2024/1/27

第6回 GRACEセミナー

周術期ルミナールタイプ薬物療法
ー最新情報ー

がん研究会 有明病院
乳腺センター 乳腺内科, 先端医療開発科

尾崎 由記範

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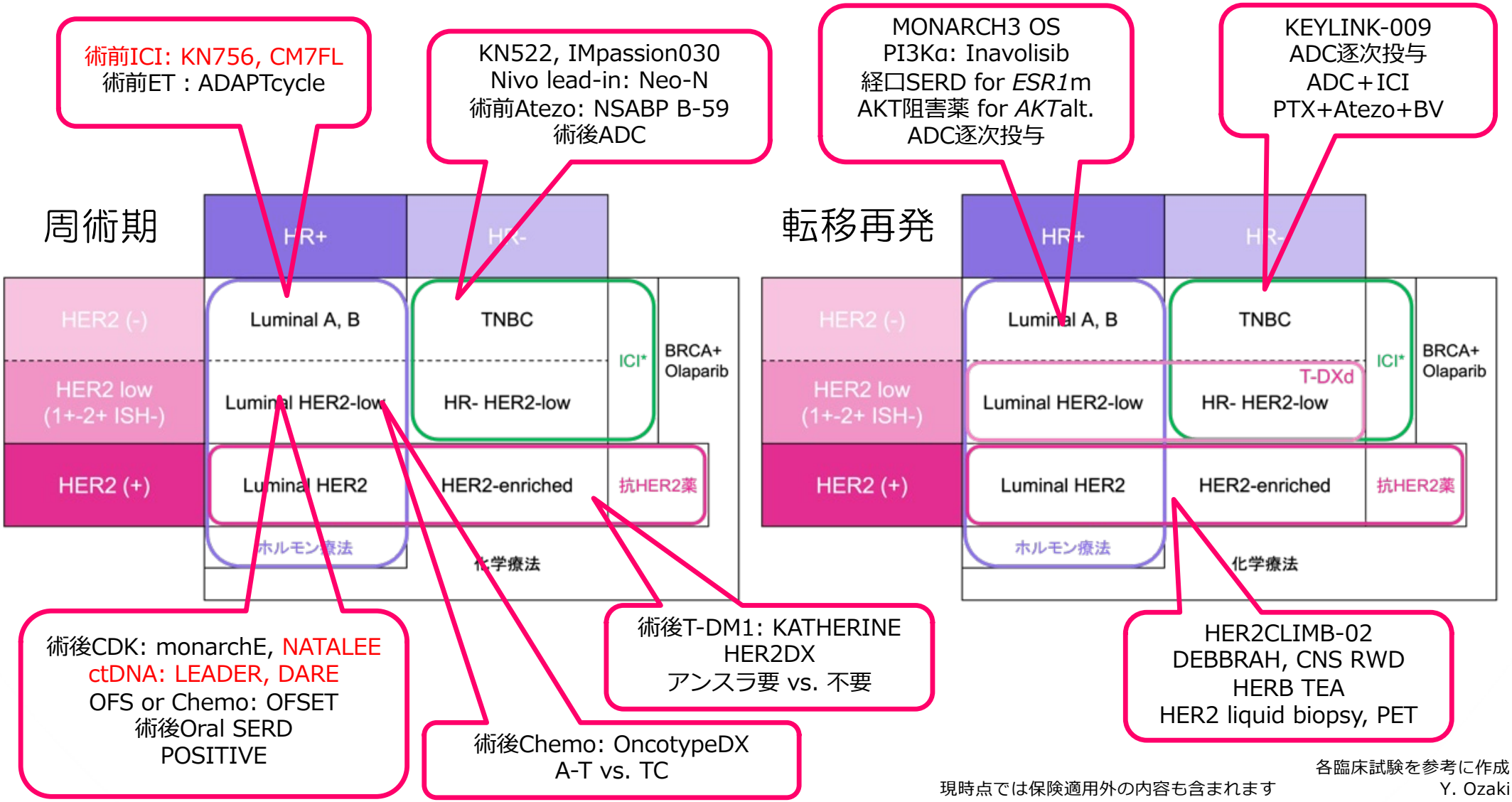
本日の話題

- 術前免疫チェックポイント阻害薬: KEYNOTE-756, CheckMate-7FL
- 術後CDK4/6阻害薬: NATALEE
- ctDNA：おさえておきたいSABCS2023データ
- 将来展望と私見

2023年12月版

乳癌のサブタイプ分類と治療戦略



現時点では保険適用外の内容も含まれます

各臨床試験を参考に作成
Y. Ozaki

KEYNOTE-756: Phase 3 Study of Neoadjuvant Pembrolizumab or Placebo + Chemotherapy Followed by Adjuvant Pembrolizumab or Placebo + Endocrine Therapy for Early-Stage High-Risk ER+/HER2– Breast Cancer

Fatima Cardoso[1], Heather McArthur[2], Peter Schmid[3], Javier Cortes[4], Nadia Harbeck[5], Melinda L Telli[6], David W. Cescon[7], Joyce O' Shaughnessy[8], Peter A. Fasching[9], Zhimin Shao[10], Delphine Loirat[11], Yeon Hee Park[12], Manuel Gonzalez Fernandez[13], Zhenzhen Liu[14], Hiroyuki Yasojima[15], Yu Ding[16], Liyi Jia[16], Vassiliki Karantza[16], Konstantinos Tryfonidis[16], Aditya Bardia[17]

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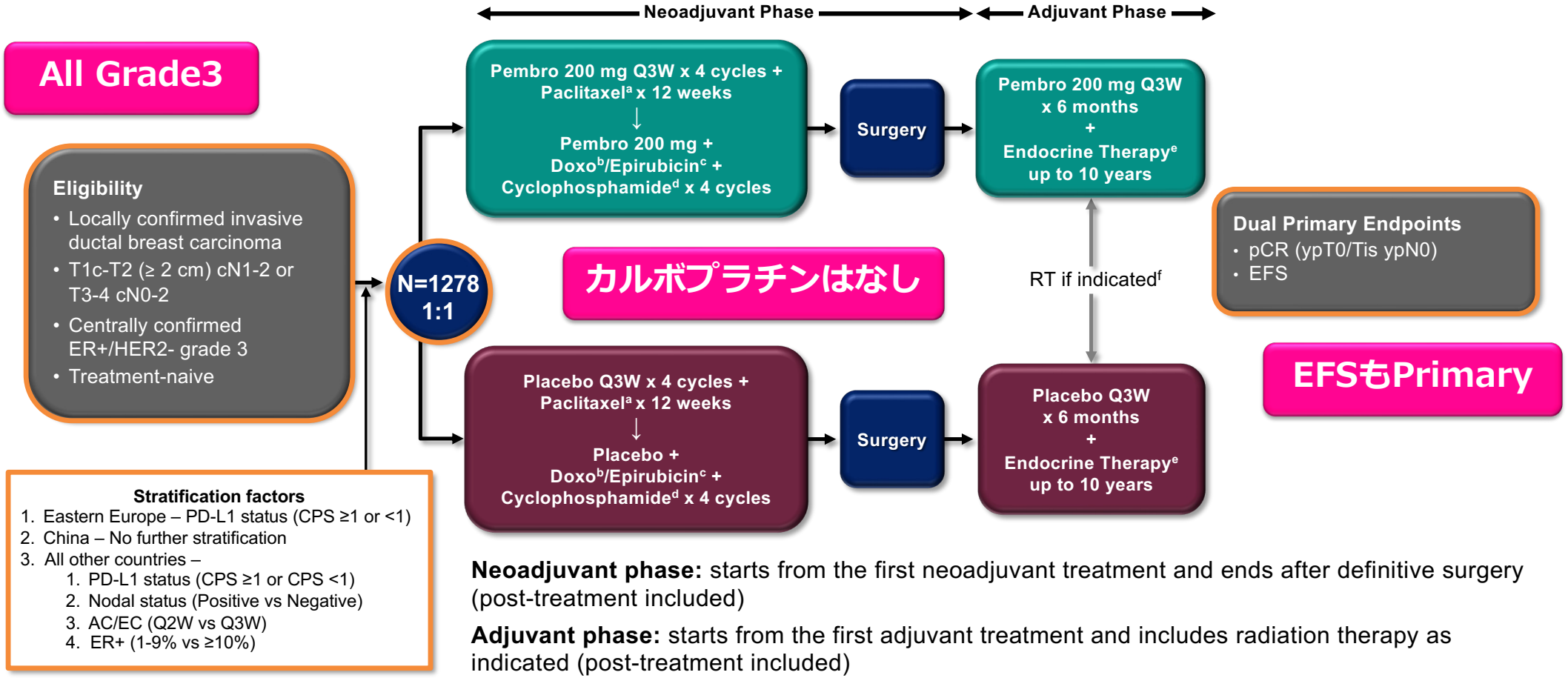
KEYNOTE-756 Study Design (NCT03725059)



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Paclitaxel dose was 80 mg/m^2 QW. [b]Doxorubicin dose was 60 mg/m^2 Q3W. [c]Epirubicin dose was 100 mg/m^2 Q3W. [d]Cyclophosphamide dose was 600 mg/m^2 Q3W or Q2W.
[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

Baseline Characteristics, ITT Population

Characteristic, n (%)	All Participants[a], N = 1278	
	Pembrolizumab Arm N = 635	Placebo Arm N = 643
Age, median (range), yrs	49 (24-82)	49 (19-78)
ECOG PS 1	65 (10.2)	55 (8.6)
PD-L1[b] CPS ≥1	482 (75.9)	489 (76.0)
Anthracycline schedule		
Q3W	415 (65.4)	425 (66.1)
Q2W	183 (28.8)	187 (29.1)
Not started	37 (5.8)	31 (4.8)
Tumor size		
T1/T2	402 (63.3)	413 (64.2)
T3/T4	233 (36.7)	230 (35.8)
Nodal involvement		
Positive	570 (89.8)	582 (90.5)
Negative	65 (10.2)	61 (9.5)
ER positivity ≥10%	601 (94.6)	600 (93.3)

