事例検討④　資料

HRD
homologous recombination deficiency

アカデミア・アセンブリ 全体会議 検討日
2024年5月23日 (木)

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HRD

(Homologous recombination deficiency)

症例提示（仮想症例です）

【症例】40歳代男性（ECOG PS: 0）
【臨床診断】肝内胆管癌術後再発、多発骨転移
【病理組織学的診断】adenocarcinoma, moderately to poorly differentiated

【現病歴】
X-1年01月　肝左葉切除術*　pT3pN0 Stage III
X-1年10月　PETにて多発骨転移
X-1年11月　GEM+CDDP+S-1による治療開始。ランマーク併用
X　年01月　がん遺伝子パネル検査に提出（*の検体を使用）
X　年02月　PETで骨転移への取り込みは減弱
X　年04月　腎機能が悪化（Cre 1.0⇒1.3)

【既往歴】特記事項無し
【家族歴】母：直腸癌（70歳代）、父方祖母：胃癌（70歳代）
【生活歴】喫煙歴：なし、アルコール多飲歴：なし、アレルギー：なし
【Germline開示希望】あり

がん遺伝子パネル検査結果

【解析検体】肝切除検体（X-1年1月）
【腫瘍細胞含有割合】20%（enriched region)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - Cannot Be Determined	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - Cannot Be Determined	**No therapies or clinical trials.** See Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
PALB2 - R414* VAF 49.0%	none	Niraparib
		Olaparib
		Rucaparib
		Talazoparib
10 Trials see p. 10		
ARID1A - R1276* VAF 2.2%	none	none
8 Trials see p. 8		

エキスパートパネルでの解釈

【検出された病的バリアント】
PALB2 R414*　（エビデンスレベル：C)
*ARID*1*A*　R1276*（エビデンスレベル：F)

【Druggableな病的バリアント（エビデンスレベル A-D）】
PALB2 R414*

【二次的所見疑いバリアント】
PALB2 R414*

【がん遺伝子パネル検査結果に基づく候補治療】
*PALB2 R414**
1．PARP阻害薬
2．プラチナ含有レジメン（投与中）

HR関連遺伝子

Gene	Tumour types with somatic alterations (mutations, gene deletions and promoter hypermethylation)	Tumour types and syndromes with germline mutations
ATM	T-PLL, breast cancer, GBM, ccRCC, lung adenocarcinoma, sarcoma, and prostate, gastric, bladder, colorectal, uterine and pancreatic cancer	Leukaemia, lymphoma, medulloblastoma, glioma and ataxia telangiectasia Breast ca., Ovarian ca., Pancreatic ca.
ATR	Breast, colorectal, head and neck, gastric and uterine cancer	Oropharyngeal cancer and familial cutaneous telangiectasia and cancer syndrome
BAP1	ccRCC, cholangiosarcoma, liver cancer and uveal melanoma	Mesothelioma and uveal melanoma
BRCA1	TNBC, HGS-OvCa, lung cancer, prostate cancer, mCRPC and PDAC	TNBC, HGS-OvCa and PDAC
BRCA2	Breast cancer, HGS-OvCa, PDAC, prostate cancer, mCRPC, gastric, bladder and lung cancer, DLBCL and sarcoma	Breast cancer, HGS-OvCa, PDAC and leukaemia
CDK12	HGS-OvCa?, mCRPC and gastric cancer	
CHEK2 (CHK2)	Uterine cancer and HGS-OvCa	Breast cancer
FANCA	HGS-OvCa and lung adenocarcinoma	AML, leukaemia and Fanconi anaemia
FANCC		AML, leukaemia and Fanconi anaemia
FANCD2	ccRCC	AML, leukaemia and Fanconi anaemia
FANCE		AML, leukaemia and Fanconi anaemia
FANCF		AML, leukaemia and Fanconi anaemia
PALB2	Gastric cancer and HGS-OvCa	Wilms tumour, medulloblastoma, AML, Fanconi anaemia, breast cancer, PDAC and HGS-OvCa
NBS1 (NBN)	Gastric and uterine cancer	Nijmegen breakage syndrome Breast ca.?, Pan-cancer
WRN	HGS-OvCa, mCRPC, lung adenocarcinoma and uterine cancer	Werner syndrome
RAD51C	HGS-OvCa	Breast cancer and HGS-OvCa
RAD51D		Breast cancer and HGS-OvCa
MRE11A	Colorectal cancer	Breast ca.
CHEK1 (CHK1)	PDAC and sarcoma	
BLM		Bloom syndrome
RAD51B	HGS-OvCa	
BRIP1	HGS-OvCa	Breast ca., Ovarian ca.

Nat. Rev. Cancer (2016) 16, 110–120

PARP inhibitor indication #1

Maintenance after treatment with chemotherapy

◎：FDA/PMDA approval, ○ ：FDA approval/PMDA non-approval , △：FDA non-approval /PMDA non-approval

	HRD	*BRCA 1/2*	*ATM*	*PALB2*	Other HRD-related gene
Germline	Ovarian cancer: ◎Olaparib, ◎Niraparib	Breast cancer (HER2-negative): ◎Olaparib Pancreatic cancer : ◎ Olaparib Ovarian cancer: ◎Olaparib ○*Rucaparib*	–	Pancreatic cancer : ○*Rucaparib*	–
Somatic	Ovarian cancer: ◎Olaparib, ◎Niraparib	Breast cancer (HER2-negative): △ Olaparib Pancreatic cancer : △ Olaparib Ovarian cancer: ◎Olaparib ○*Rucaparib*	–	Pancreatic cancer : ○*Rucaparib* ？？	–

Ovarian cancer (Platinum sensitive): ◎ Niraparib, ◎ Olaparib

Other HRD-related gene：*BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.

PARP inhibitor indication #1

Maintenance after treatment with chemotherapy

◎：FDA/PMDA approval, ○ ：FDA approval/PMDA non-approval , △：FDA non-approval /PMDA non-approval

	HRD	*BRCA 1/2*	*ATM*	*PALB2*	Other HRD-related gene
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Somatic	Ovarian cancer: ◎Olaparib, ◎Niraparib	Breast cancer (HER2-negative): △ Olaparib Pancreatic cancer : △ Olaparib Ovarian cancer: ◎Olaparib ○Rucaparib	–	Pancreatic cancer : ○Rucaparib？？	–

Ovarian cancer (Platinum sensitive): ◎ Niraparib, ◎ Olaparib

Other HRD-related gene：*BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.

プラチナ感受性進行性膵癌のおけるRucaparibのメンテナンス療法

original reports

Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in *BRCA1*, *BRCA2*, or *PALB2*

Kim A. Reiss, MD[1,2]; Rosemarie Mick, MS[1,3]; Mark H. O'Hara, MD[1,2]; Ursina Teitelbaum, MD[1,2]; Thomas B. Karasic, MD[1,2]; Charles Schneider, MD[1,2]; Stacy Cowden, RN[1]; Traci Southwell, RN[1]; Janae Romeo, MBE[1]; Natallia Izgur, RN[1]; Zain M. Hannan, BA[1]; Rashmi Tondon, MD[1,4]; Katherine Nathanson, MD[1,2]; Robert H. Vonderheide, MD, DPhil[1,2]; Max M. Wattenberg, MD[1,2]; Gregory Beatty, MD, PhD[1,2]; and Susan M. Domchek, MD[1,2]

対象

- （Germline or Somatic）

BRCA1, BRCA2, または *PALB2*

- プラチナベース化学療法が16週間有効である症例

16週間以上のプラチナベース化学療法 → Rucaparib 600 mg orally twice a day

Characteristic	Patients, n = 42 (%)
Age at diagnosis, median (range), years	61.5 (35-81)
Sex	
Female	24 (57)
Male	18 (43)
Mutation	
Germline *BRCA1*	7 (17)
Germline *BRCA2*	27 (64)
Germline *PALB2*	6 (14)
Somatic *BRCA2*	2 (5)
History of curative-intent resection	
Yes	9 (21)
No	33 (79)
Time from metastatic diagnosis to study start,[a] months	
Median	5.6
Range	2.5-62.5
Line of therapy for metastatic disease[a]	
First	40 (100)
Platinum treatment duration, months	
4-6	26 (62)
6-12	5 (12)
> 12	3 (7)
< 4	8 (19)
Allergy	1 (13)
Intolerance	5 (63)
Prior neuropathy	2 (25)

