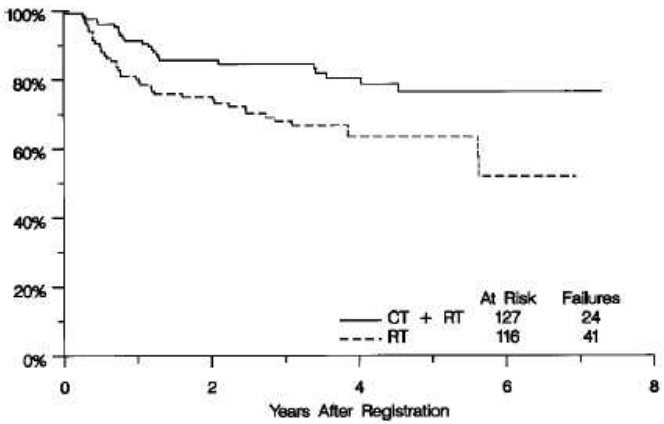


Fig 1. Progression-free survival for 127 patients randomized to receive CT + RT and for 116 patients randomized to receive RT alone.

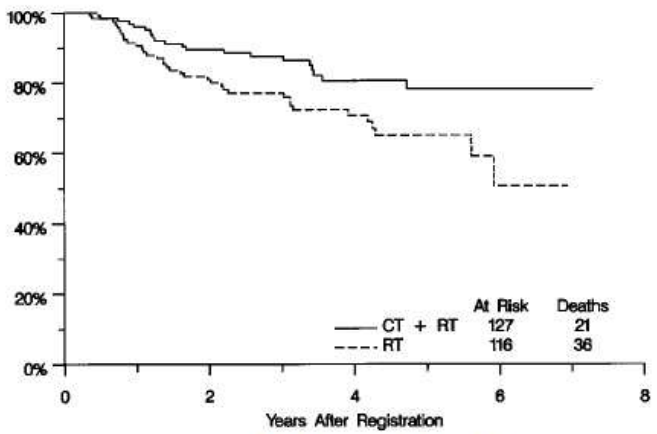


Fig 2. Overall survival for 127 patients randomized to receive CT + RT and for 116 patients randomized to receive RT alone.