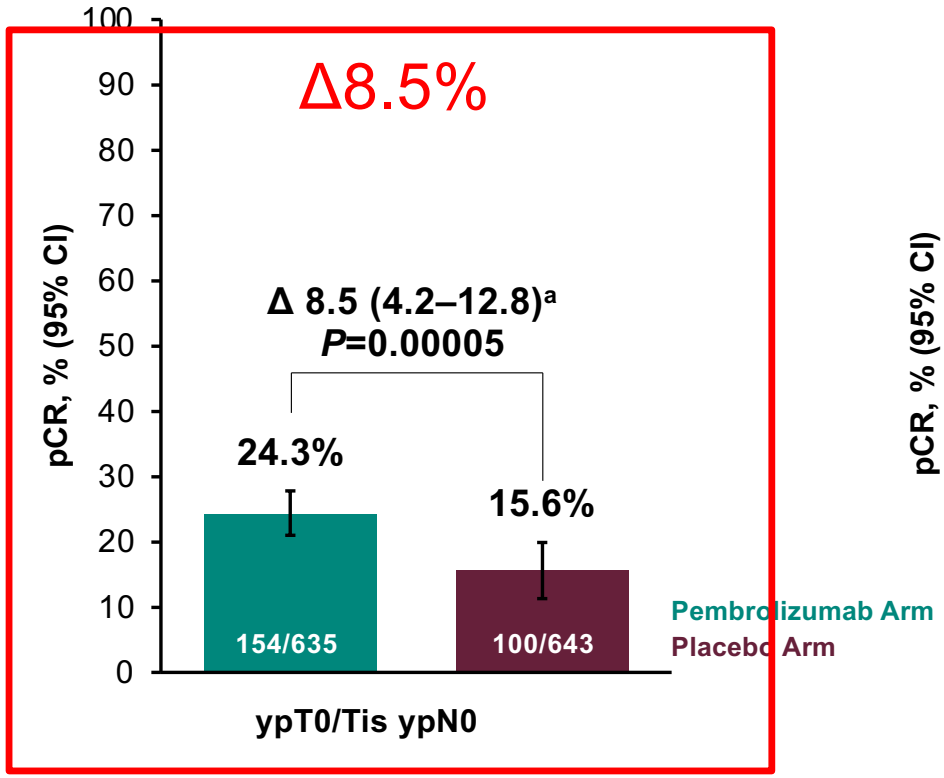
CPS ≥1

All GRADE 3

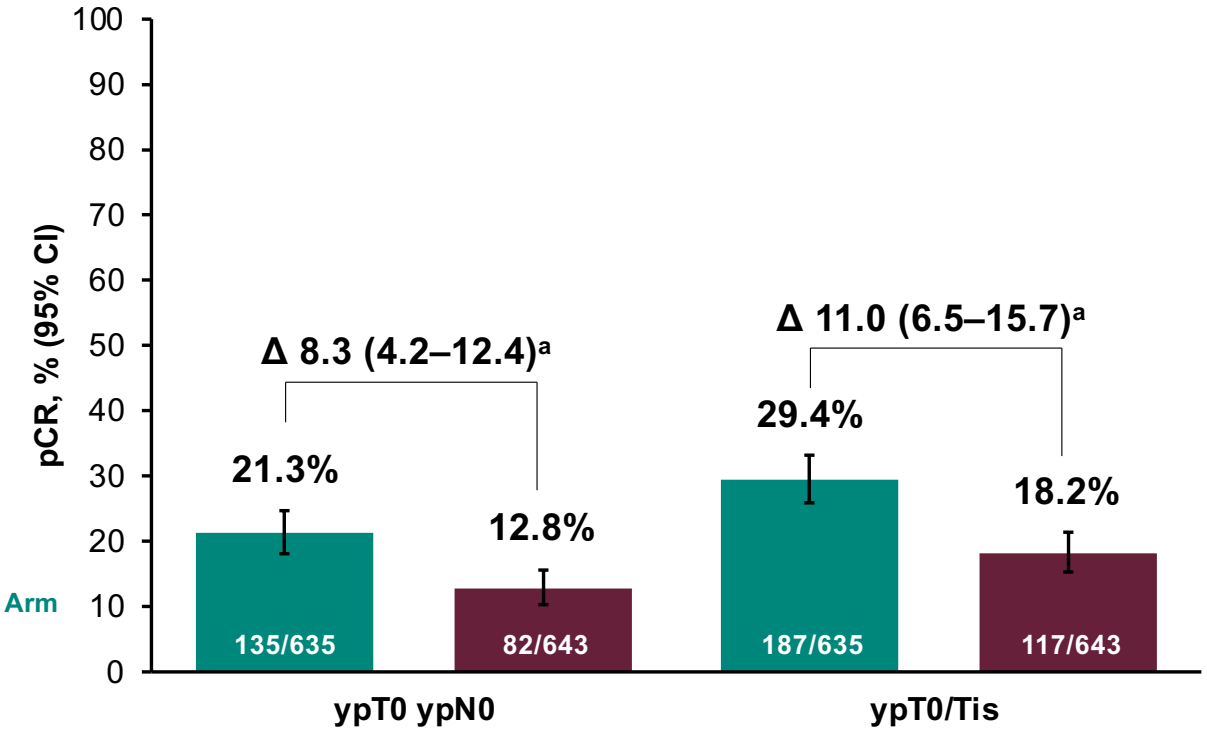
[a]All participants had centrally confirmed grade 3 disease. [b]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100). Data cutoff date: May 25, 2023.

Pathological Complete Response at IA1

Primary Endpoint

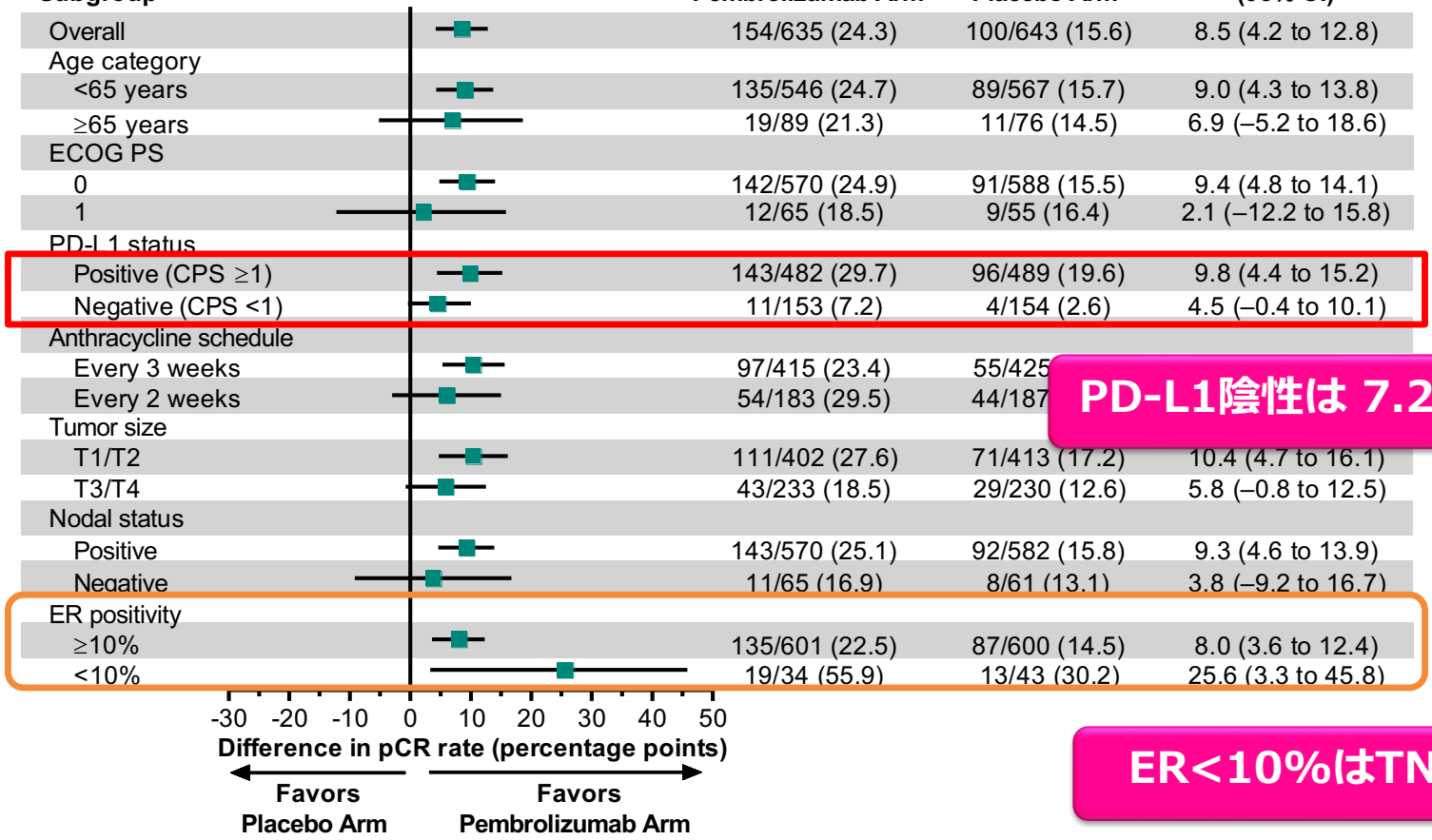


Secondary Endpoints: Other pCR Definitions



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by the analysis randomization stratification factors. Data cutoff date: May 25, 2023.

Pathological Complete Response (ypT0/Tis ypN0) in Subgroups



Subgroup	No. with pCR/No. of Participants (%) Pembrolizumab Arm	Placebo Arm	pCR Rate Difference (95% CI)
Overall	154/635 (24.3)	100/643 (15.6)	8.5 (4.2 to 12.8)
Age category			
<65 years	135/546 (24.7)	89/567 (15.7)	9.0 (4.3 to 13.8)
≥65 years	19/89 (21.3)	11/76 (14.5)	6.9 (–5.2 to 18.6)
ECOG PS			
0	142/570 (24.9)	91/588 (15.5)	9.4 (4.8 to 14.1)
1	12/65 (18.5)	9/55 (16.4)	2.1 (–12.2 to 15.8)
PD-L1 status			
Positive (CPS ≥1)	143/482 (29.7)	96/489 (19.6)	9.8 (4.4 to 15.2)
Negative (CPS <1)	11/153 (7.2)	4/154 (2.6)	4.5 (–0.4 to 10.1)
Anthracycline schedule			
Every 3 weeks	97/415 (23.4)	55/425	
Every 2 weeks	54/183 (29.5)	44/187	
Tumor size			
T1/T2	111/402 (27.6)	71/413 (17.2)	10.4 (4.7 to 16.1)
T3/T4	43/233 (18.5)	29/230 (12.6)	5.8 (–0.8 to 12.5)
Nodal status			
Positive	143/570 (25.1)	92/582 (15.8)	9.3 (4.6 to 13.9)
Negative	11/65 (16.9)	8/61 (13.1)	3.8 (–9.2 to 16.7)
ER positivity			
≥10%	135/601 (22.5)	87/600 (14.5)	8.0 (3.6 to 12.4)
<10%	19/34 (55.9)	13/43 (30.2)	25.6 (3.3 to 45.8)

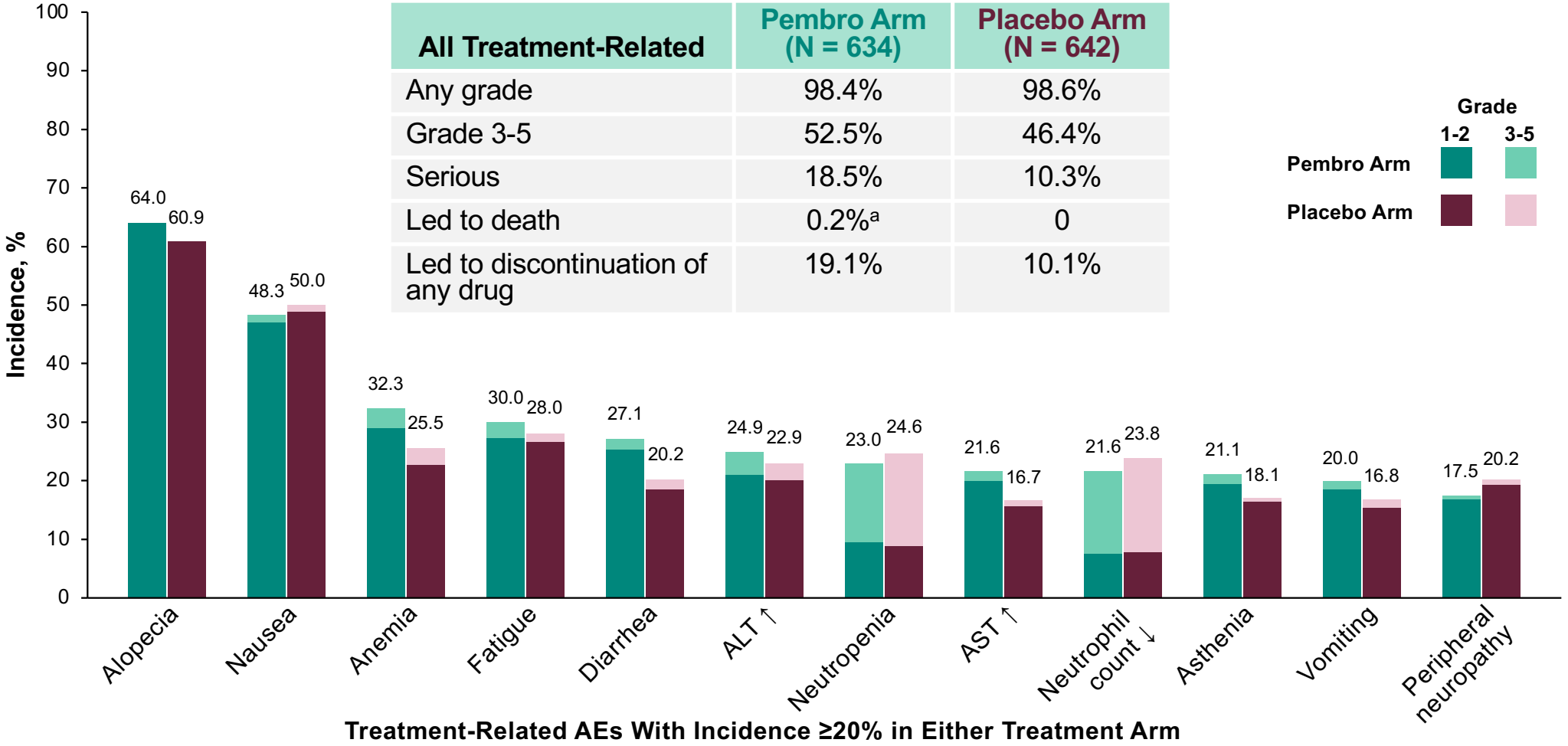
PD-L1陰性は 7.2% vs 2.6%

ER<10%はTNBC-like

For the overall population, analysis is based on Miettinen and Nurminen method stratified by the analysis randomization stratification factors. For other subgroups, analysis is based on unstratified Miettinen and Nurminen method. Data cutoff date: May 25, 2023.