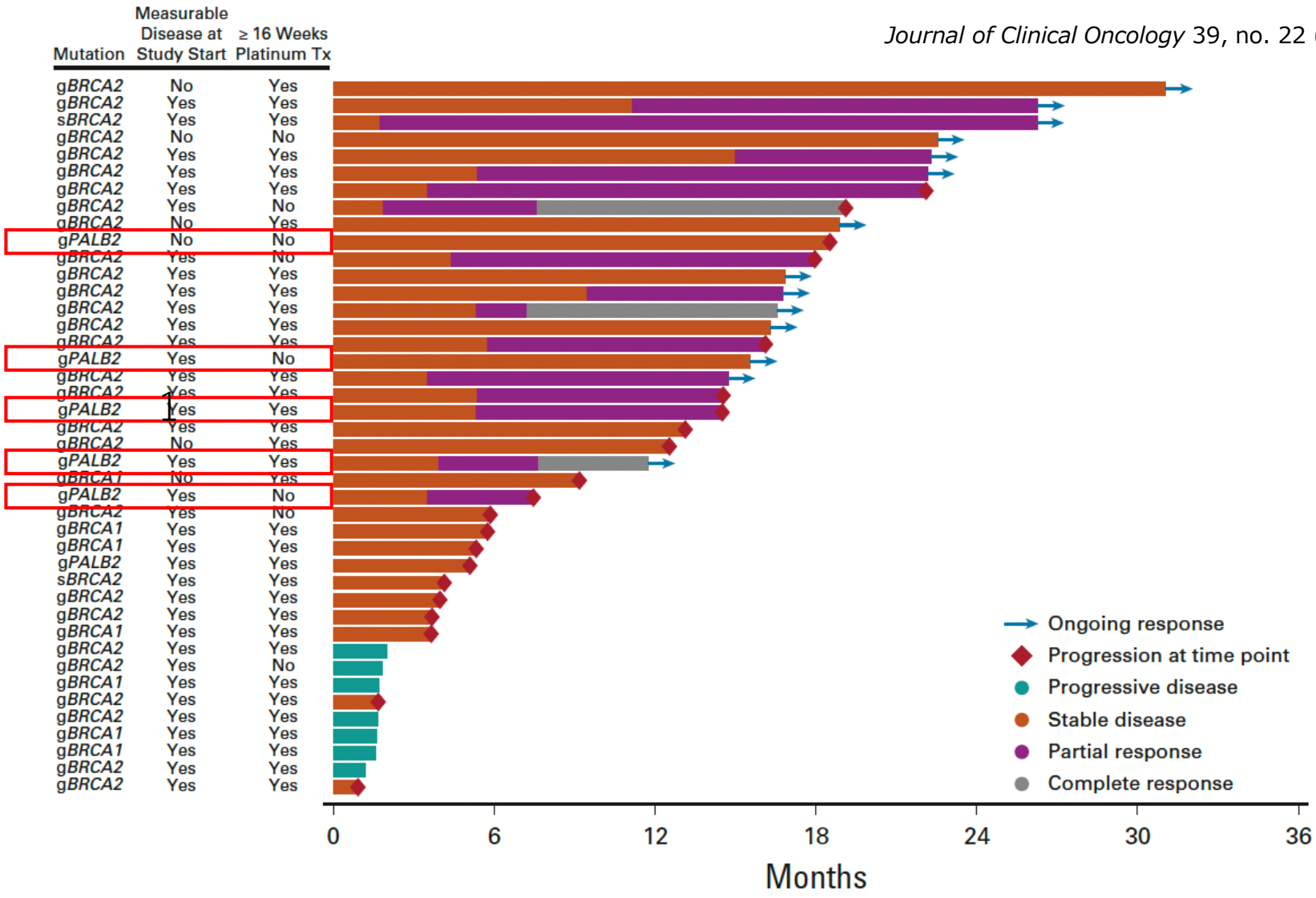
体細胞*PALB2*変異は含まれていない

Journal of Clinical Oncology 39, no. 22 (August 01, 2021) 2497-2505.

Rucaparibの抗腫瘍効果

Journal of Clinical Oncology 39, no. 22 (August 01, 2021) 2497-2505.

Germline *PALB2*
ではPR3例



体細胞*PALB2*変異に対するPARP阻害剤の有効性は確立していない。

PARP inhibitor indication #2

Subsequent-line treatment (PARP-inhibitor-naïve)

◎： FDA/PMDA approval, ○ ： FDA approval/PMDA non-approval , △： FDA non-approval /PMDA non-approval

	HRD	BRCA 1/2	ATM	PALB2	Other HRD-related gene
Germline	Castration-resistant prostate cancer: ○Olaparib	Breast cancer (HER2-negative): ◎ Talazoparib, ◎ Olaparib Castration-resistant prostate cancer: ◎Olaparib, ◎Talazoparib Castration-resistant prostate cancer: ○ Rucaparib	○ Castration-resistant prostate cancer: Olaparib	○ Castration-resistant prostate cancer: Olaparib	○ Castration-resistant prostate cancer: Olaparib
Somatic	Castration-resistant prostate cancer: ○Olaparib	Castration-resistant prostate cancer: ◎Olaparib, ◎Talazoparib Castration-resistant prostate cancer: ○Rucaparib	○ Castration-resistant prostate cancer: Olaparib	○ Castration-resistant prostate cancer: Olaparib	○ Castration-resistant prostate cancer: Olaparib

PARP inhibitor indication #2

Subsequent-line treatment (PARP-inhibitor-naïve)

No consensuses in the experts:
Re-treatment with a PARP inhibitor if the recurrence occurred more than 12 months from the last dose of PARP inhibitor

PARP inhibitor indication #2

Subsequent-line treatment (PARP-inhibitor-naïve)

◎：FDA/PMDA approval, ○ ：FDA approval/PMDA non-approval , △：FDA non-approval /PMDA non-approval

	HRD	BRCA 1/2	ATM	PALB2	Other HRD-related gene
Germline	Castration-resistant prostate cancer: ○Olaparib	Breast cancer (HER2-negative): ◎ Talazoparib, ◎ Olaparib Castration-resistant prostate cancer: ◎Olaparib, ◎Talazoparib Castration-resistant prostate cancer: ○ Rucaparib	○ Castration-resistant prostate cancer: Olaparib	○ Castration-resistant prostate cancer: Olaparib	○ Castration-resistant prostate cancer: Olaparib
Somatic	Castration-resistant prostate cancer: ○Olaparib	Castration-resistant prostate cancer: ◎Olaparib, ◎Talazoparib Castration-resistant prostate cancer: ○Rucaparib	○ Castration-resistant prostate cancer: Olaparib	○ Castration-resistant prostate cancer: Olaparib	○ Castration-resistant prostate cancer: Olaparib

去勢抵抗性前立腺癌

ORIGINAL ARTICLE

Olaparib for Metastatic Castration-Resistant Prostate Cancer

Johann de Bono, M.B., Ch.B., Ph.D., Joaquin Mateo, M.D., Ph.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Neal Shore, M.D., Shahneen Sandhu, M.D., Kim N. Chi, M.D., Oliver Sartor, M.D., Neeraj Agarwal, M.D., David Olmos, M.D., Ph.D., Antoine Thiery-Vuillemin, M.D., Ph.D., Przemyslaw Twardowski, M.D., et al.