J Clin Oncol 2000; 18: 1606

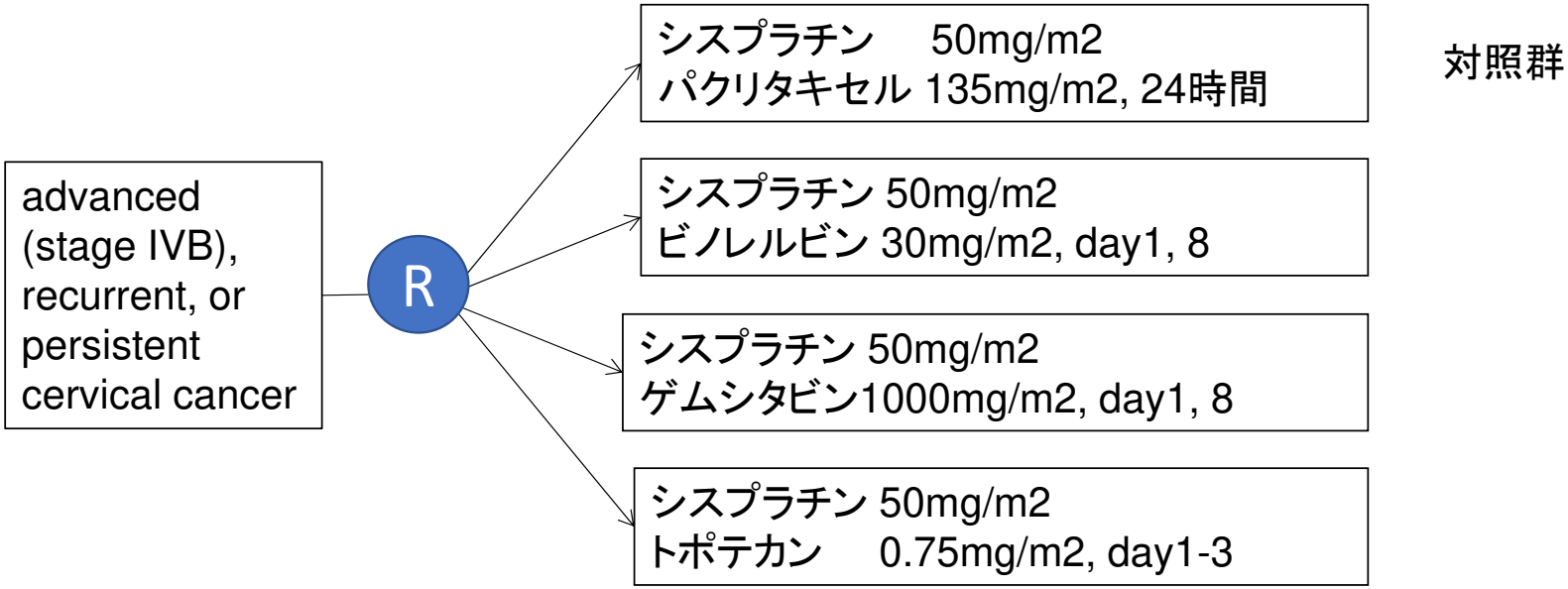
Stage III, IVA

- 2001年に報告されたメタアナリシスで、あらゆる試験において、シスプラチン併用レジメンを用いた同時化学放射線療法が放射線単独と比較し有意に生存期間を延長することが示された（HR 0.7, P<0.0001)[1]。
- FP療法もしくはシスプラチン単独療法（40mg/m2 weekly)が用いられる[2,3,4]。

日本婦人科腫瘍学会　子宮頸癌治療ガイドライン　2017年度版

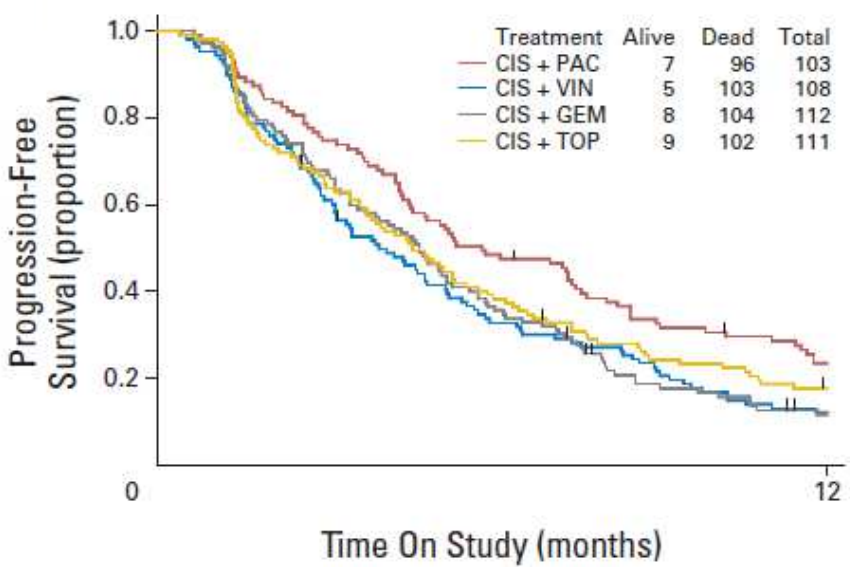
1. Lancet 2001; 358: 781
2. J Clin Oncol 2008; 20: 966
3. N Engl J Med 1999; 340: 1137
4. N Engl J Med 1999; 340: 1144