Treatment-Related AEs in **Neoadjuvant** Phase

All Treatment-Related	Pembro Arm (N = 634)	Placebo Arm (N = 642)
Any grade	98.4%	98.6%
Grade 3-5	52.5%	46.4%
Serious	18.5%	10.3%
Led to death	0.2%[a]	0
Led to discontinuation of any drug	19.1%	10.1%

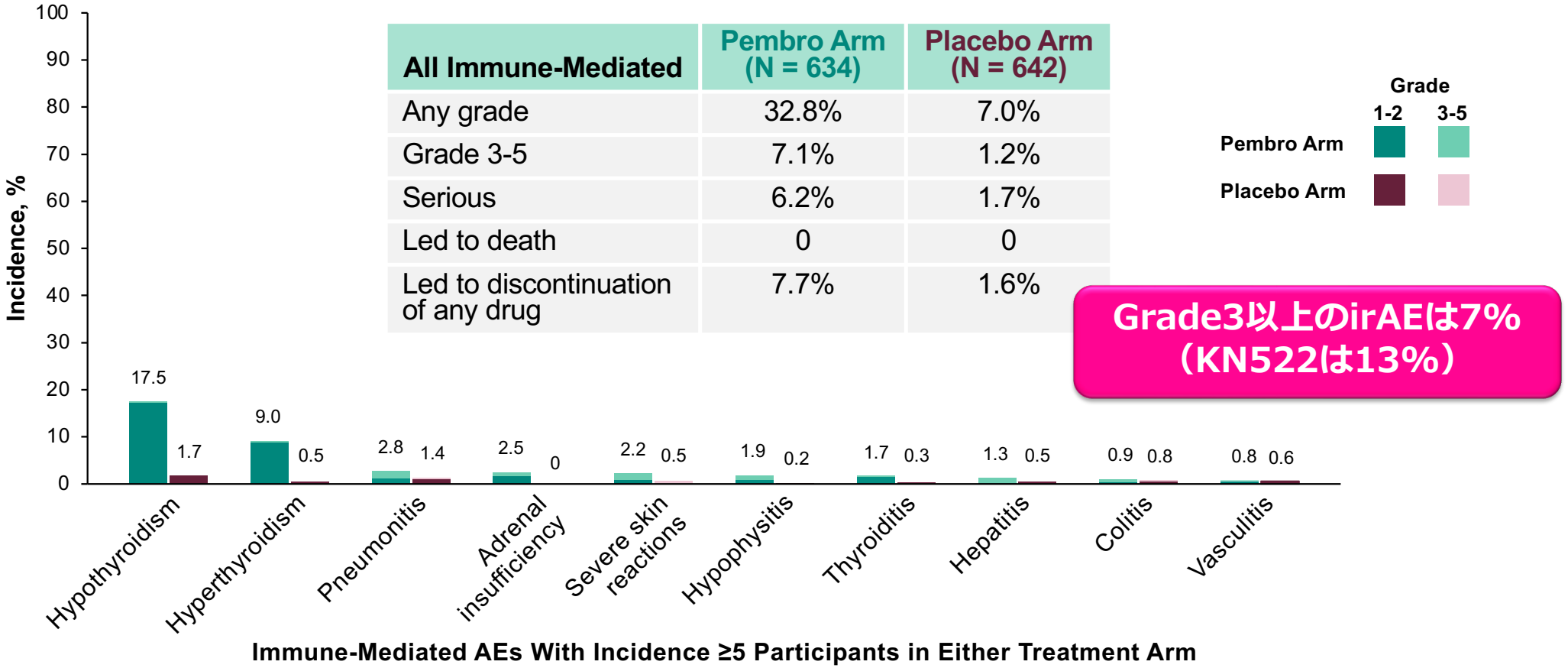


Treatment-Related AEs With Incidence ≥20% in Either Treatment Arm

[a]**1 patient from acute myocardial infarction, considered related to QT.** Data cutoff date: May 25, 2023.

Immune-Mediated AEs in **Neoadjuvant** Phase

All Immune-Mediated	Pembro Arm (N = 634)	Placebo Arm (N = 642)
Any grade	32.8%	7.0%
Grade 3-5	7.1%	1.2%
Serious	6.2%	1.7%
Led to death	0	0
Led to discontinuation of any drug	7.7%	1.6%



Immune-Mediated AEs With Incidence ≥5 Participants in Either Treatment Arm

Grade3以上のirAEは7%（KN522は13%）

Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed.
Data cutoff date: May 25, 2023.

Summary

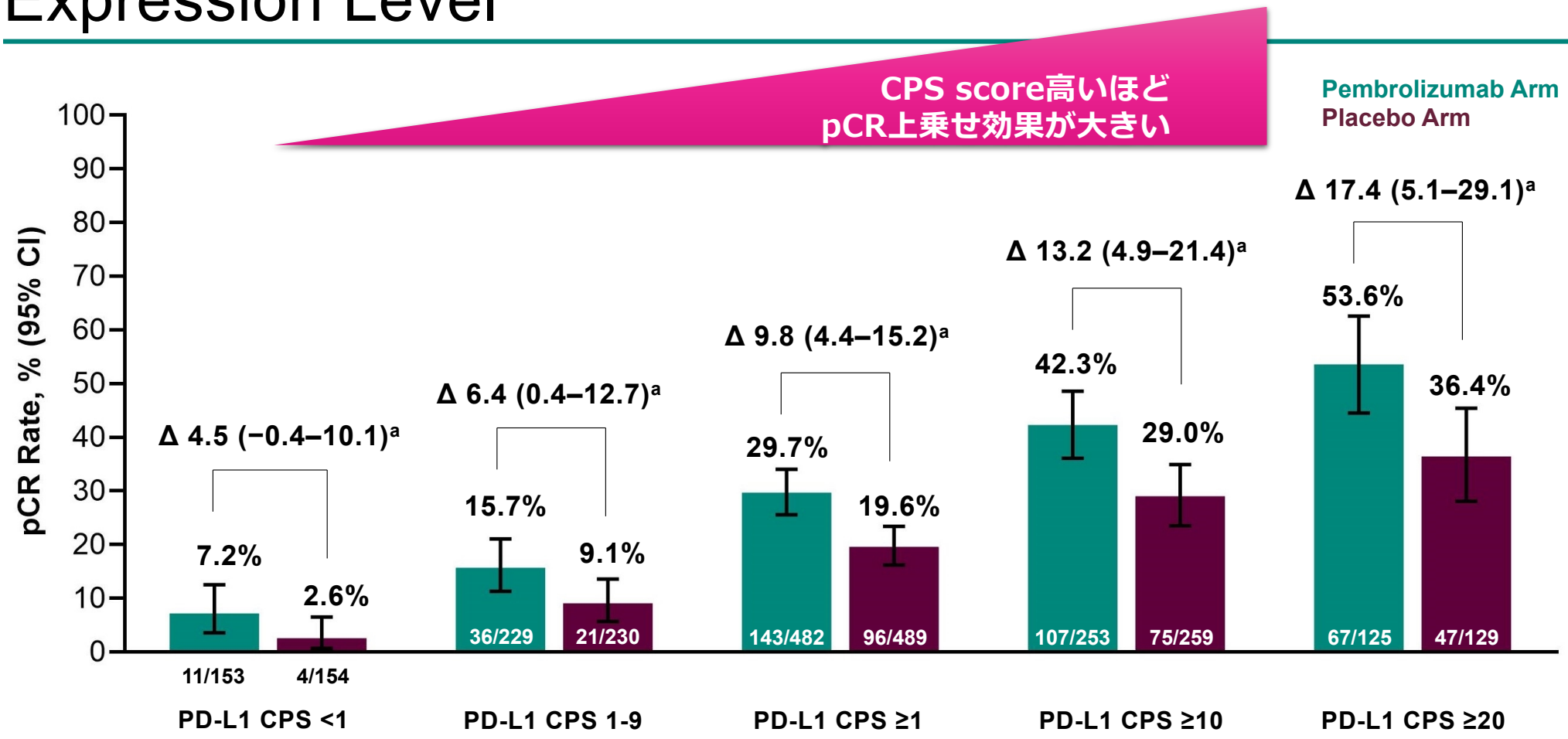
- KEYNOTE-756 is the **first fully accrued phase 3 immunotherapy study** in high-risk, early-stage ER+/HER2– breast cancer and met its dual primary endpoint (pCR)
- The addition of pembrolizumab to NAC led to **a statistically significant increase in pCR** (ypT0/Tis ypN0) **of 8.5 percentage points** (P=0.00005) in the ITT population, regardless of PD-L1 status

PD-L1に関わらずpCRの改善が示された

- A consistent benefit was seen with pCR defined as ypT0 ypN0 and ypT0/Tis
- Safety was consistent with the known profiles of each regimen; no new safety signals were observed
- **The study is powered to test EFS as the dual primary endpoint.** At this early timepoint, EFS results are still immature and continue to be evaluated

EFSはdual primary endpointで結果待ち

Pathological Complete Response at IA1 by PD-L1 Expression Level



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by geographic region (China vs Eastern Europe vs all other countries). Data cutoff date: May 25, 2023.

MADRID 2023 ESMO congress

A randomized, double-blind trial of nivolumab vs placebo with neoadjuvant chemotherapy followed by adjuvant endocrine therapy in patients with high-risk, ER+ HER2− primary breast cancer

Sherene Loi,[1] Giuseppe Curigliano,[2,3] Roberto Salgado,[1,4] Roberto Iván Romero Díaz,[5] Suzette Delaloge,[6] Carlos Ignacio Rojas García,[7] Marleen Kok,[8] Cristina Saura,[9] Nadia Harbeck,[10] Elizabeth A. Mittendorf,[11] Denise A. Yardley,[12] Lajos Pusztai,[13] Alberto Suárez Zaizar,[14] Andrei Ungureanu,[15] Felipe Ades,[16] Rajalakshmi Chandra,[16] Raheel Nathani,[16] Misena Pacius,[16] Jenny Qun Wu,[16] Heather McArthur[17]

[1]Peter McCallum Cancer Center, Melbourne, Australia; [2]European Institute of Oncology, IRCCS, Milan, Italy; [3]University of Milan, Milan, Italy; [4]GZA-ZNA Hospitals, Antwerp, Belgium; [5]Consultorio de Oncólogo Médico, Oaxaca, Mexico; [6]Institut Gustave Roussy, Villejuif, France; [7]Bradford Hill Investigación Clinica, Región Metropolitana, Santiago, Chile; [8]Netherlands Cancer Institute, Amsterdam, The Netherlands; [9]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]Ludwig Maximilians University Hospital, Munich, Germany; [11]Dana Farber Cancer Institute, Boston, MA, USA; [12]Sarah Cannon Research Institute and Tennessee Oncology PLLC, Nashville, TN, USA; [13]Smilow Cancer Hospital at Yale, New Haven, CT, USA; [14]CENEIT Oncológicos, Mexico City, Mexico; [15]Radiotherapy Center CLUJ S.R.L., Florești, Romania; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]University of Texas Southwestern Medical Center, Dallas, TX, USA

Presentation number LBA20

CA209-7FL study design

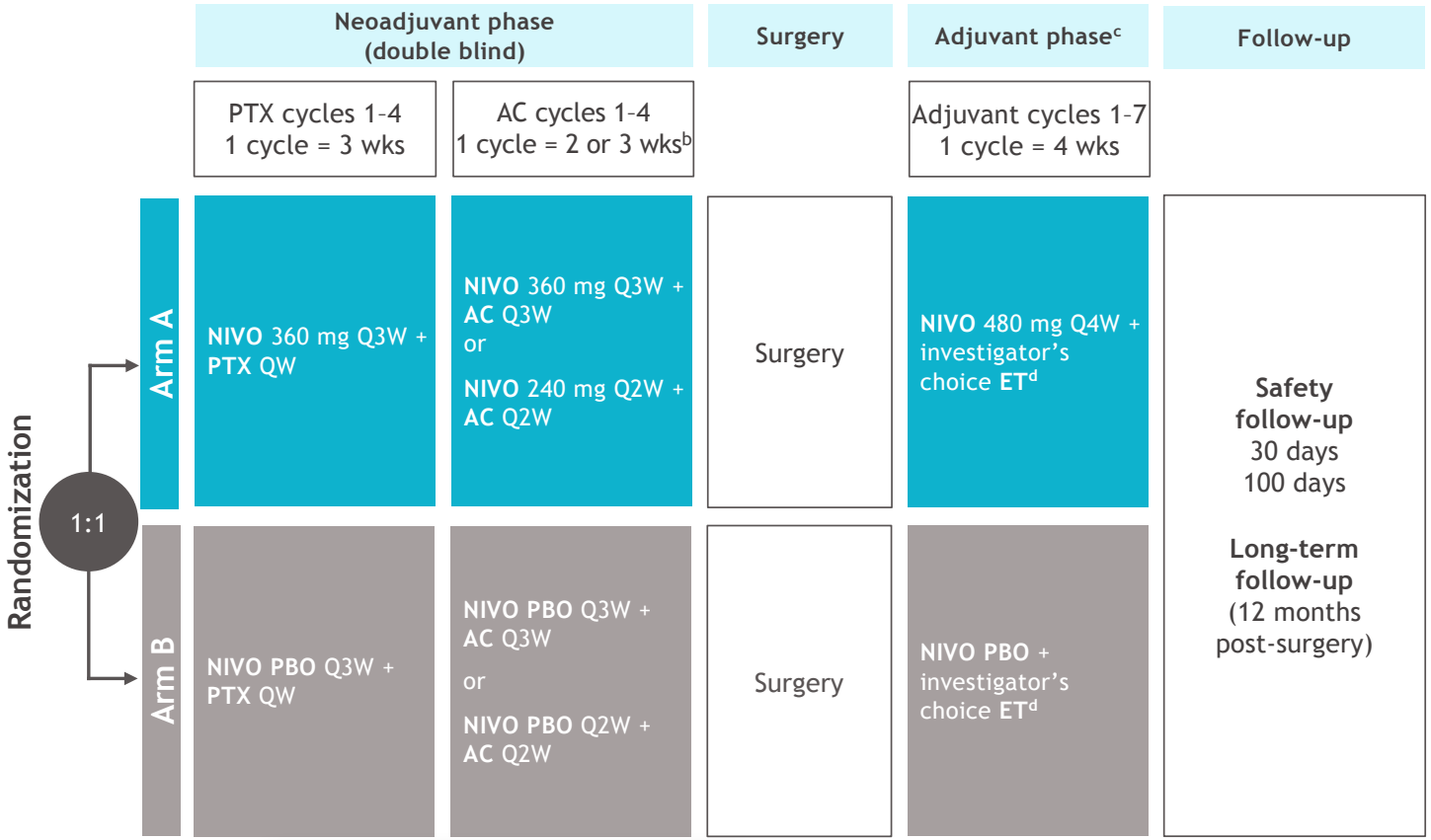
Screening

Key inclusion criteria

- Newly diagnosed ER+ HER2− breast cancer
- Confirmed ER+ breast cancer
- T1c-T2, cN1–cN2 or T3-T4, cN0-cN2
- Grade 3 with ER ≥ 1% or grade 2 with ER 1–10%[a]
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0–1

Stratification factors

- PD-L1 IC (≥ 1% or < 1%)
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)



Grade2も許容

カルボプラチンなし

[a]Grade … tigator's choice: anthracycline dosing … y the investigator. [c]After protocol amendment 3, the study was unblinded in the adj … eive NIVO PBO. [d]Available ET agents i … stane.