Olaparib単剤 vs. 新規ホルモン剤

対象：
- 18歳以上
- 去勢抵抗性前立腺癌
- Enzalutamide or Abirateroneに不応
- タキサンの治療歴は許容

- Cohort A:

BRCA1, *BRCA2*, and *ATM*

- Cohort B:

BRIP1, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*

（*FANCA*は含まない）

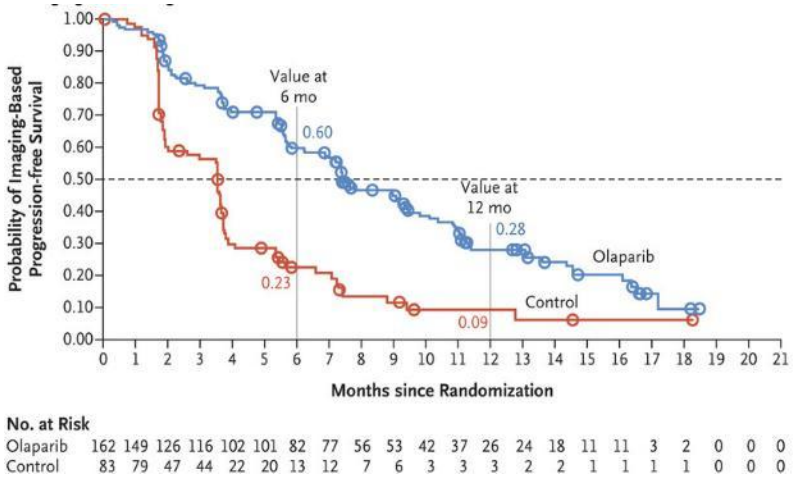
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cohort A		Cohorts A and B	
	Olaparib (N=162)	Control (N=83)	Olaparib (N=256)	Control (N=131)
Median age at randomization (range) — yr	68 (47–86)	67 (49–86)	69 (47–91)	69 (49–87)
Age ≥65 yr at randomization — no. (%)	108 (67)	60 (72)	174 (68)	97 (74)
Metastatic disease at initial diagnosis — no. (%)	38 (23)	19 (23)	66 (26)	25 (19)
Missing data	7 (4)	4 (5)	11 (4)	7 (5)
Gleason score ≥8 — no./total no. (%)†	105/157 (67)	54/80 (67)	183/251 (73)	95/127 (75)
Patients with alterations in a single gene — no. (%)‡				
BRCA1	8 (5)	5 (6)	8 (3)	5 (4)
BRCA2	80 (49)	47 (57)	81 (32)	47 (36)
ATM	60 (37)	24 (29)	62 (24)	24 (18)
CDK12	NA	NA	61 (24)	28 (21)
Median PSA at baseline (IQR) — μg/liter	62.2 (21.9–280.4)	112.9 (34.3–317.1)	68.2 (24.1–294.4)	106.5 (37.2–326.6)
Measurable disease at baseline — no. (%)§	95 (59)	46 (55)	149 (58)	72 (55)
Metastases at baseline — no. (%)§				
Bone only	57 (35)	23 (28)	86 (34)	38 (29)
Visceral: lung or liver	46 (28)	32 (39)	68 (27)	44 (34)
Other	49 (30)	23 (28)	88 (34)	41 (31)
ECOG performance status — no. (%)				
0	84 (52)	34 (41)	131 (51)	55 (42)
1	67 (41)	46 (55)	112 (44)	71 (54)
2	11 (7)	3 (4)	13 (5)	4 (3)
Missing data	0	0	0	1 (1)
Previous new hormonal agent — no. (%)¶				
Enzalutamide only	68 (42)	40 (48)	105 (41)	54 (41)
Abiraterone only	62 (38)	29 (35)	100 (39)	54 (41)
Enzalutamide and abiraterone	32 (20)	14 (17)	51 (20)	23 (18)
Previous taxane use — no. (%)	106 (65)	52 (63)	170 (66)	84 (64)
Docetaxel only	74 (46)	32 (39)	115 (45)	58 (44)
Cabazitaxel only	2 (1)	0	3 (1)	0
Docetaxel and cabazitaxel	29 (18)	20 (24)	51 (20)	26 (20)
Paclitaxel only	1 (<1)	0	1 (<1)	0

N Engl J Med 2020; 382:2091-2102

無増悪生存期間

Cohort A



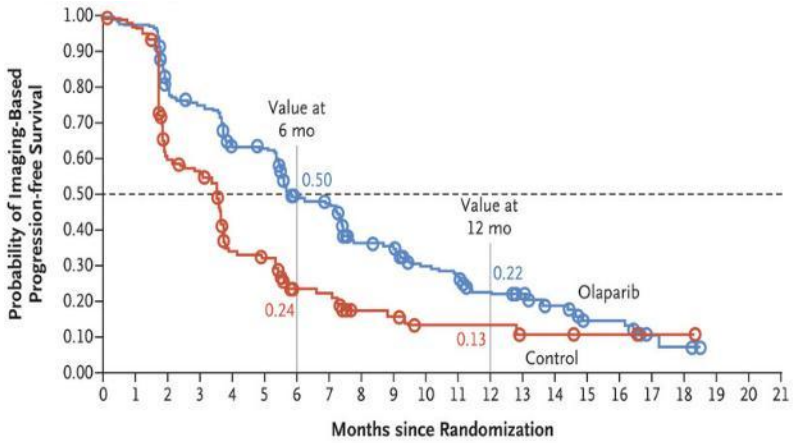
No. at Risk

Olaparib	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
Control	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

	Median *mo*
Olaparib	7.4
Control	3.6

Hazard ratio for progression or death, 0.34 (95% CI, 0.25–0.47)
P<0.001

Cohort A + Cohort B



No. at Risk

Olaparib	256	239	188	176	145	143	106	100	67	63	48	43	31	28	21	11	11	3	2	0	0	0
Control	131	123	73	67	38	35	20	19	9	8	5	5	5	3	3	2	2	1	1	0	0	0

	Median *mo*
Olaparib	5.8
Control	3.5

Hazard ratio for progression or death, 0.49 (95% CI, 0.38–0.63)
P<0.001

N Engl J Med 2020; 382:2091-2102

無増悪生存期間のサブグループ解析

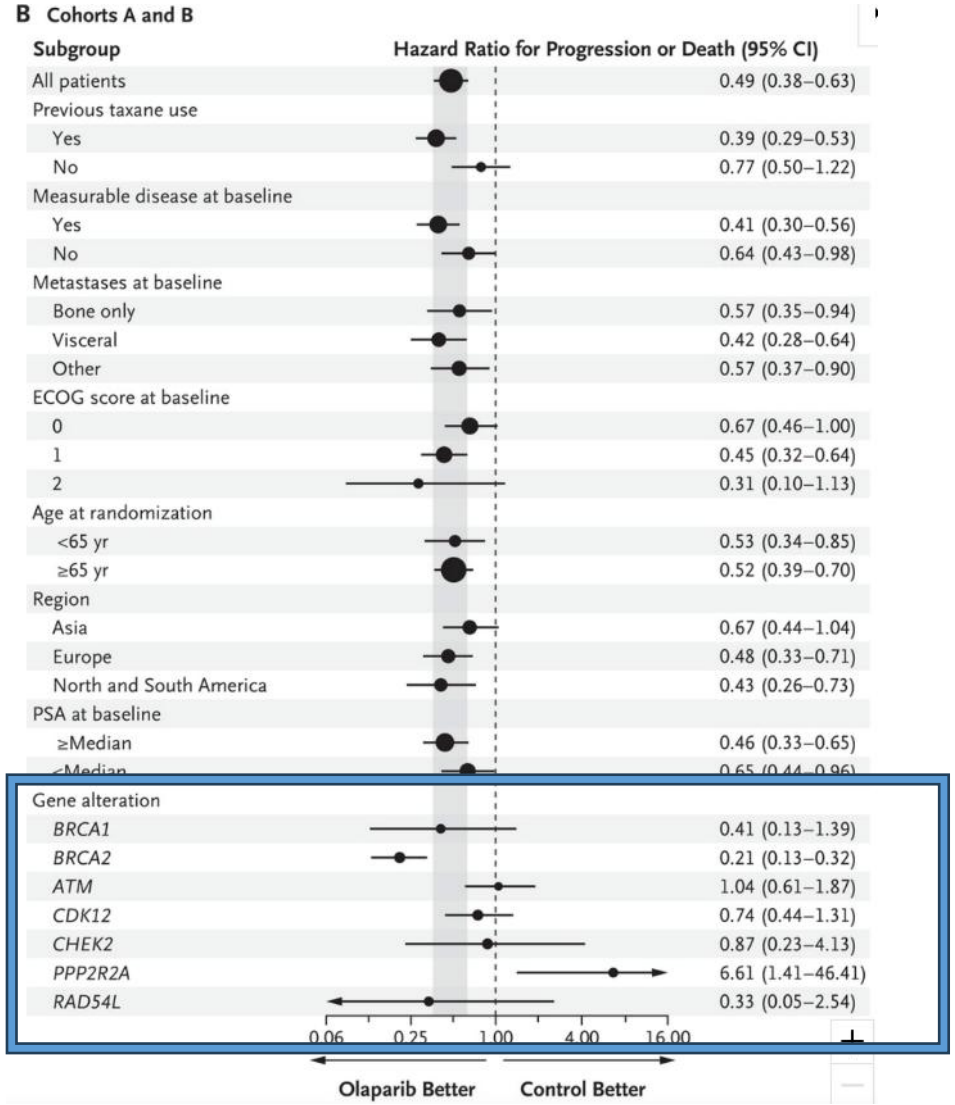
- Cohort A:

BRCA1, *BRCA2*, and *ATM*

- Cohort B:

BRIP1, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB 2*, *PPP2R2A RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*

（*FANCA*は含まない）



N Engl J Med 2020; 382:2091-2102

去勢抵抗性前立腺癌に対するRucaparib

ORIGINAL ARTICLE

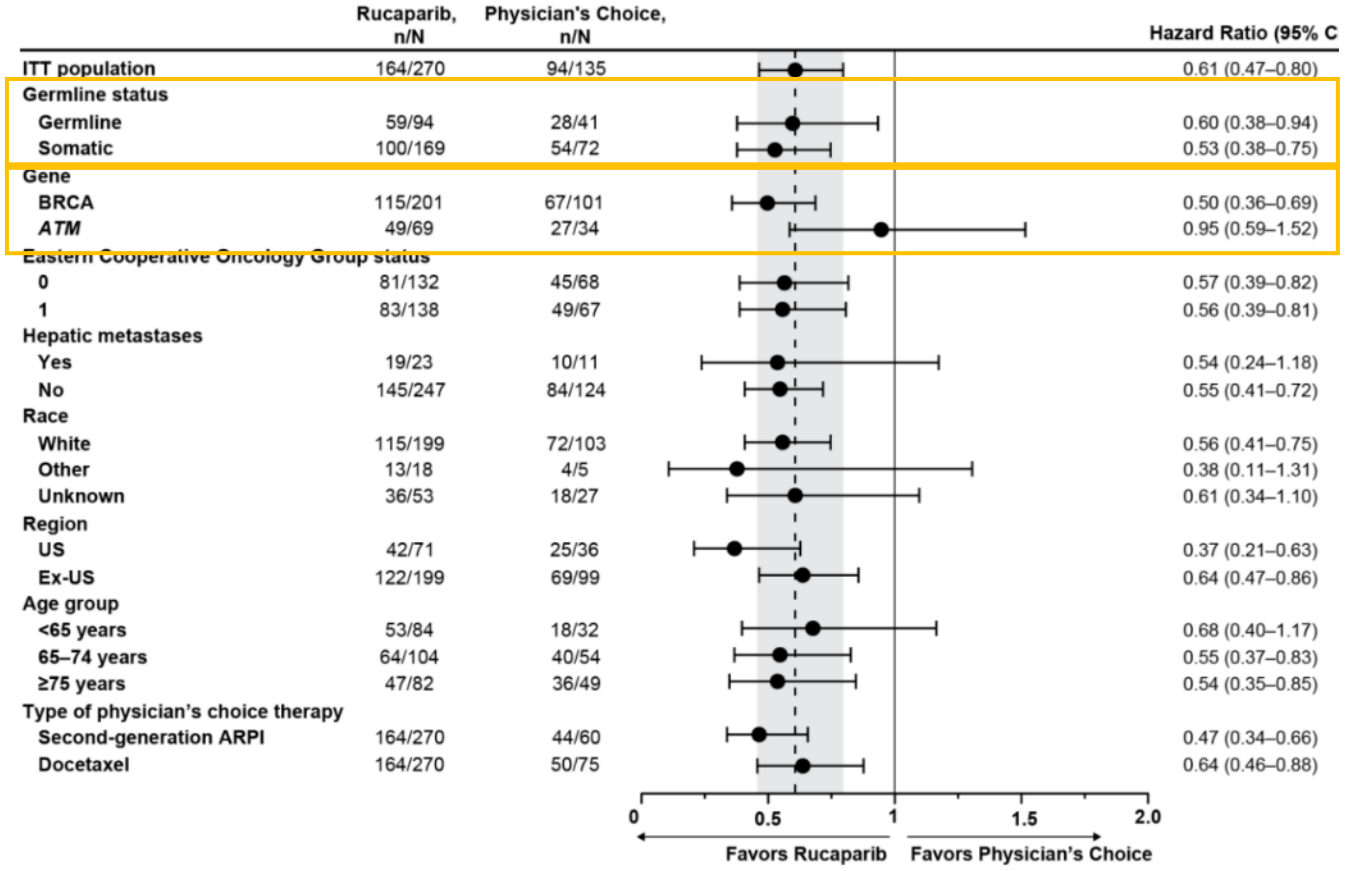
Rucaparib or Physician's Choice in Metastatic Prostate Cancer

Karim Fizazi, M.D., Ph.D., Josep M. Piulats, M.D., Ph.D., M. Neil Reaume, M.D., Peter Ostler, M.D., Ray McDermott, M.B., B.Ch., B.A.O., Ph.D., Joel R. Gingerich, M.D., Elias Pintus, M.D., Srikala S. Sridhar, M.D., Richard M. Bambury, M.D., Urban Emmenegger, M.D., Henriette Lindberg, M.D., Ph.D., David Morris, M.D., et al., for the TRITON3 Investigators*

対象：
去勢抵抗性前立腺がん（*BRCA* または *ATM* 遺伝子変異）
第2世代ホルモン剤不応（abiraterone acetate, enzalutamide, apalutamide, 治験薬）
去勢抵抗性後にタキサン未実施

Rucaparib単剤 (600 mg twice daily)
VS
Physician's choice control
(docetaxel または 第2世代ホルモン剤)