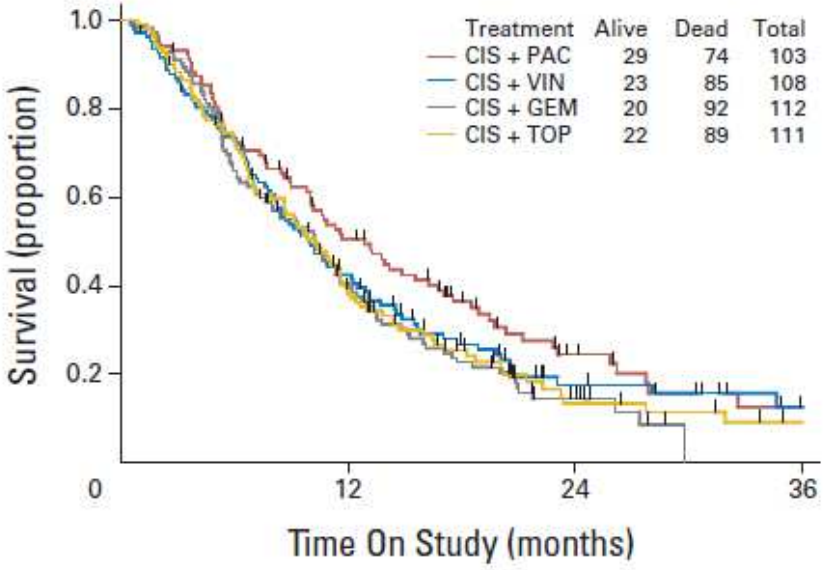
再発子宮頸がんに対するシスプラチン併用療法 GOG204



J Clin Oncol 2009; 27: 4649

再発子宮頸がんに対するシスプラチン併用療法 GOG204





パクリタキセル＋シスプラチン併用療法が標準治療

J Clin Oncol 2009; 27: 4649

JCOG0505

Multicenter (30 specialized institutions), Randomized Phase III Trial

Stage IVB, persistent or recurrent cervical cancer; not amenable to curative surgery / radiotherapy

*** Balancing factors:**

- Tumors outside of the prior irradiation field (yes or no)
- PS 0-1 or 2
- SCC or non-SCC
- Institution

RANDOMIZE*

Standard arm: TP
Paclitaxel **135** mg/m^2 **24h** d1
Cisplatin 50 mg/m^2 2h **d2**

every 21 days for 6 cycles

Experimental arm: TC
Paclitaxel **175** mg/m^2 **3h** d1
Carboplatin AUC 5 1h **d1**

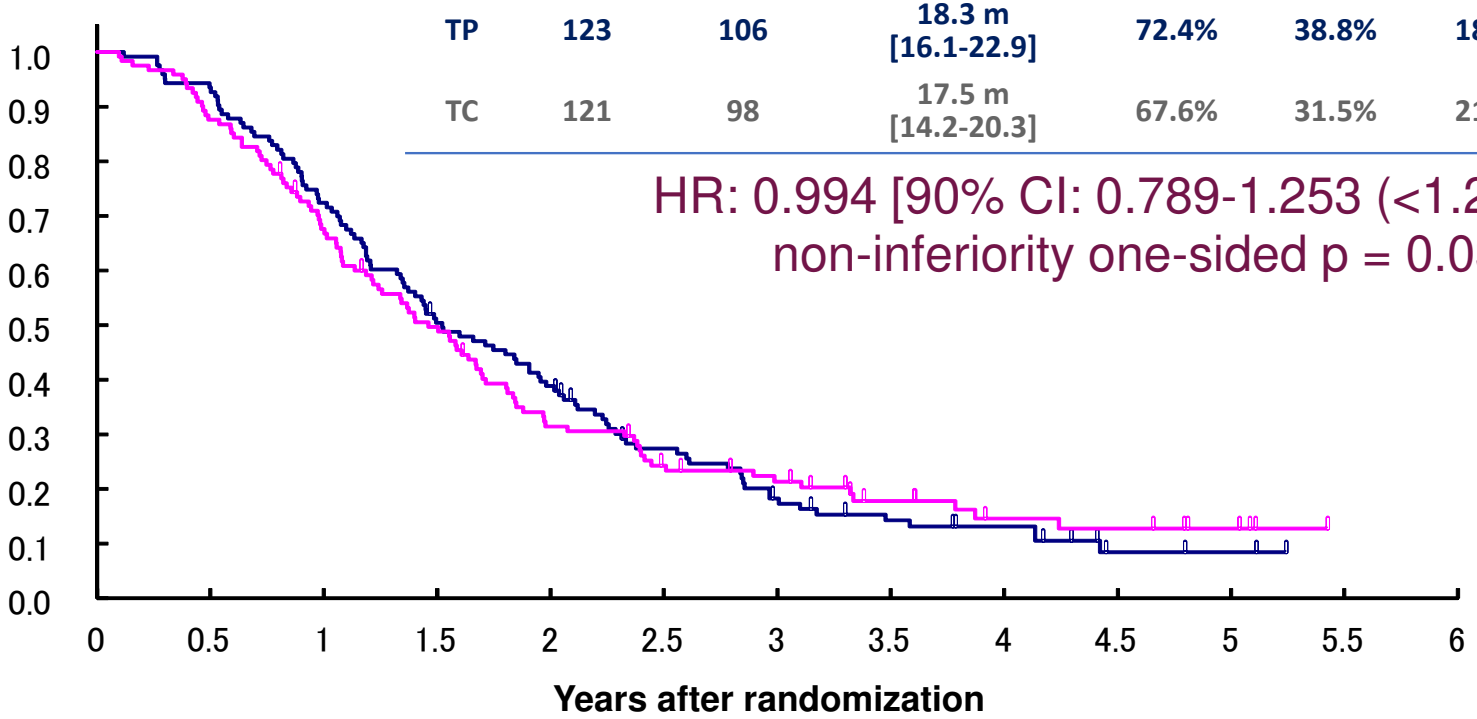
Primary endpoint: OS
Secondary endpoints: PFS, RR, adverse events, QOL