AC, anthracycline + cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; ER+, estrogen receptor-positive; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2-negative; IC, immune cell; N, lymph node involvement; NIVO, nivolumab; PBO, placebo; PD-L1, programmed death ligand 1; PTX, paclitaxel; QXW, every X weeks; T, size and extent of primary tumor; wk, week.

Study endpoints and primary endpoint power calculation

Primary endpoint

- pCR in the mITT population[a]

pCRのみ

Secondary endpoints

- pCR[a] in the PD-L1+ population[b]
- RCB class (0/1/2/3) frequency and RCB 0–1 rate
- RCB class frequency and RCB 0-1 rate in the PD-L1+ population
- Safety and tolerability

Exploratory endpoint

- EFS (unavailable for this presentation)

Primary endpoint (pCR) power calculation

Efficacy population	ITT	mITT
Sample size	521	510
Accrual duration, months	29	
Hypothesized rates: control vs experimental [arm B vs arm A], %	12 vs 22	
Alpha 2-sided	0.05	
Power for pCR, %	87	86

[a]pCR defined as no invasive residual disease in breast and lymph nodes (ypT0/Tis, ypN0[1]) by a local pathologist. The pCR rate is defined as the percentage of participants who achieved pCR in the mITT population of all randomized participants excluding those enrolled at Russian sites with insufficient follow-up to assess pCR at the time of site closure. Participants who did not undergo surgery were counted as non-pCR and included in the denominator. [b]PD-L1–expressing tumor-infiltrating IC as percentage of tumor area using the VENTANA SP142 assay, per central assessment.
EFS, event-free survival; IC, immune cell, (m)ITT, (modified) intent-to-treat; pCR, pathological complete response; PD-L1, programmed death ligand 1; RCB, residual cancer burden; RCB-0: no residual disease; RCB-1: minimal residual disease; RCB-2: moderate residual disease; RCB-3: extensive residual disease; T, clinical tumor size; ypT0, absence of pathological invasive carcinoma in breast following neoadjuvant chemotherapy; ypTis, pathological carcinoma in situ following neoadjuvant chemotherapy; ypN0, pathological negative lymph nodes following neoadjuvant chemotherapy. 1. AJCC Cancer Staging Manual; 8th edition, 3rd printing, Amin MB, Edge SB, Greene FL, et al. (Eds), Springer, Chicago 2018.

Patient baseline characteristics in mITT population (n = 510)

- Of 830 patients screened, 521 were randomized in total and 510 were randomized in the primary efficacy population (mITT)

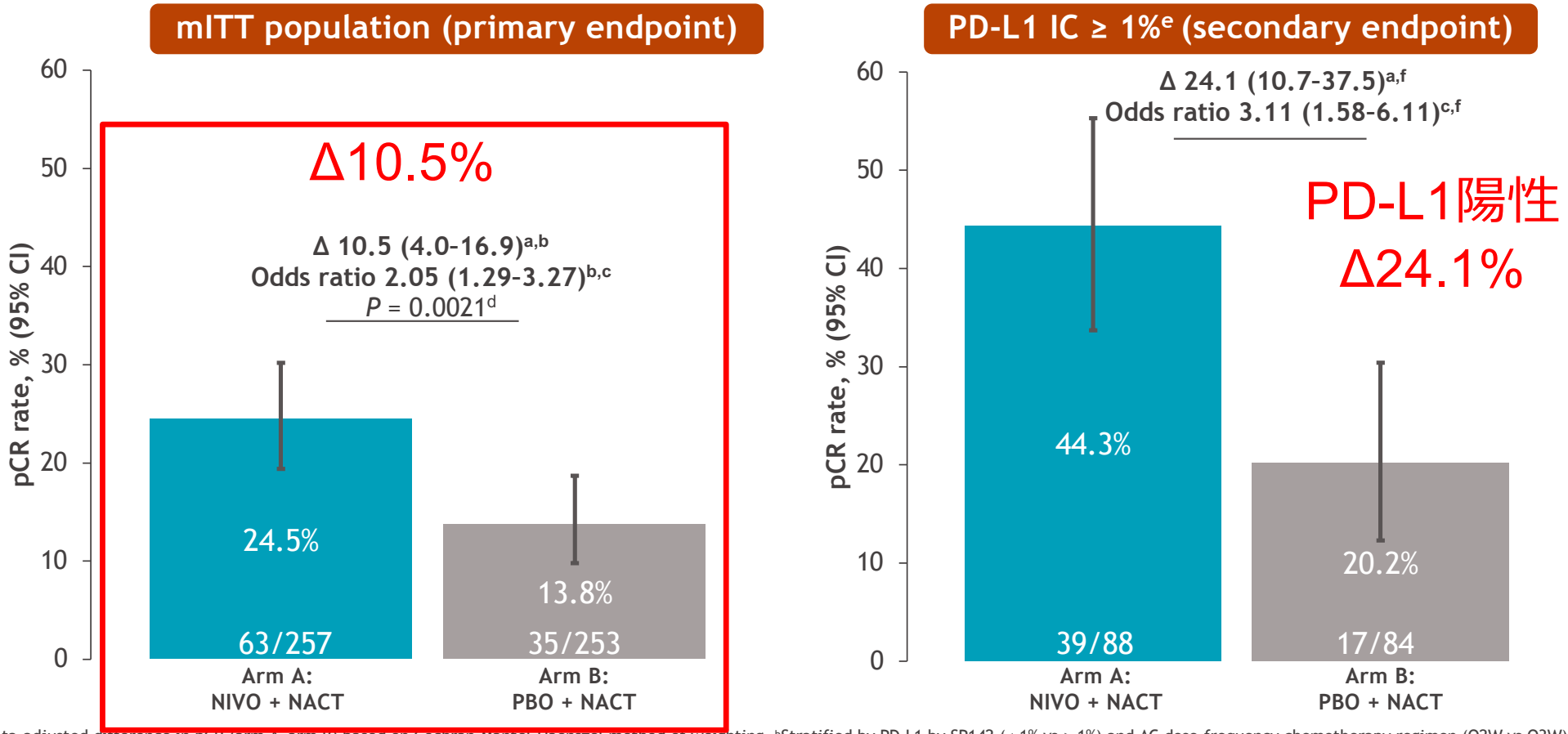
	Arm A: NIVO + NACT, n = 257	Arm B: PBO + NACT, n = 253
Median age, years (range)	50 (24-78)	51 (23-79)
ECOG PS, n (%)		
0	221 (86)	222 (88)
1	36 (14)	31 (12)
Tumor grade,[a] n (%)		
Grade 2	6 (2)	1 (< 1)
Grade 3	251 (98)	252 (> 99)
Stage[b] (TNM classification[1]), n (%)		
Stage II	135 (53)	138 (55)
Stage III	118 (46)	105 (42)
Not assigned/reported	4 (2)	7 (3)
PD-L1,[c] n (%)		
< 1%	169 (66)	169 (67)
≥ 1%	88 (34)	84 (33)
Axillary nodal status, n (%)		
Positive	205 (80)	201 (79)
Negative	52 (20)	52 (21)
AC dose-frequency chemotherapy regimen, n (%)		
Q2W	132 (51)	134 (53)
Q3W	125 (49)	119 (47)

[a]Locally assessed. [b]Arm B included 1 patient with stage ...ssing tumor-infiltrating IC as percentage of tumo... ...ssessment. AC, anthracycline + cyclophosphamide; ECOG PS, Easte... ...nune cell; mITT, modified intent-to-treat; NACT... ..., placebo; PD-L1, programmed death ligand 1; QXW, every X wee... ...tumor; N, extent of spread to the lymph nodes; ... ...anual; 8th edition, 3rd printing, Amin MB, Edge SB, Greene FL, et al (Eds), Springer, Chicago 2018.

ほぼ全例 Grade3

SP142 IC ≥1

pCR rate in mITT population and by PD-L1 IC ≥ 1%



[a]Strata-adjusted difference in pCR (arm A–arm B) based on Cochran-Mantel-Haenszel method of weighting. [b]Stratified by PD-L1 by SP142 (< 1% vs ≥ 1%) and AC dose-frequency chemotherapy regimen (Q2W vs Q3W) per IRT. [c]Strata-adjusted odds ratio (arm A over arm B) using Mantel-Haenszel method. [d]Two-sided *P* value from stratified Cochran-Mantel-Haenszel test. [e]PD-L1 ICs and PD-L1-expressing tumor-infiltrating ICs as percentage of tumor area using the VENTANA SP142 assay. [f]Stratified by AC dose-frequency chemotherapy regimen.

AC, anthracycline + cyclophosphamide; CI, confidence interval; IC, immune cell; IRT, interactive response technology; mITT, modified intent-to-treat; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death ligand 1; QXW, every X weeks.

Summary

- The primary endpoint of CheckMate 7FL was met; in patients with high-risk, ER+/HER2− primary breast cancer, the addition of NIVO to NACT resulted in a statistically significant increase in pCR of 10.5% (24.5% in arm A vs 13.8% in arm B)

pCRの改善が示された

- RCB 0–1 rate (secondary endpoint) was also improved by 9.2% with the addition of NIVO (30.7% in arm A vs 21.3% in arm B)
- NIVO benefit was greater in patients with PD-L1 IC ≥ 1%
  - ΔpCR of 24.1% (44.3% in arm A vs 20.2% in arm B)
  - ΔRCB 0-1 of 28.5% (54.5% in arm A vs 26.2% in arm B)

PD-L1陽性でベネフィット大きい

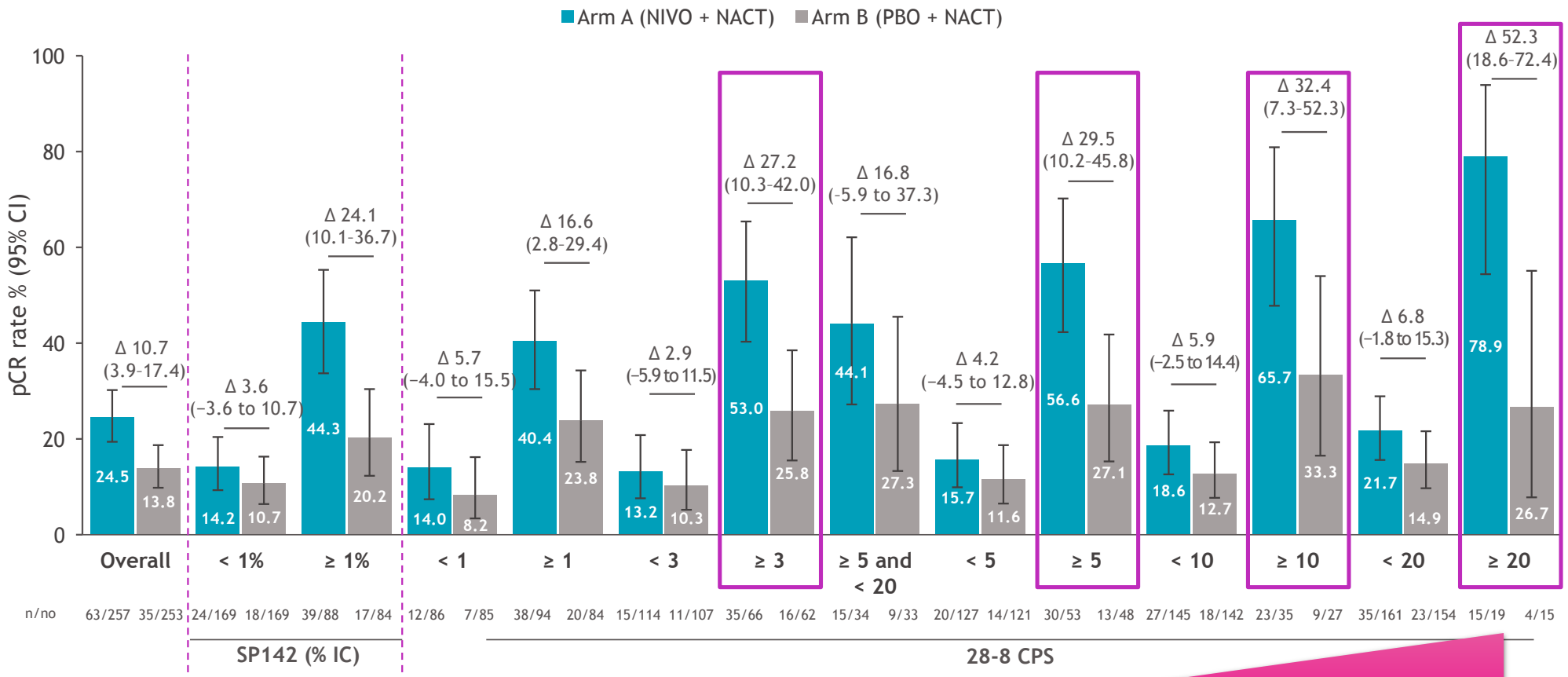
- No meaningful difference in the feasibility of surgery was observed between the two arms
- Safety of the NIVO + NACT combination was consistent with the known safety profiles of the treatment components, with no new safety signals reported
- Additional biomarker data will be presented at a future congress