無増悪生存期間のサブグループ解析



N Engl J Med 2023;388:719-732

Pooled analysis （HRD 前立腺がんPARP阻害剤）

検討遺伝子
ATM, BRCA1, BRCA2, CDK12, CHEK2, PALB2

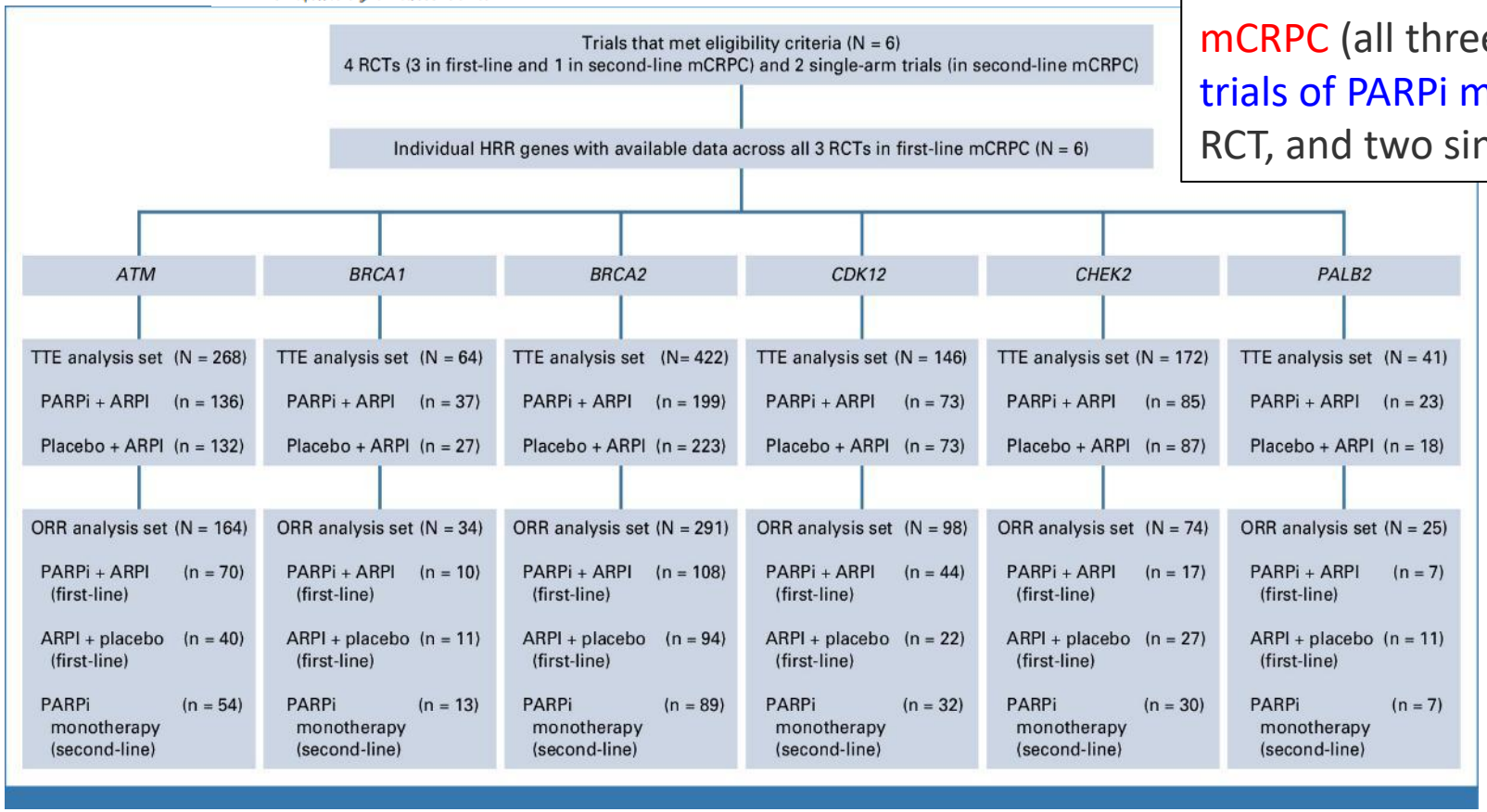
Original Reports | Genitourinary Cancer

Check for updat

Efficacy of Poly(ADP-ribose) Polymerase Inhibitors by Individual Genes in Homologous Recombination Repair Gene-Mutated Metastatic Castration-Resistant Prostate Cancer: A US Food and Drug Administration Pooled Analysis

Jaleh Fallah, MD[1]; Jianjin Xu, PhD[1]; Chana Weinstock, MD[1]; Xin Gao, PhD[1]; Brian L. Heiss, MD[1]; William F. Maguire, MD, PhD[1]; Elaine Chang, MD[1]; Sundeep Agrawal, MD[1]; Shenghui Tang, PhD[1]; Laleh Amiri-Kordestani, MD[1,2]; Richard Pazdur, MD[1,2]; Paul G. Kluetz, MD[1,2]; and Daniel L. Suzman, MD[1]

DOI https://doi.org/10.1200/JCO.23.02105



3 trials of PARPi plus ARPI in first-line mCRPC (all three were RCTs), and 3 trials of PARPi monotherapy (one RCT, and two single-arm trials)

J Clin Oncol. 2024 May 10;42(14):1687-1698

Pooled analysis （HRD 前立腺がんPARP阻害剤）

Androgen receptor pathway inhibitorに対するPARP阻害剤の上乗せ効果（PFS, OS）

b: 補正で解析（Trial, ECOG PS, 転移部位（骨のみかいなか）, Gleason score）

Gene Mutation	End Point	Arm	No.	No. of Events	Median Survival, Months	HR[a] (95% CI)	HR[b] (95% CI)
*ATM*m (N = 268)	rPFS (BICR)	PARPi + ARPI	136	67	19 (16-28)	1.05 (0.74 to 1.49)	1.02 (0.71 to 1.45)
		Placebo + ARPI	132	59	19 (16-NE)		
	OS	PARPi + ARPI	136	63	33 (26-NE)	1.18 (0.82 to 1.71)	1.12 (0.77 to 1.62)
		Placebo + ARPI	132	55	33 (28-NE)		
*BRCA1*m (N = 64)	rPFS (BICR)	PARPi + ARPI	37	14	20 (14-NE)	0.51 (0.23 to 1.1)	0.52 (0.2 to 1.33)
		Placebo + ARPI	27	15	12 (4-NE)		
	OS	PARPi + ARPI	37	16	29 (15-NE)	0.74 (0.34 to 1.61)	0.73 (0.28 to 1.89)
		Placebo + ARPI	27	13	26 (13-28)		
*BRCA2*m (N = 422)	rPFS (BICR)	PARPi + ARPI	199	60	NA (22-NE)	0.31 (0.23 to 0.42)	0.27 (0.19 to 0.37)
		Placebo + ARPI	223	144	10 (8-11)		
	OS	PARPi + ARPI	199	77	33 (29-NE)	0.66 (0.49 to 0.89)	0.6 (0.44 to 0.82)
		Placebo + ARPI	223	112	24 (22-28)		
*CDK12*m (N = 146)	rPFS (BICR)	PARPi + ARPI	73	32	17 (16-NE)	0.5 (0.32 to 0.8)	0.51 (0.32 to 0.82)
		Placebo + ARPI	73	44	14 (8-17)		
	OS	PARPi + ARPI	73	32	36 (25-NE)	0.63 (0.39 to 0.99)	0.64 (0.4 to 1.03)
		Placebo + ARPI	73	44	27 (20-33)		
*CHEK2*m (N = 172)	rPFS (BICR)	PARPi + ARPI	85	37	14 (14-25)	1.06 (0.67 to 1.66)	1.00 (0.63 to 1.59)
		Placebo + ARPI	87	43	18 (13-22)		
	OS	PARPi + ARPI	85	39	26 (23-NE)	1.53 (0.95 to 2.46)	1.48 (0.92 to 2.4)
		Placebo + ARPI	87	32	34 (26-NE)		
*PALB2*m (N = 41)	rPFS (BICR)	PARPi + ARPI	23	12	14 (8-NE)	0.52 (0.23 to 1.17)	0.43 (0.15 to 1.21)
		Placebo + ARPI	18	13	9 (2-20)		
	OS	PARPi + ARPI	23	12	25 (15-NE)	0.78 (0.34 to 1.8)	0.59 (0.21 to 1.65)
		Placebo + ARPI	18	11	20 (11-NE)		

Androgen receptor pathway inhibitor (ARPI)