J Clin Oncol 2015; 33: 2129-35

Overall Survival

Arm	N	Events	Median(m) [95% CI]	1-yr OS	2-yr OS	3-yr OS
TP	**123**	**106**	**18.3 m [16.1-22.9]**	**72.4%**	**38.8%**	**18.3%**
TC	121	98	17.5 m [14.2-20.3]	67.6%	31.5%	21.3%

HR: 0.994 [90% CI: 0.789-1.253 (<1.29)]
non-inferiority one-sided p = 0.032#



#stratified Cox regression with "tumors outside prior irradiation field[yes/no]" as strata

J Clin Oncol 2015; 33: 2129-35

子宮頸癌に対するBevacizumab

GOG 240

Carcinoma of the cervix
- Primary stage IVB
- Recurrent/persistent
- Measureable disease
- GOG PS 0–1
- No prior chemotherapy for recurrence

(N=452)

Stratification factors:
- Stage IVB vs recurrent/persistent disease
- Performance status
- Prior cisplatin Rx as radiation-sensitizer

Activated: 4/6/09
Closed to accrual: 1/3/12

RANDOMIZE

1:1:1:1

I
- Paclitaxel 135 or 175 mg/m² IV
- Cisplatin 50 mg/m² IV

II
- Paclitaxel 135 or 175 mg/m² IV
- Cisplatin 50 mg/m² IV
- Bevacizumab 15 mg/kg IV

III
- Paclitaxel 175 mg/m² IV
- Topotecan 0.75 mg/m² d1-3

IV
- Paclitaxel 175 mg/m² IV
- Topotecan 0.75 mg/m² d1-3
- Bevacizumab 15 mg/kg IV

Chemo alone

Q21d Rx to PD, toxicity, CR

Chemo + Bev

KS Tewari (study chair). www.ClinicalTrials.gov Identifier: NCT00803062.

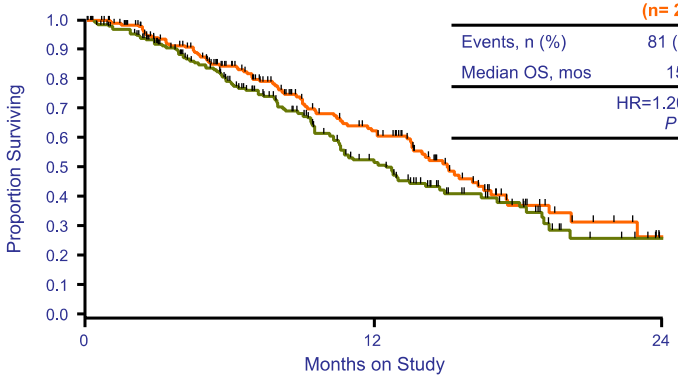
Primary endpoint: OS 1) by adding Bev, 2) by adding non-platinum chemo
Secondary endpoint: PFS, ORR