EFSについては言及なし・・・

ER+, estrogen receptor-positive; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2-negative; IC, immune cell; mITT, modified intent-to-treat; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; pCR, pathological complete response; PD-L1, programmed death ligand 1; RCB, residual cancer burden; TRAE, treatment-related adverse event.

pCR by PD-L1 status determined by SP142 (IC%) and 28-8 CPS (cutoffs 1-20)

CheckMate 7FL
San Antonio Breast Cancer Symposium®, December 5-9, 2023

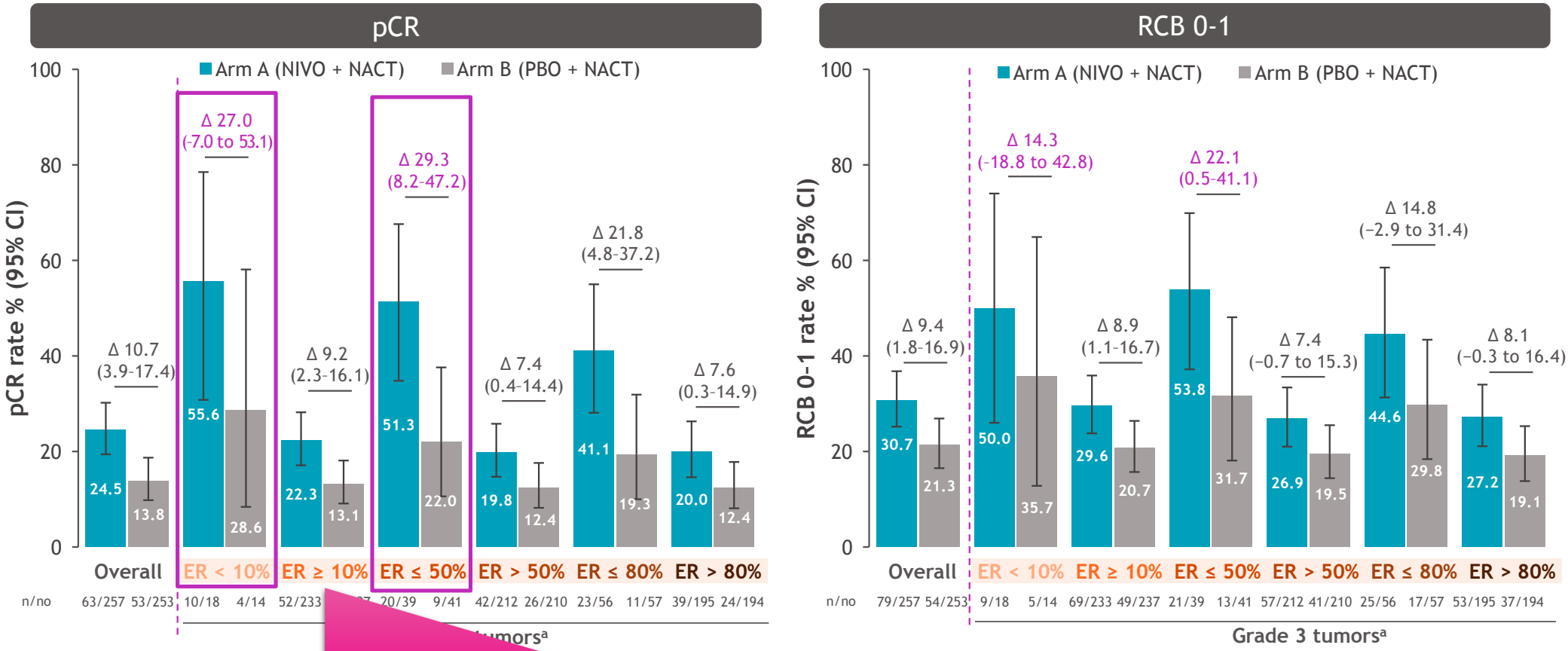


- PD-L1 CPS ≥ 3 was determined as the optimal cut-off for the prediction of NIVO benefit based on the ROC and lift
- The benefit of NIVO was increased in patients with PD-L1+ tumors defined by both SP142 IC (≥ 1%)

CPS score高いほど pCR上乗せ効果が大きい

28-8 CPS, Dako 28-8 assay using CPS algorithm; CPS, combined positive score; IC
pCR, pathological complete response; PD-L1, programmed death ligand 1; ROC, receiver operating characteristic; SP142, Ventana PD-L1 SP142 assay.

pCR and RCB 0-1 by tumor ER expression



- ER > 50%, ER > 80% and PR ≥ 10
- NIVO benefit on pCR and RCB 0-
- umors with low ER (≤ 50%)

ER≤50%
pCRの差大きい

[a]Tumor grade as per the eCRF. eCRF, electronic case report form; ER, estrogen receptor; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; no, subpopulation total; PBO, placebo; pCR, pathological complete response; RCB, residual cancer burden.

KN756, 7FLまとめと私見

共通点

- Grade3のハイリスクに絞った患者選択
- カルボプラチンはなし
- いずれの試験でもpCRの有意な改善が示された
- PD-L1 CPS score highで差が大きい
- ER弱陽性で差が大きい

相違点

- KN756では、pCRとEFSが　Dual primary endpoint
- 7FLでは、EFSは探索的

論点

- Practice changingか？　→ No
- pCRの意義は？　→ 一定の意義があるがEFS待ち
- 患者選択は？　→ Grade3, PD-L1 high？ ER ≤10？
- 毒性とのバランスは？　→EFS次第か？

本日の話題

- 術前免疫チェックポイント阻害薬: KEYNOTE-756, CheckMate-7FL
- 術後CDK4/6阻害薬: NATALEE
- ctDNA：おさえておきたいSABCS2023データ
- 将来展望と私見

2023 ASCO ANNUAL MEETING

Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2− early breast cancer: primary results from the Phase III NATALEE trial

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PRESENTED BY: Dennis Slamon MD, PhD

NATALEE study design[1,2]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 y

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

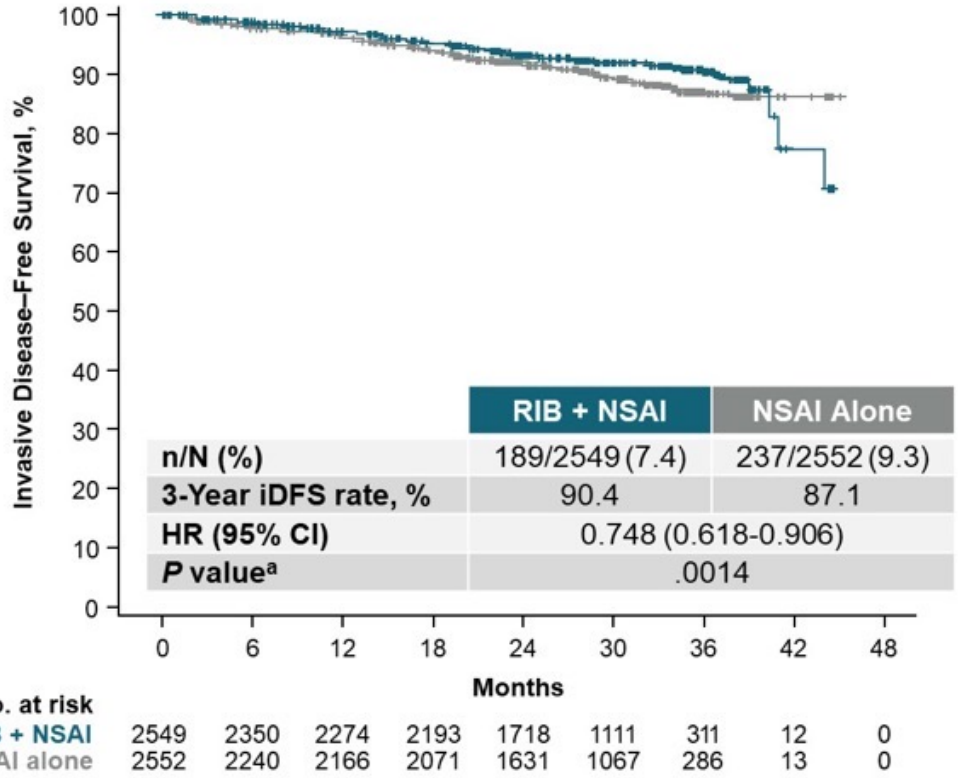
Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl) [abstract TPS597].

PRESENTED BY: Dennis Slamon MD, PhD

Ribociclib achieved highly significant iDFS benefit



	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	.0014	

No. at risk									
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

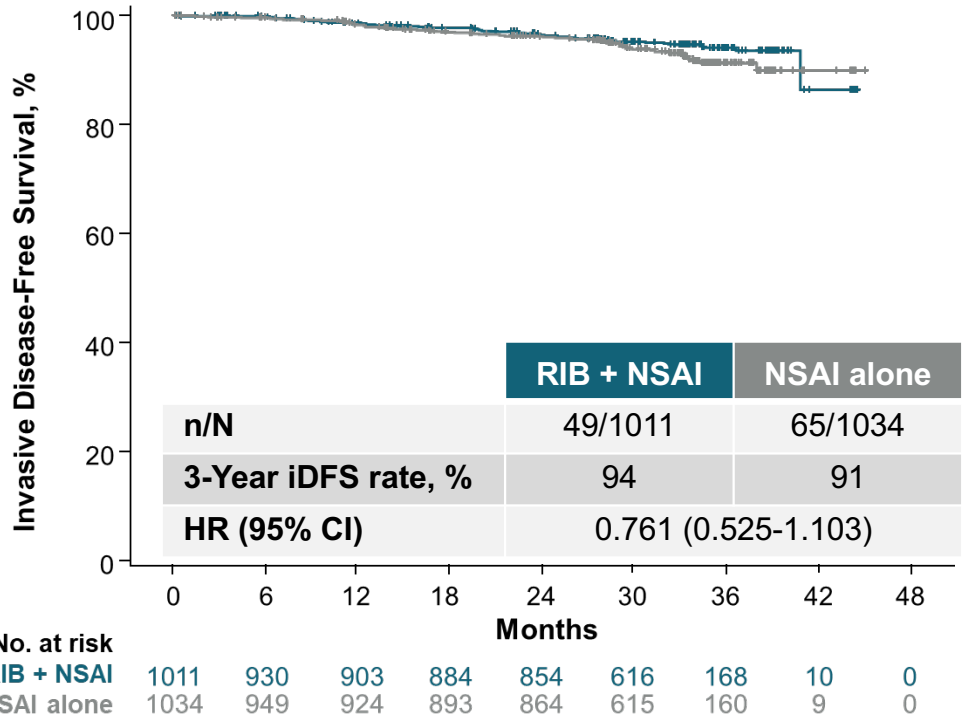
- Median follow-up for iDFS was 27.7 months
- Based on the *P* value of 0.0014, the IDMC concluded that the results met the criteria to demonstrate statistically significant and clinically superior efficacy
- Absolute iDFS benefit with RIB + NSAI at 3 years was 3.3%
- Risk of invasive disease was reduced by 25.2% with RIB + NSAI vs NSAI alone
- Ongoing patients will remain on treatment and follow-up will continue as prespecified

iDFS, invasive disease–free survival; IDMC, Independent Data Monitoring Committee; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value.