J Clin Oncol. 2024 May 10;42(14):1687-1698

Pooled analysis （HRD 前立腺がんPARP阻害剤）

b: 補正で解析（Trial, ECOG PS, 転移部位（骨のみかいなか）, Gleason score）

TABLE 2. rPFS and OS by HRR Gene Mutation

Gene Mutation	End Point	Arm	No.	No. of Events	Median Survival, Months	HR[a] (95% CI)	HR[b] (95% CI)
*ATM*m (N = 268)	rPFS (BICR)	PARPi + ARPI	136	67	19 (16-28)	1.05 (0.74 to 1.49)	1.02 (0.71 to 1.45)
		Placebo + ARPI	132	59	19 (16-NE)		
	OS	PARPi + ARPI	136	63	33 (26-NE)	1.18 (0.82 to 1.71)	1.12 (0.77 to 1.62)
		Placebo + ARPI	132	55	33 (28-NE)		
*BRCA1*m (N = 64)	rPFS (BICR)	PARPi + ARPI	37	14	20 (14-NE)	0.51 (0.23 to 1.1)	0.52 (0.2 to 1.33)
		Placebo + ARPI	27	15	12 (4-NE)		
	OS	PARPi + ARPI	37	16	29 (15-NE)	0.74 (0.34 to 1.61)	0.73 (0.28 to 1.89)
		Placebo + ARPI	27	13	26 (13-28)		
*BRCA2*m (N = 422)	rPFS (BICR)	PARPi + ARPI	199	60	NA (22-NE)	0.31 (0.23 to 0.42)	0.27 (0.19 to 0.37)
		Placebo + ARPI	223	144	10 (8-11)		
	OS	PARPi + ARPI	199	77	33 (29-NE)	0.66 (0.49 to 0.89)	0.6 (0.44 to 0.82)
		Placebo + ARPI	223	112	24 (22-28)		
*CDK12*m (N = 146)	rPFS (BICR)	PARPi + ARPI	73	32	17 (16-NE)	0.5 (0.32 to 0.8)	0.51 (0.32 to 0.82)
		Placebo + ARPI	73	44	14 (8-17)		
	OS	PARPi + ARPI	73	32	36 (25-NE)	0.63 (0.39 to 0.99)	0.64 (0.4 to 1.03)
		Placebo + ARPI	73	44	27 (20-33)		
*CHEK2*m (N = 172)	rPFS (BICR)	PARPi + ARPI	85	37	14 (14-25)	1.06 (0.67 to 1.66)	1.00 (0.63 to 1.59)
		Placebo + ARPI	87	43	18 (13-22)		
	OS	PARPi + ARPI	85	39	26 (23-NE)	1.53 (0.95 to 2.46)	1.48 (0.92 to 2.4)
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*PALB2*m (N = 41)	rPFS (BICR)	PARPi + ARPI	23	12	14 (8-NE)	0.52 (0.23 to 1.17)	0.43 (0.15 to 1.21)
		Placebo + ARPI	18	13	9 (2-20)		
	OS	PARPi + ARPI	23	12	25 (15-NE)	0.78 (0.34 to 1.8)	0.59 (0.21 to 1.65)
		Placebo + ARPI	18	11	20 (11-NE)		

症例数が限定的

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Pooled analysis （HRD 前立腺がんPARP阻害剤）

TABLE 3. ORR of PARPi in mCRPC, by HRR Gene Mutation

HRR Gene Mutation	ORR by BICR, % (x/y), (95% CI)[a]			Difference Between PARPi + ARPI *v* Placebo + ARPI in First-Line mCRPC (Δ)
	Second-Line mCRPC	First-Line mCRPC		
	PARPi Monotherapy[b]	Placebo + ARPI[c]	PARPi + ARPI[c]	
*ATM*m	7 (5/70) (3 to 16)	42 (17/40) (19 to 66)	59 (32/54) (46 to 71)	Δ = +17%
*BRCA1*m	20 (2/10) (1 to 83)	18 (2/11) (5 to 51)	46 (6/13) (18 to 80)	Δ = +28%
*BRCA2*m	47 (51/108) (38 to 57)	27 (25/94) (19 to 36)	60 (53/89) (44 to 79)	Δ = +33%
*CDK12*m	5 (2/44) (1 to 16)	32 (7/22) (16 to 53)	62 (20/32) (45 to 77)	Δ = +30%
*CHEK2*m	0 (0/17) (0 to 100)	33 (9/27) (14 to 60)	43 (13/30) (27 to 61)	Δ = +10%
*PALB2*m	14 (1/7) (2 to 58)	45 (5/11) (20 to 73)	43 (3/7) (14 to 77)	Δ = −2%

J Clin Oncol. 2024 May 10;42(14):1687-1698

HER2陰性乳がん（HRD)に対するOlaparib

original reports

TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes

Nadine M. Tung, MD[1,2]; Mark E. Robson, MD[3]; Steffen Ventz, PhD[4]; Cesar A. Santa-Maria, MD, MSCI[5]; Rita Nanda, MD[6]; Paul K. Marcom, MD[7]; Payal D. Shah, MD[8]; Tarah J. Ballinger, MD[9]; Eddy S. Yang, MD, PhD[10]; Shaveta Vinayak, MD, MS[11]; Michelle Melisko, MD[12]; Adam Brufsky, MD, PhD[13]; Michelle DeMeo, BS[4]; Colby Jenkins, MS[1]; Susan Domchek, MD[8]; Alan D'Andrea, MD[2,4]; Nancy U. Lin, MD[2,4]; Melissa E. Hughes, MS[4]; Lisa A. Carey, MD[14]; Nick Wagle, MD[2,4]; Gerburg M. Wulf, MD, PhD[1,2]; Ian E. Krop, MD, PhD[2,4]; Antonio C. Wolff, MD[5]; Eric P. Winer, MD[2,4]; and Judy E. Garber, MD, MPH