N Engl J Med 2014; 370: 734

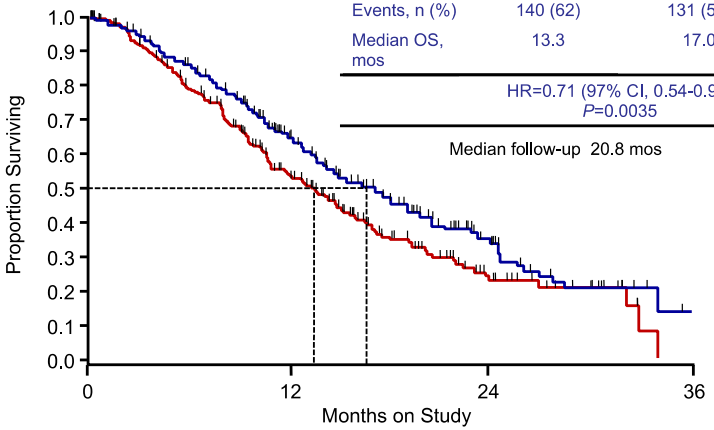
Platinum vs. Non-platinum chemotehrapy

- Topotecan + paclitaxel shown to not be superior or inferior to cispaltin + paclitaxel

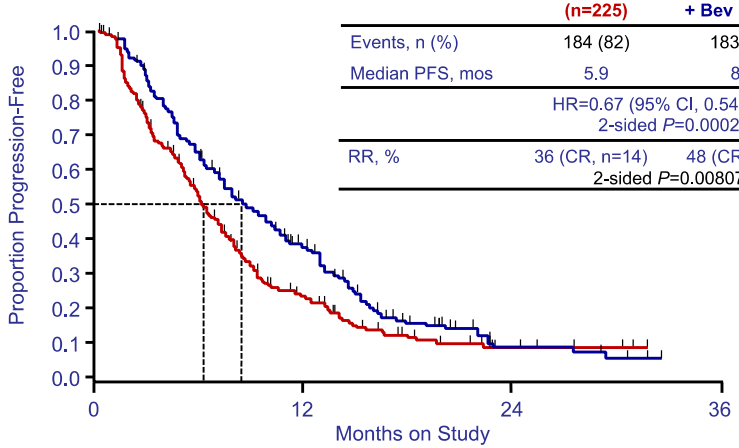
GOG 240



	Cis + Pac (n= 229)	Topo + Pac (n= 223)
Events, n (%)	81 (35)	93 (42)
Median OS, mos	15	12.5
	HR=1.20 (98.74% CI; 0.82–1.76) *P* (one-sided)=0.880	



	Chemotherapy (n=225)	Chemotherapy Bev (n=227)
Events, n (%)	140 (62)	131 (58)
Median OS, mos	13.3	17.0
	HR=0.71 (97% CI, 0.54-0.94) *P*=0.0035	
	Median follow-up 20.8 mos	



	Chemotherapy (n=225)	Chemotherapy + Bev (n=227)
Events, n (%)	184 (82)	183 (81)
Median 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	

N Engl J Med 2014; 370: 734

KEYNOTE-158 Phase II Basket Trial (Update): Pembrolizumab Monotherapy in Advanced Cervical Cancer

international, multicohort, open-label phase II study

Adult patients with advanced cervical cancer that progressed on or was intolerant to ≥1 line of standard therapy; ECOG PS 0-1; tumor sample for biomarker analysis (N = 98)