NATALEE iDFS by anatomic stage

Consistent iDFS benefit with ribociclib + NSAI in patients with stage II or III disease

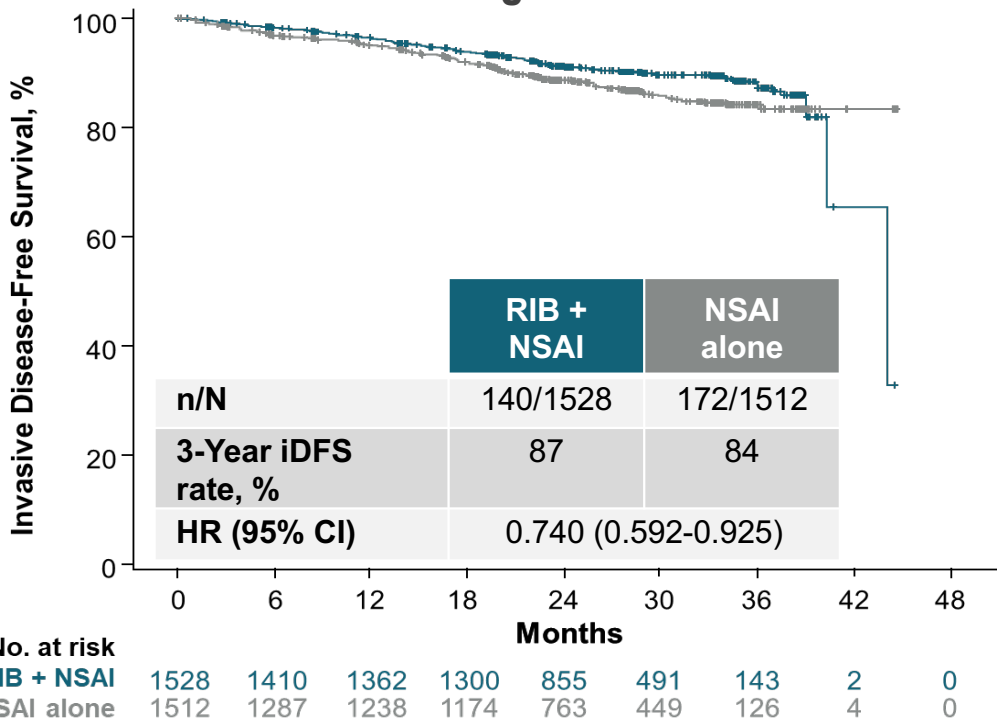
Stage II



	RIB + NSAI	NSAI alone
n/N	49/1011	65/1034
3-Year iDFS rate, %	94	91
HR (95% CI)	0.761 (0.525-1.103)	

No. at risk									
RIB + NSAI	1011	930	903	884	854	616	168	10	0
NSAI alone	1034	949	924	893	864	615	160	9	0

Stage III



	RIB + NSAI	NSAI alone
n/N	140/1528	172/1512
3-Year iDFS rate, %	87	84
HR (95% CI)	0.740 (0.592-0.925)	

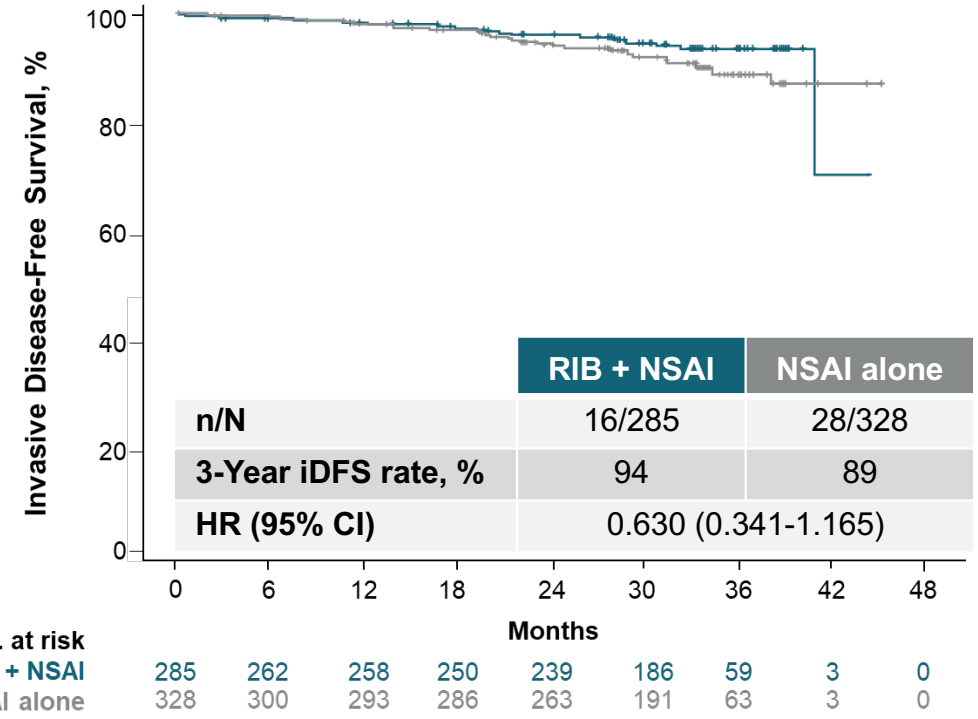
No. at risk									
RIB + NSAI	1528	1410	1362	1300	855	491	143	2	0
NSAI alone	1512	1287	1238	1174	763	449	126	4	0

iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

NATALEE iDFS by nodal status

Ribociclib + NSAI prolonged iDFS regardless of nodal status

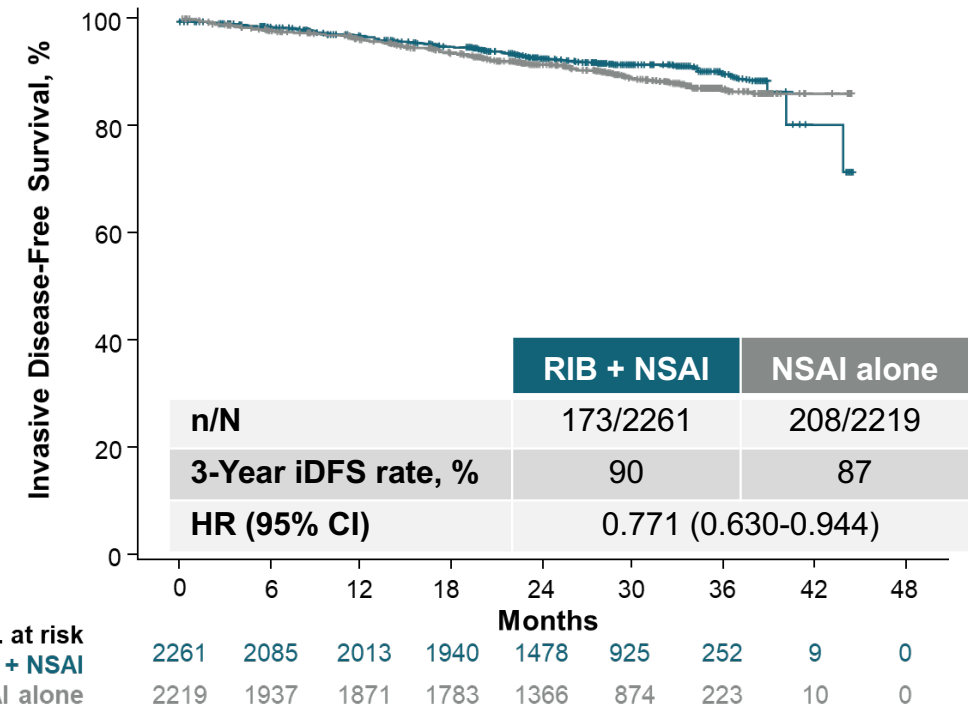
N0



	RIB + NSAI	NSAI alone
n/N	16/285	28/328
3-Year iDFS rate, %	94	89
HR (95% CI)	0.630 (0.341-1.165)	

No. at risk									
RIB + NSAI	285	262	258	250	239	186	59	3	0
NSAI alone	328	300	293	286	263	191	63	3	0

N1-N3



	RIB + NSAI	NSAI alone
n/N	173/2261	208/2219
3-Year iDFS rate, %	90	87
HR (95% CI)	0.771 (0.630-0.944)	

No. at risk									
RIB + NSAI	2261	2085	2013	1940	1478	925	252	9	0
NSAI alone	2219	1937	1871	1783	1366	874	223	10	0

iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Conclusions

- NATALEE met its primary end point at the second interim efficacy analysis, demonstrating a statistically significant and clinically meaningful improvement in iDFS with ribociclib + NSAI over NSAI alone
- iDFS benefit was consistent across prespecified key patient subgroups
- Results for secondary end points consistently favored ribociclib + NSAI over NSAI alone
- The 3-year regimen of ribociclib at a 400-mg starting dose in the adjuvant setting was well tolerated

NATALEE results support ribociclib + NSAI as a new treatment of choice in a broad population of patients with stage II or III HR+/HER2− EBC at risk of recurrence, including patients with node-negative disease

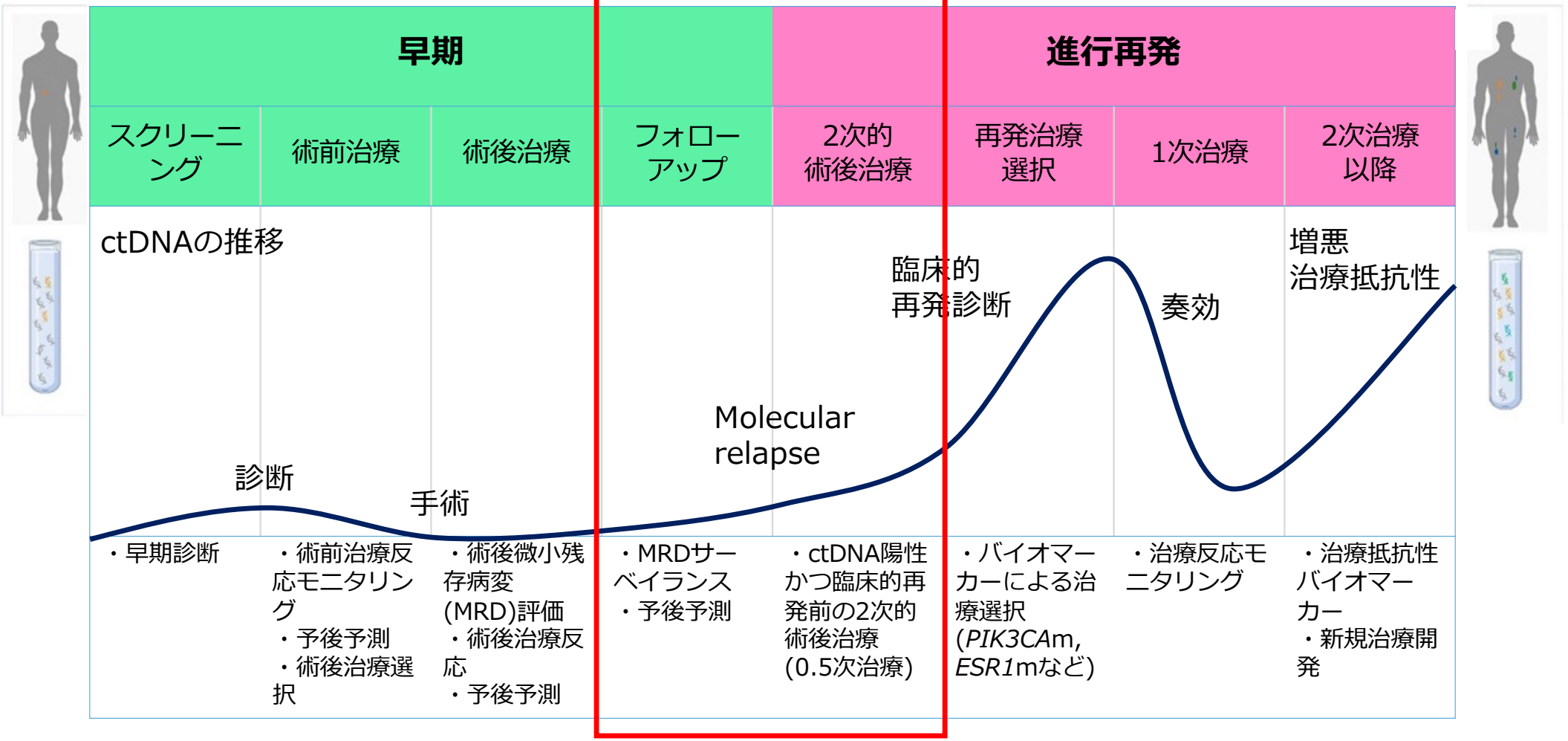
Ribociclib 400mg 3年間は再発高リスクstage II-IIIに対する
標準的選択肢となる