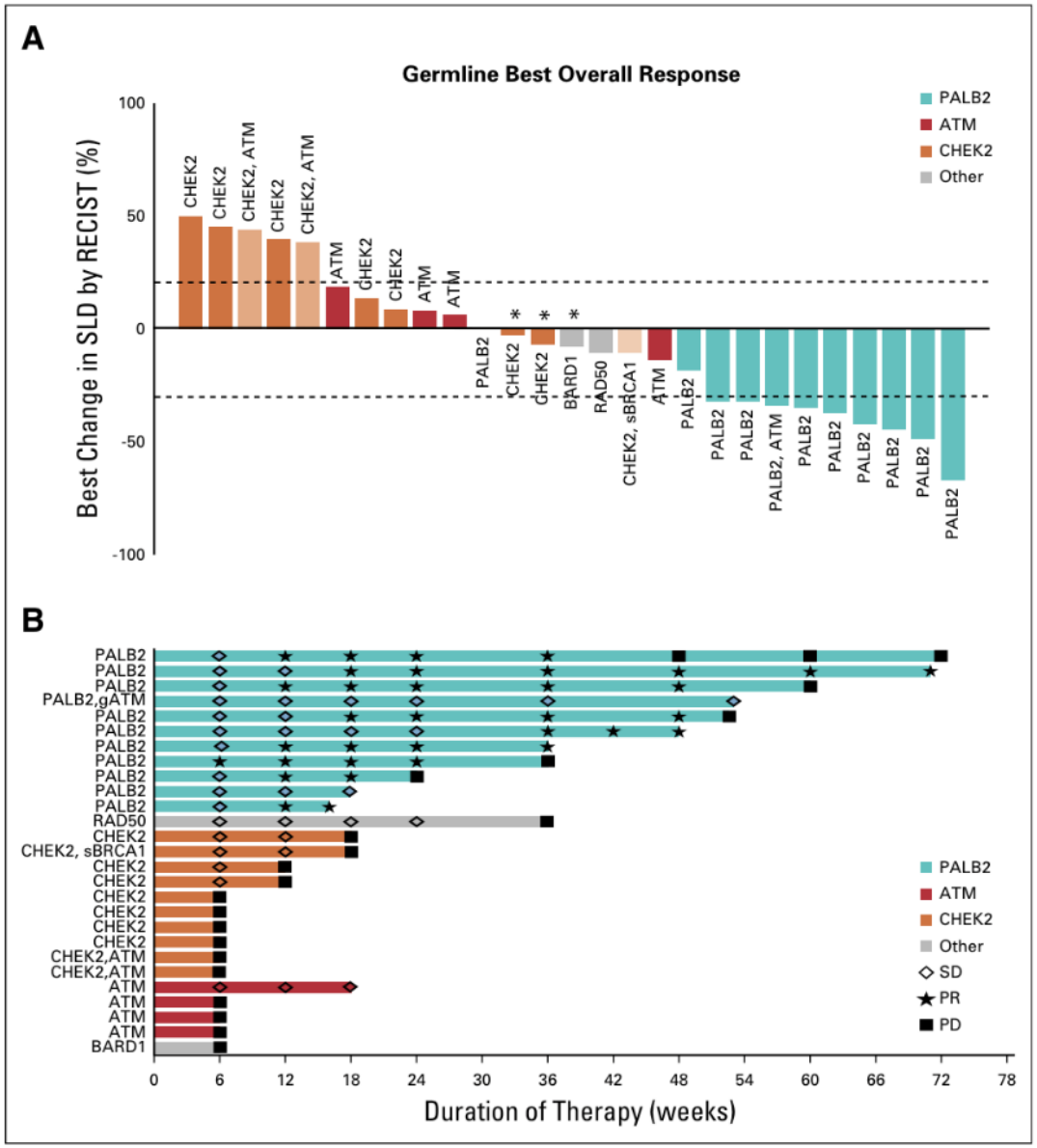
Cohort 1 : Germline
Cohort 2 : Somatic

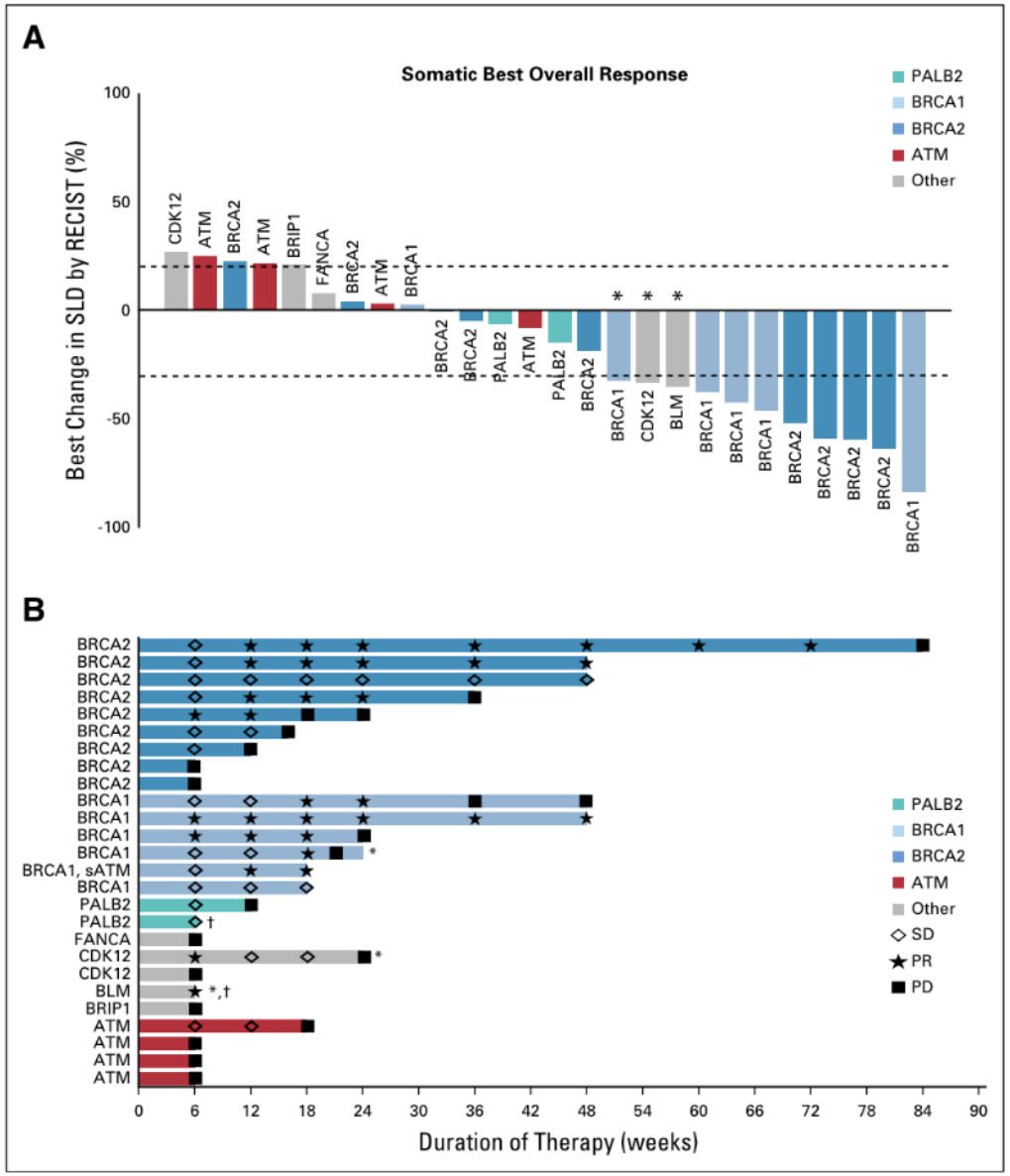
TABLE 1. Patient and Tumor Characteristics

Characteristic	Total (N = 54)	Cohort 1 (n = 27)	Cohort 2[a] (n = 27)
Age, years, mean (range)	59 (30-87)	54 (30-87)	59 (34-79)
Subtype[b]			
ER+ HER2−[c]	41 (76)	23 (85)	18 (67)
TNBC	10 (19)	2 (7)	8 (30)
HER2+	3 (6)	2 (7)	1 (4)
No. of lines of prior chemotherapy in metastatic setting, mean (range)	1 (0-4)	0 (0-2)	1 (0-4)[d]
No prior chemotherapy	10 (19)	6 (22)	4 (15)
Prior platinum	3 (6)	0 (0)	3 (11)
Prior CDK 4/6i among ER+ HER2−	38 (93)	22 (96)	16 (89)
Genes (n = 1 unless specified)	*ATM* (8)	*CHEK2* (8)[e]	*BRCA1* (6)[f]
	BARD1	*ATM* (4)	*BRCA2* (10)[a]
	BLM	ATM & *CHEK2* (2)	*ATM* (4)[g]
	BRIP1	*PALB2* (11)[h]	*PALB2* (2)
	s*BRCA1* (6)[e]	*BARD1*	*CDK12* (2)
	s*BRCA2* (10)	*RAD50*	*BRIP1*
	CDK12 (2)		*BLM*
	CHEK2 (8)[i]		*FANCA*
	ATM & *CHEK2* (2)		
	FANCA		
	PALB2 (13)		
	RAD50		

J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

HER2陰性乳がん（HRD)に対するOlaparib





J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

HER2陰性乳がん（HRD)に対するOlaparib

TABLE 2. Responses by Cohort

Response	Cohort 1 (germline)		Cohort 2 (somatic)	
	All	gPALB2 Mutations	All	sBRCA1/2[a] Mutations
Best response				
(Confirmed) CR	0	0	0	0
(Confirmed) PR	9	9	8	8
SD	8	2	10	6
PD	10	0	8	2
ORR, % (90% CI)	33 (19 to 51)	82 (53 to 96)	31 (15 to 49)	50 (28 to 72)
CBR, % (90% CI)	50 (33 to 67)	100 (74 to 100)	48 (30 to 66)	66 (42 to 85)
DOR, months, median (90% CI)	9 (7.5 to NA)	9 (7.5 to NA)	6.3 (3.1 to NA)	6.3 (3.1 to NA)
PFS, months, median (90% CI)	4.5 (1.7 to 12)	13.3 (12 to NA)	4.1 (2.8 to 6.3)	6.3 (4.4 to NA)
Time to onset of response, weeks, median (90% CI)	12.1 (11.4 to 20.8)	12.1 (11.4 to 20.8)	10.3 (8.4 to 11.9)	10.3 (8.4 to 11.9)

J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

まとめ

- 化学療法後のメンテナンス療法において、生殖細胞*PALB2*変異に対するPARP阻害剤単剤の有効性を報告したものはあるが、体細胞*PALB2*変異に対する有効性は確立していない。
- 進行がん（転移、再発）に対する単剤療法において、PARP阻害剤単剤の有効性は*BRCA1*変異、*BRCA2*変異では確立されている。
- 進行がん（転移、再発）に対する単剤療法において 、*CDK12*変異に対する*PARP*阻害剤単剤の効果は明確ではない。*CDK12*変異に関しては前立腺がんにおいてアンドロゲン受容体シグナル阻害剤との併用において有効である可能性がある。
- ホルモン陰性乳がん （転移、再発） では生殖細胞*PALB2*変異に対するPARP阻害剤単剤の有効性を示す報告がある。
- 進行がん（転移、再発）に対する単剤療法において 他のHRD関連遺伝子では確立していない。

卵巣がんに対するPARP阻害剤のSystematic Reviews

Cochrane Library
Cochrane Database of Systematic Reviews

Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer (Review)

Tattersall A, Ryan N, Wiggans AJ, Rogozińska E, Morrison J

3群での検討

1. 1stライン
2. プラチナ感受性
3. プラチナ抵抗性

Summary of findings 6. Summary of findings table - Platinum-resistant recurrent EOC: PARPi monotherapy compared with chemotherapy

Platinum-resistant recurrent EOC: PARPi monotherapy compared with chemotherapy

Patient or population: platinum-resistant recurrent EOC
Setting: specialist hospital
Intervention: PARPi monotherapy
Comparison: Chemotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Chemotherapy	Risk with PARPi monotherapy				
Overall survival - not reported	-	-	-	-	-	
Progression-free survival - not reported	-	-	-	-	-	
Any severe adverse events (grade 3 or higher) (G3+ SevAE) assessed with: unclear	515 per 1000	**598 per 1000** (407 to 876)	**RR 1.16** (0.79 to 1.70)	100 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c]	The evidence suggests that PARPi monotherapy results in little to no difference in any SevAE (grade 3 or higher).
Quality of Life - not reported	-	-	-	-	-	

Cochrane Database Syst Rev. 2022 Feb 16;2(2):CD007929.