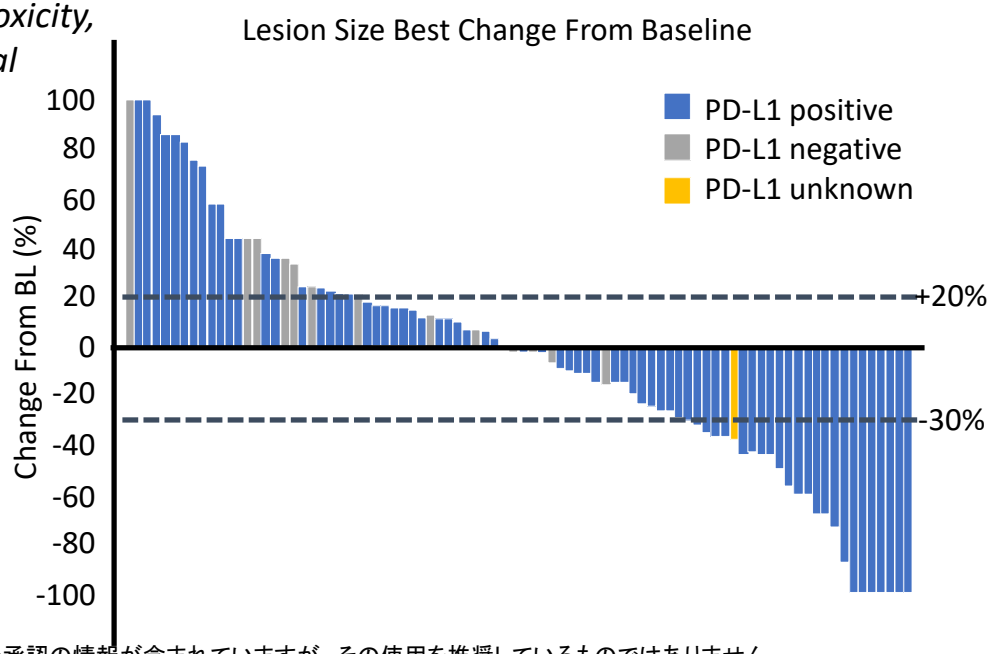
→ Pembrolizumab 200 mg Q3W

For 2 yr or until unacceptable toxicity, progression, or withdrawal

Primary endpoint: ORR per RECIST v1.1 (per independent central review)

Secondary endpoints: DoR, PFS, OS, safety

Parameter	Overall (N = 98)	PD-L1+ (n = 82)	PD-L1- (n = 15)
ORR, % (95% CI)	14.3 (8.0-22.8)	17.1 (9.7-27.0)	0 (0-21.8)
Best response, n (%)			
▪ CR	5 (5.1)	5 (6.1)	0
▪ PR	9 (9.2)	9 (11.0)	0
▪ SD	16 (16.3)	13 (15.9)	3 (20.0)



1. Chung. JCO. 2019;37:1470. 2. Chung. SGO 2021. Abstr 41.

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KEYNOTE-826: pembrolizumab + Chemotherapy Bevacizumab in patients with Persistent, recurrent or metastatic cervical cancer

Key Eligibility Criteria

- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy permitted)
- ECOG PS 0 or 1

Stratification Factors

- Metastatic disease at diagnosis (yes vs no)
- PD-L1 CPS (<1 vs 1 to <10 vs ≥10)
- Planned bevacizumab use (yes vs no)

R 1:1

Pembrolizumab 200 mg IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Placebo IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