本邦未承認の薬剤情報を含みます

本日の話題

- 術前免疫チェックポイント阻害薬: KEYNOTE-756, CheckMate-7FL
- 術後CDK4/6阻害薬: NATALEE
- ctDNA：おさえておきたいSABCS2023データ
- 将来展望と私見

ctDNAの臨床応用



Trends in Molecular Medicine, 2021-10-01, Volume 27, Issue 10, Pages 1014-1015,

ESMOガイドラインをもとに筆者作

Tumor-informed アプローチ
Tumor-naive アプローチ

Tumor-informedアプローチ

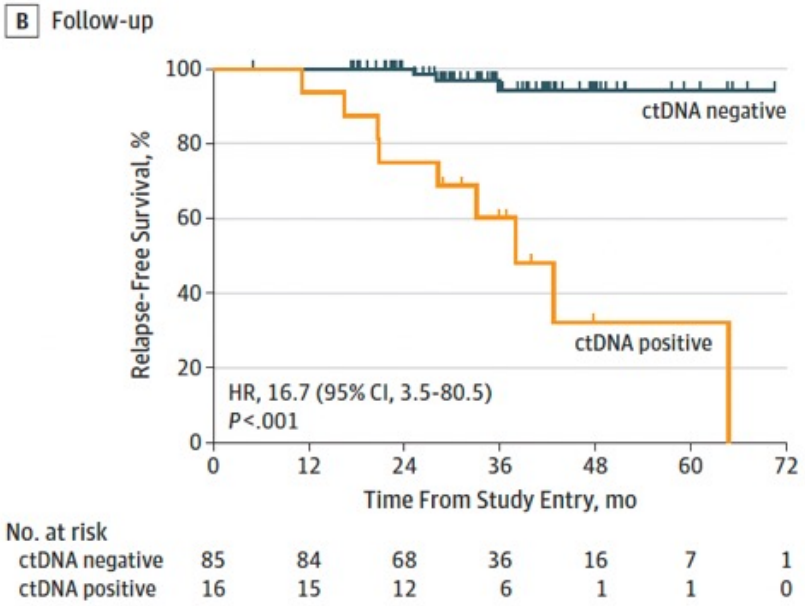
- ベースの腫瘍組織かつ/または血漿が必要
- ベースライン検体の遺伝子解析の結果に基づき解析対象遺伝子を選択（個別化）
- 特異的な遺伝子の選定により検出限界が低い
- Signatera, RaDaR, CAPP-seq, PCM assay

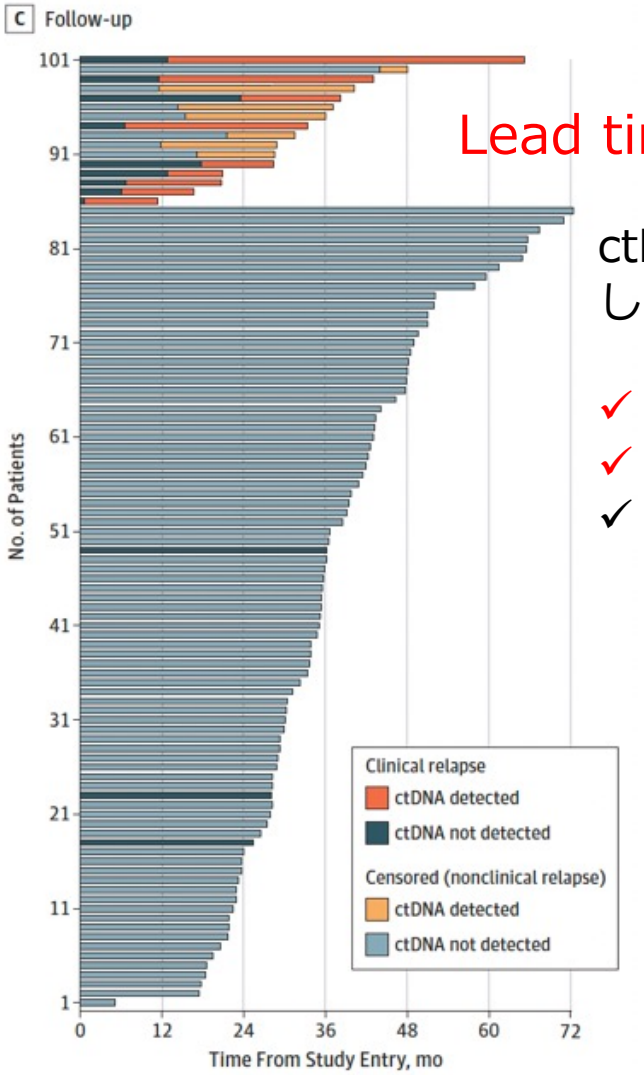
Tumor-naiveアプローチ

- ベースラインの組織が不要
- 事前に設定された遺伝子を解析対象とする
- TATが短い
- GuardantReveal, FoundationOne Liquid, Safe-SeqS, TEX-seq

Assessment of Molecular Relapse Detection in Early-Stage Breast Cancer

Isaac Garcia-Murillas, Nicholas Turner et al.





Lead time 10.7 months

ctDNAが検出されずに再発した6症例

- ✓ 脳転移のみ3例
- ✓ 局所領域再発のみ2例
- ✓ 卵巣のみ1例

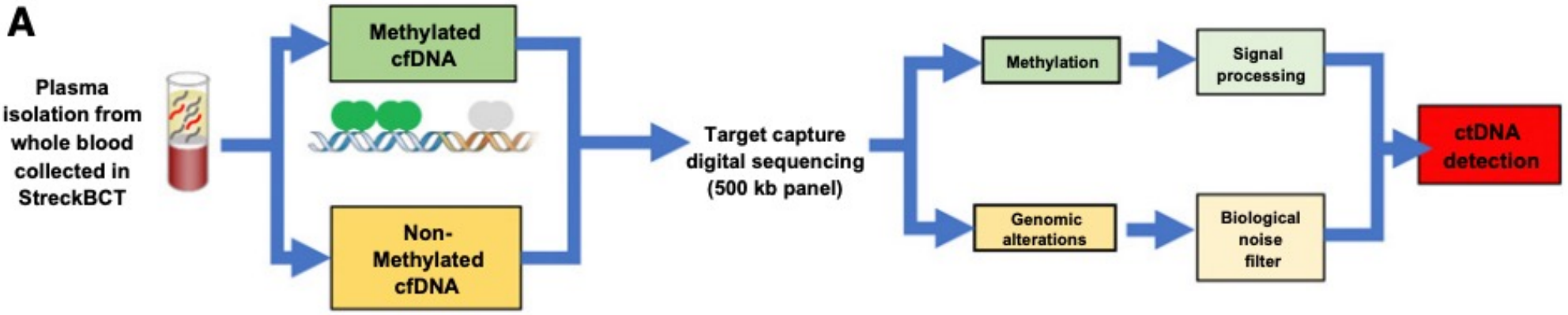
→Unmet needs

JAMA Oncol. 2019;5(10):1473-1478. doi:10.1001/jamaoncol.2019.1838

Guardant シリーズ

GUARDANT REVEAL
Residual Disease and Recurrence Monitoring

- ✓ 組織不要
- ✓ エピジェネティックな変化を検出することで感度を向上



https://guardanthealthjapan.com/

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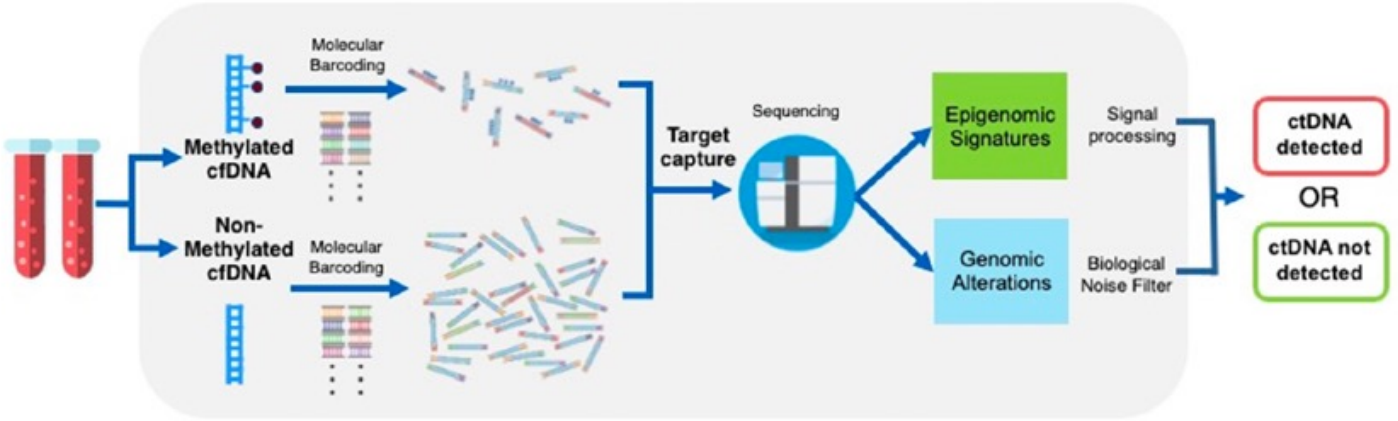
Analysis of ctDNA for the detection of minimal residual disease (MRD) using a tissue-free, multiomic assay in patients with early-stage breast cancer

Wolfgang Janni, MD, PhD
Ulm University Hospital, Ulm, Germany

Objectives and Methods

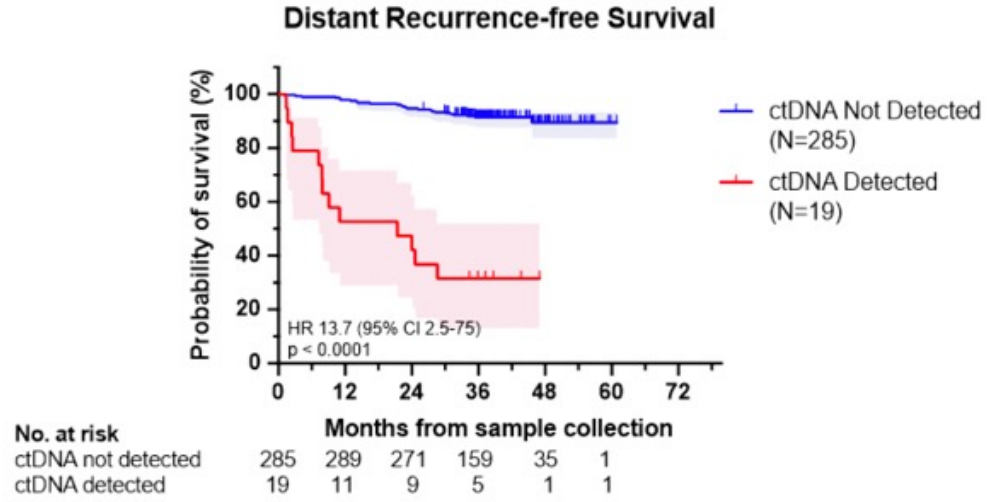
- The presence of ctDNA was retrospectively evaluated in 311 patients with stage I-III breast cancer who were enrolled in the adjuvant SUCCESS-A study (NCT02181101).
- cfDNA was analyzed at a single time point approximately 2 years post-adjuvant chemotherapy (median 29 months post-surgery) using the tissue-free Guardant Reveal assay.
- The objectives were to evaluate the sensitivity and specificity for recurrence prediction and to determine the prognostic significance of ctDNA in the post-adjuvant treatment setting.

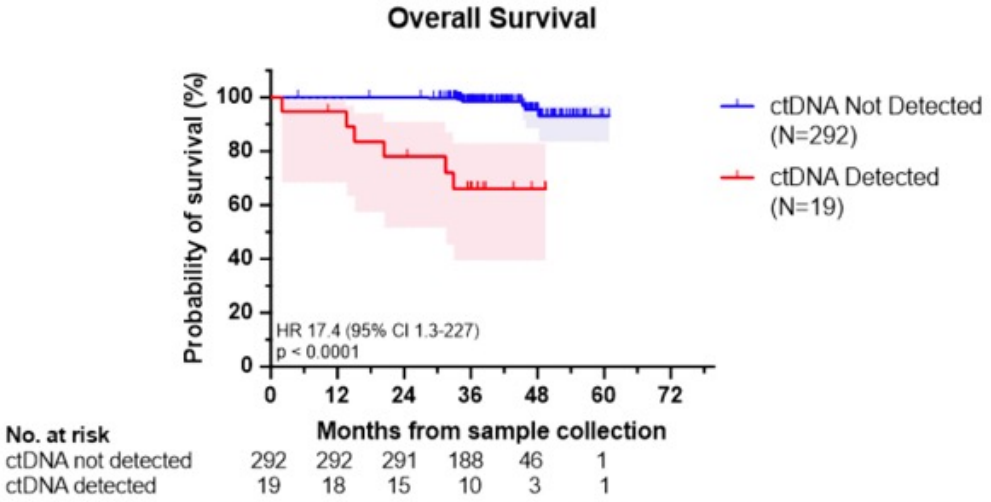


A "ctDNA detected result" is defined by the de novo identification of tumor-specific contribution to methylation profile exceeding predefined thresholds.