卵巣がんに対するPARP阻害剤のSystematic Reviews

プラチナ感受性

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Chemotherapy alone	Risk with PARPi with chemotherapy				
Overall survival (OS) assessed with: not reported	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	(1 RCT)	-	
Progression-free survival (PFS) assessed with: e of disease progression at 12 months follow-up follow-up: median 33 months	Moderate 220 per 1000	**224 per 1000** (158 to 313)	**HR 1.02** (0.69 to 1.51)	75 (1 RCT)	⨁⊖⊖⊖ Very low[a,b,c,d,e]	The evidence is very uncertain about the effect of PARPi with chemotherapy on progression-free survival.
Quality of Life - not reported	-	-	-	-	-	
Any severe adverse event (grade 3 or higher) (G3+ SevAE) assessed with: not reported	573 per 1000	**654 per 1000** (510 to 843)	**RR 1.14** (0.89 to 1.47)	156 (1 RCT)	⨁⨁⊖⊖ Low[b,d]	PARPi with chemotherapy may result in little to no difference in any severe adverse event (grade 3 or higher).

Cochrane Database Syst Rev. 2022 Feb 16;2(2):CD007929.

卵巣がんに対するPARP阻害剤のSystematic Reviews

プラチナ抵抗性

Summary of findings 6. Summary of findings table - Platinum-resistant recurrent EOC: PARPi monotherapy compared with chemotherapy

Platinum-resistant recurrent EOC: PARPi monotherapy compared with chemotherapy

Patient or population: platinum-resistant recurrent EOC
Setting: specialist hospital
Intervention: PARPi monotherapy
Comparison: Chemotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Chemotherapy	Risk with PARPi monotherapy				
Overall survival - not reported	-	-	-	-	-	
Progression-free survival - not reported	-	-	-	-	-	
Any severe adverse events (grade 3 or higher) (G3+ SevAE) assessed with: unclear	515 per 1000	**598 per 1000** (407 to 876)	**RR 1.16** (0.79 to 1.70)	100 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c]	The evidence suggests that PARPi monotherapy results in little to no difference in any SevAE (grade 3 or higher).
Quality of Life - not reported	-	-	-	-	-	

Cochrane Database Syst Rev. 2022 Feb 16;2(2):CD007929.

Companion diagnostics approved for selection of PARPi

Cancer	Assay	Sample type	Therapy	Trial
Ovarian	BRACAnalysis CDx	Blood	Olaparib	SOLO1 Study
	FoundationOne CDx	Tumor	Olaparib	SOLO1 Study
	Myriad myChoice CDx test	Tumor	Olaparib	SOLO1 Study
	Myriad myChoice CDx test	Tumor	Olaparib + Bevacizumab	PAOLA-1 Study
	BRACAnalysis CDx	Blood	Rucaparib	ARIEL2 Study
	FoundationOne CDx	Tumor	Rucaparib	ARIEL3 Study
	FoundationOne Liquid CDx	Blood	Rucaparib	ARIEL2 Study
	Myriad myChoice CDx test	Tumor	Niraparib	QUADRA Study
Prostate	BRACAnalysis CDx	Blood	Olaparib	PROfound Study
	FoundationOne CDx	Tumor	Olaparib	PROfound Study
	FoundationOne Liquid CDx	Blood	Olaparib	PROfound Study
Breast	BRACAnalysis CDx	Blood	Olaparib	OlympiAD Study
	BRACAnalysis CDx	Blood	Talazoparib	EMBRACA study
Pancreatic	BRACAnalysis CDx	Blood	Olaparib	POLO Study

The Oncologist (2022) 27, 167-174 （一部改変）

CQ. HRDとPARP阻害薬について

- BRCA1/2変異のある固形がん (乳がん/卵がん/前立腺がん/膵がん以外) でPARP阻害薬を推奨/提案しますか

  (はい、いいえ、わからない/棄権)

- gATM変異のある前立腺がんに対して、olaparibを推奨しますか

  (はい、いいえ、わからない/棄権)

- BRCA1/2以外のHRD関連遺伝子変異に対して、(適応外使用として) PARP阻害薬を推奨しますか

  (はい、いいえ、わからない/棄権)

- BRCA1/2以外のHRD関連遺伝子変異に対して、NCCH1901試験のNiraparibを推奨しますか

  (1) PALB2

  (2) その他

  (はい、いいえ、わからない/棄権)

- gPALB2かどうか　(はい 1、いいえ 23、わからない/棄権 11)

- 拠点病院、NCCH1901　はい 24/ いいえ 0

Gene	Tumour types with somatic alterations (mutations, gene deletions and promoter hypermethylation)	Tumour types and syndromes with germline mutations
ATM	T-PLL, breast cancer, GBM, ccRCC, lung adenocarcinoma, sarcoma, and prostate, gastric, bladder, colorectal, uterine and pancreatic cancer	Leukaemia, lymphoma, medulloblastoma, glioma and ataxia telangiectasia
ATR	Breast, colorectal, head and neck, gastric and uterine cancer	Oropharyngeal cancer and familial cutaneous telangiectasia and cancer syndrome
BAP1	ccRCC, cholangiosarcoma, liver cancer and uveal melanoma	Mesothelioma and uveal melanoma
BRCA1	TNBC, HGS-OvCa, lung cancer, prostate cancer, mCRPC and PDAC	TNBC, HGS-OvCa and PDAC
BRCA2	Breast cancer, HGS-OvCa, PDAC, prostate cancer, mCRPC, gastric, bladder and lung cancer, DLBCL and sarcoma	Breast cancer, HGS-OvCa, PDAC and leukaemia
CDK12	HGS-OvCa?, mCRPC and gastric cancer	
CHEK2 (CHK2)	Uterine cancer and HGS-OvCa	Breast cancer
FANCA	HGS-OvCa and lung adenocarcinoma	AML, leukaemia and Fanconi anaemia
FANCC		AML, leukaemia and Fanconi anaemia
FANCD2	ccRCC	AML, leukaemia and Fanconi anaemia
FANCE		AML, leukaemia and Fanconi anaemia
FANCF		AML, leukaemia and Fanconi anaemia
PALB2	Gastric cancer and HGS-OvCa	Wilms tumour, medulloblastoma, AML, Fanconi anaemia, breast cancer, PDAC and HGS-OvCa
NBS1 (NBN)	Gastric and uterine cancer	
WRN	HGS-OvCa, mCRPC, lung adenocarcinoma and uterine cancer	Werner syndrome
RAD51C	HGS-OvCa	Breast cancer and HGS-OvCa
RAD51D		Breast cancer and HGS-OvCa
MRE11A	Colorectal cancer	
CHEK1 (CHK1)	PDAC and sarcoma	
BLM		Bloom syndrome
RAD51B	HGS-OvCa	
BRIP1	HGS-OvCa	

Breast ca., Ovarian ca., Pancreatic ca.

Nijmegen breakage syndrome

Breast ca.?, Pan-cancer

Breast ca.

Breast ca., Ovarian ca.

Nat. Rev. Cancer (2016) 16, 110–120