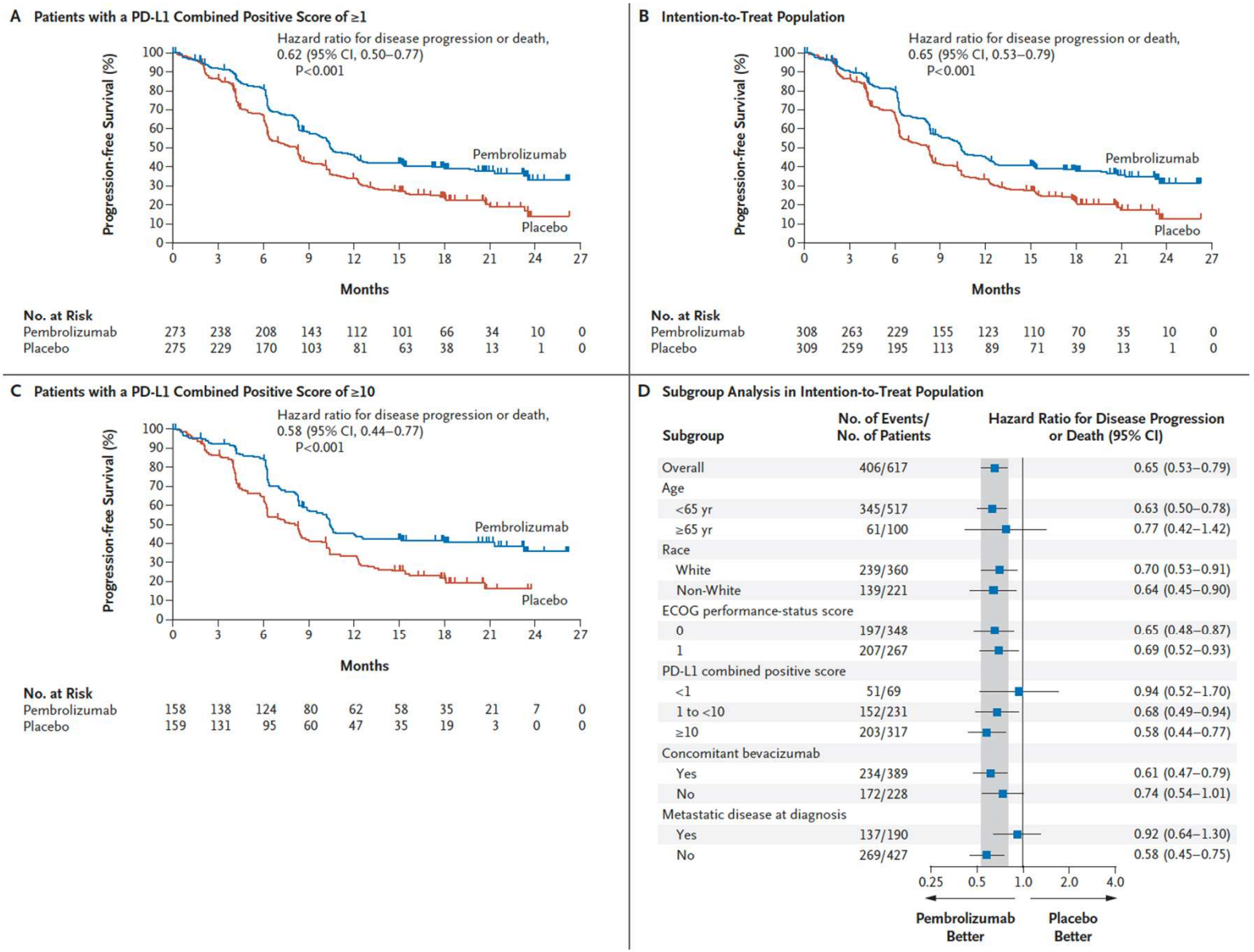
End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by investigator
- **Secondary:** ORR, DOR, 12-mo PFS, and safety
- **Exploratory:** PROs assessed per EuroQol EQ-5D-5L VAS

[a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing clinical benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation.
CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); PROs, patient-reported outcomes; VAS, visual analog scale. KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

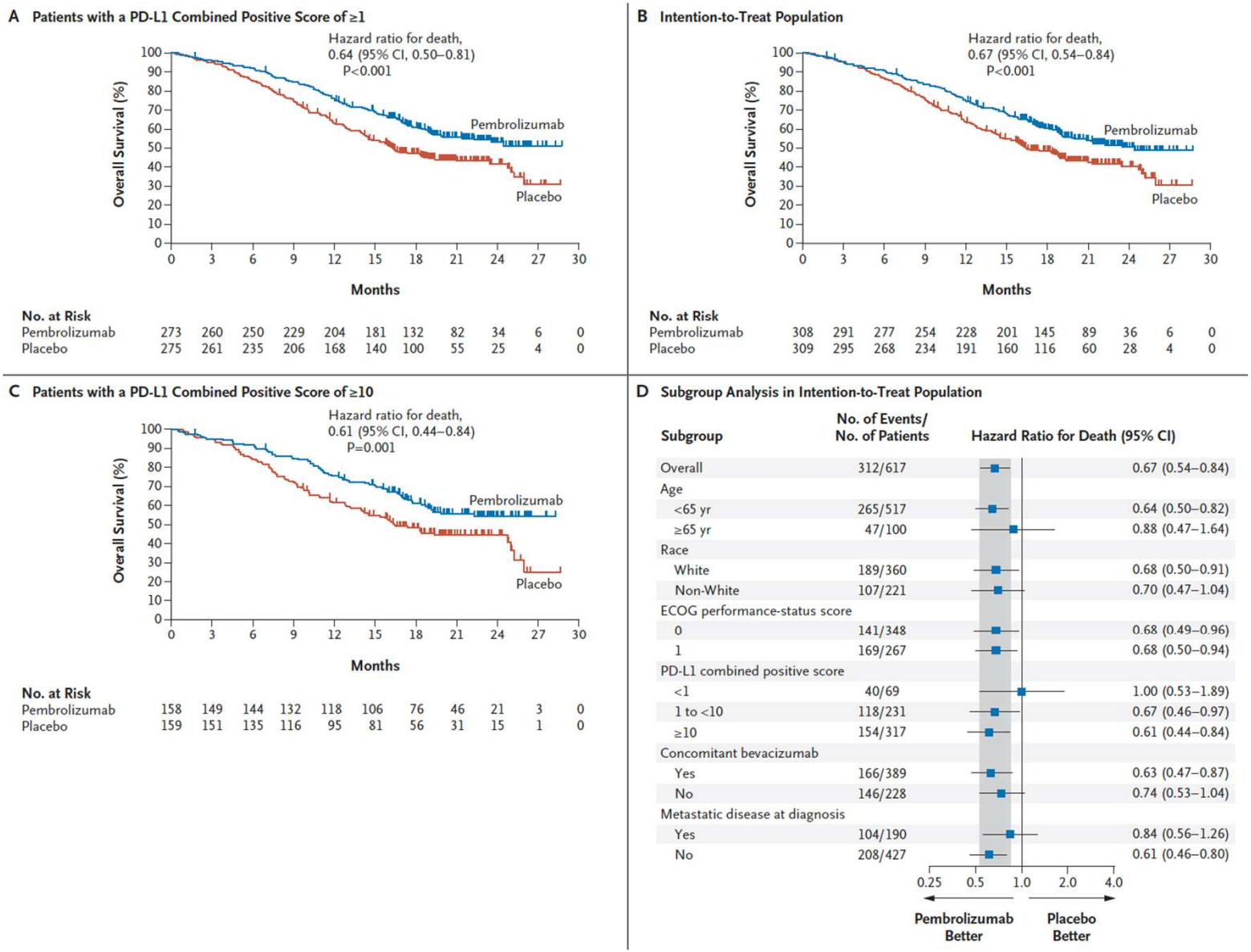
N Engl J Med 2021; 385: 1856

KEYNOTE-826: PFS



N Engl J Med 2021; 385: 1856

KEYNOTE-826: OS



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Ongoing Randomized Phase III Immunotherapy Trials in Recurrent/Metastatic Cervical Cancer

Study	Population	Treatment Arms	Estimated N	Trial Status	Primary Endpoints
R2810-ONC-ISA-1981 (NCT04646005)	▪ HPV16-positive recurrent/metastatic cervical cancer ▪ Progression after first-line therapy	Cemiplimab + ISA101b (HPV16 vaccine)	105	Recruiting	ORR (time frame: 36 mo)
STAR (NCT04068753)	▪ Recurrent or progressive cervical cancer ▪ Measurable RECIST v1.1 ▪ ECOG PS 0/1	Niraparib + dostarlimab	66	Recruiting	Response (CR or PR) at 1 yr
BEATcc (NCT03556839)	▪ Prior CRT ▪ Histology ▪ Chemotherapy backbone: cisplatin or carboplatin	Atezolizumab + bevacizumab and cisplatin or carboplatin/paclitaxel	404	Active not recruiting	OS

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Ongoing Randomized Phase III Immunotherapy Trials in Locally Advanced Cervical Cancer

Study	Population	Treatment Arms	Estimated N	Trial Status	Primary Endpoints
KEYNOTE-A18 (NCT04221945)	▪ High-risk, locally-advanced cervical cancer with FIGO 2014 Stage IB2-IIB (with node-positive disease) or FIGO 2014 Stages III-IVA ▪ Squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma	CRT ± pembrolizumab	980	Recruiting	PFS (by RECIST); OS (up to ~46 mo)
CALLA (NCT03830866)	▪ FIGO 2009 IB2-IIB node+ ▪ IIIA-IVA any nodal status ▪ Measurable RECIST v1.1 ▪ ECOG PS 0/1	CRT ± durvalumab (for 2 yr)	770	Active not recruiting	PFS

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婦人科がん治療　総括

- 卵巣がん、子宮体がん、子宮頸がんいずれにおいても、プラチナ系化学療法が中心的役割を果たす
- 卵巣がん、子宮頸がんにおいてベバシズマブの効果が示されている
- 卵巣がんにおいてPARP阻害薬の有効性が示され、初回治療ならびにプラチナ感受性再発に対し導入されている
- 子宮体がん、子宮頸がんにおいて免疫チェックポイント阻害薬の効果が示されている