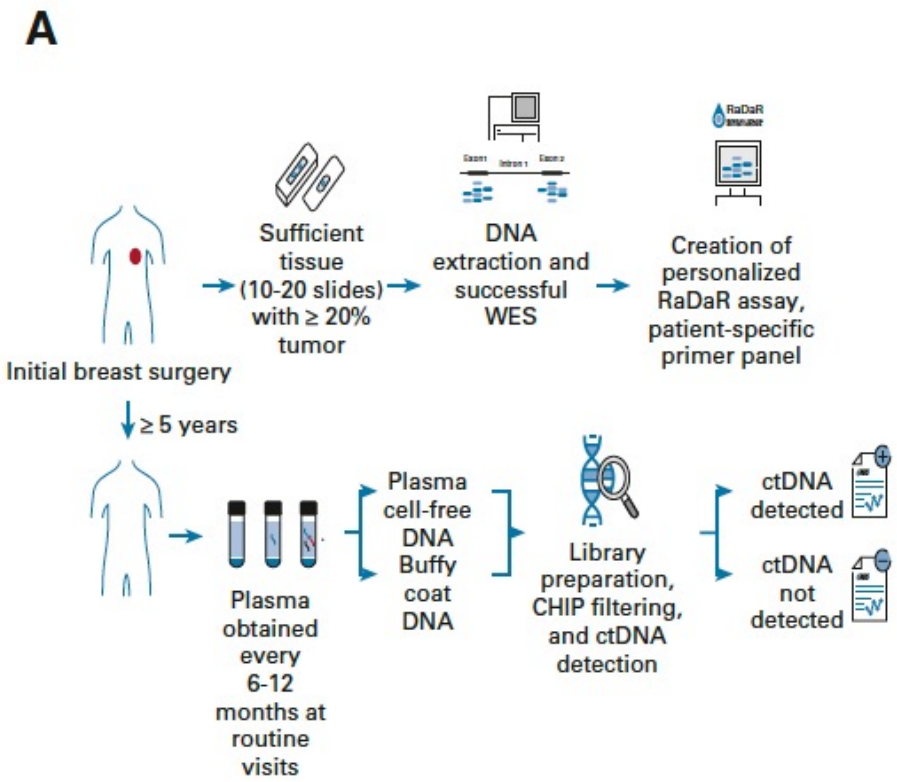
Results

- ctDNA was detected prior to distant recurrence in 13/38 (34%) patients overall, and in 9/15 (60%) of patients who had a sample collection within one year prior to distant recurrence. The specificity was 97.7% (254/260).
- ctDNA was detected up to 28.6 months prior to clinical diagnosis of distant recurrence.
- Detection of ctDNA was associated with a nearly 14-fold increased risk for distant recurrence and over 17-fold increased risk for death.

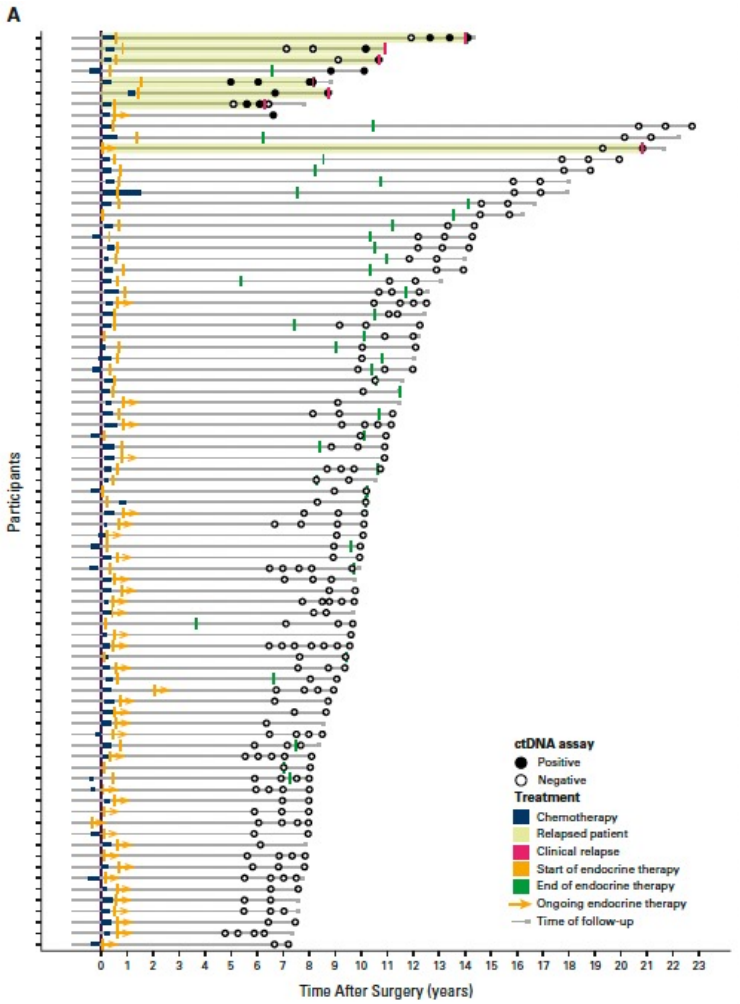




Circulating Tumor DNA and Late Recurrence in High-Risk Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Breast Cancer



J Clin Oncol. 2022 Jun 4;JCO2200908.



Inivata
A Leader in Liquid Biopsy
Subsidiary of NeoGenomics

RaDaR™
RESIDUAL DISEASE AND RECURRENCE

Background

PENELOPE^{B}

N=1250
- HR+/HER2- breast cancer
- no pCR after NACT
- CPS-EG score ≥3 or ≥2 with ypN+

Primary Endpoint: iDFS

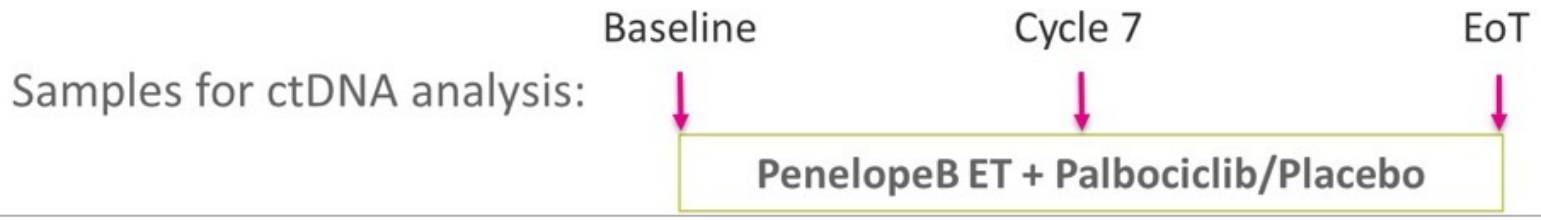
Stratification factors
- Nodal status: ypN 0-1 vs ypN2-3
- Age: ≤50 vs >50 yrs
- Ki-67: >15% vs ≤ 15%
- Region: Asian vs non Asian
- CPS-EG Score: ≥3 vs 2 and ypN+

Neoadjuvant Chemotherapy → **Surgery +/- Radiotherapy** → **R 1:1**

Palbociclib
125 mg once daily p.o.
d1-21, q28d for 13 cycles

Placebo
d1-21, q28d for 13 cycles

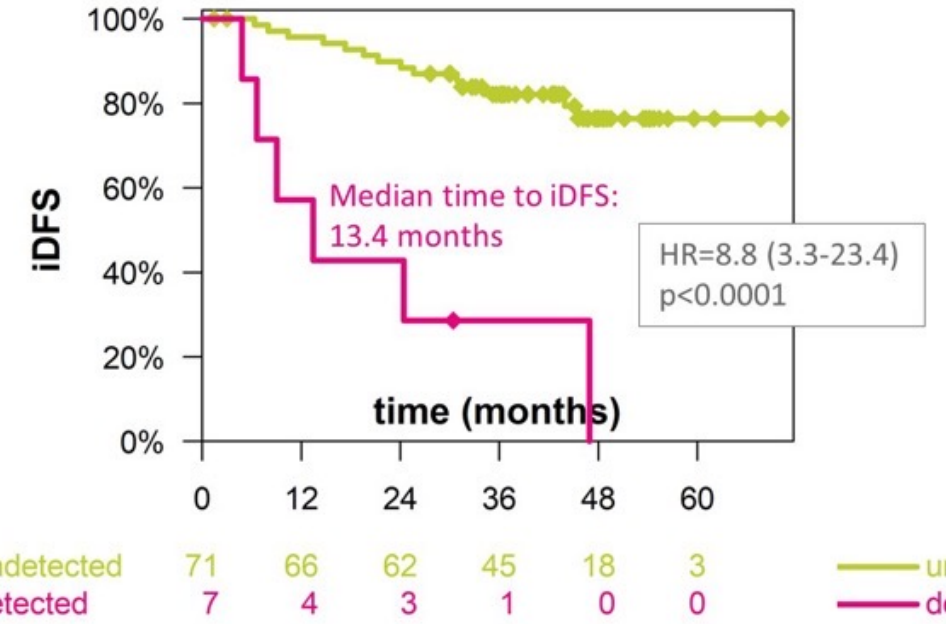
All patients received concomitantly endocrine therapy according to local standards.



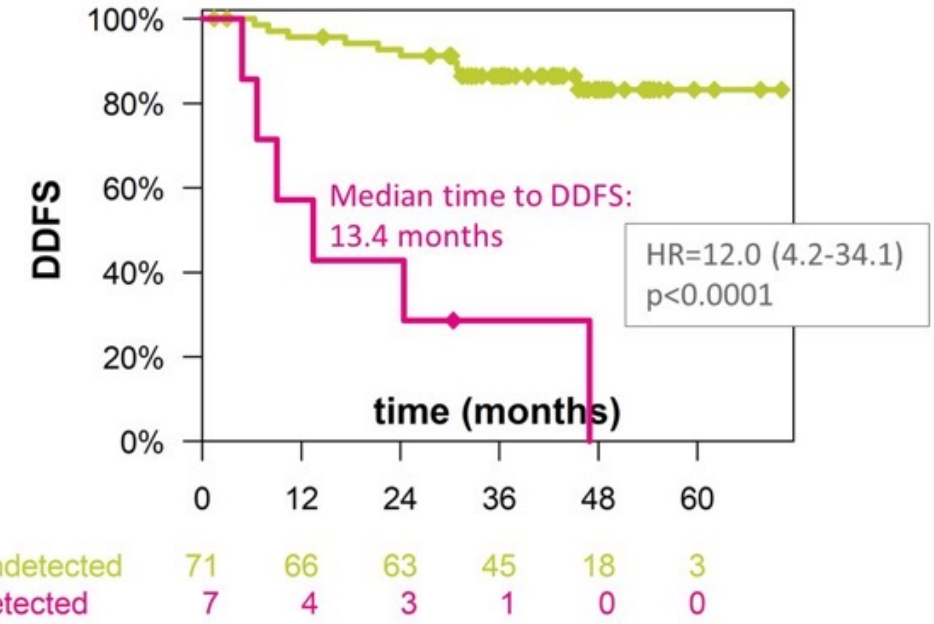
1. Loibl S et al. J Clin Oncol 2021

Results – baseline ctDNA detection

Invasive disease free survival

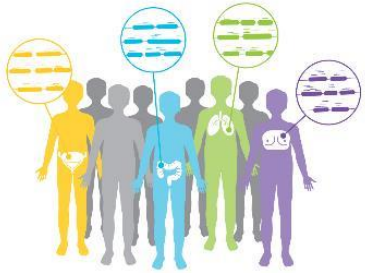


Distant disease free survival

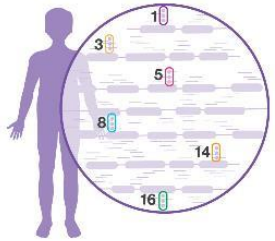


Signatera™ residual disease test (MRD)

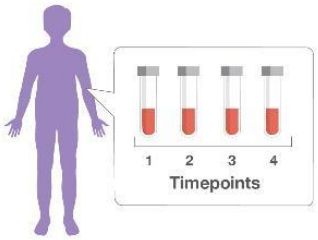
The personalized and tumor-informed approach



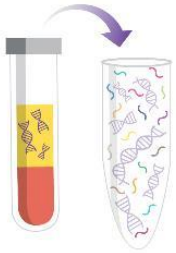
1 Analyze sequencing of tumor tissue and matched normal blood at initial timepoint



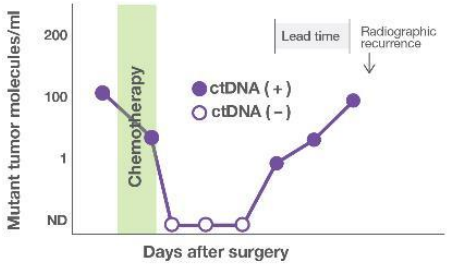
2 Select individual-specific, clonal, somatic variants and design custom primers for each patient



3 Obtain whole blood samples at longitudinal timepoints (eg, every 3 months)



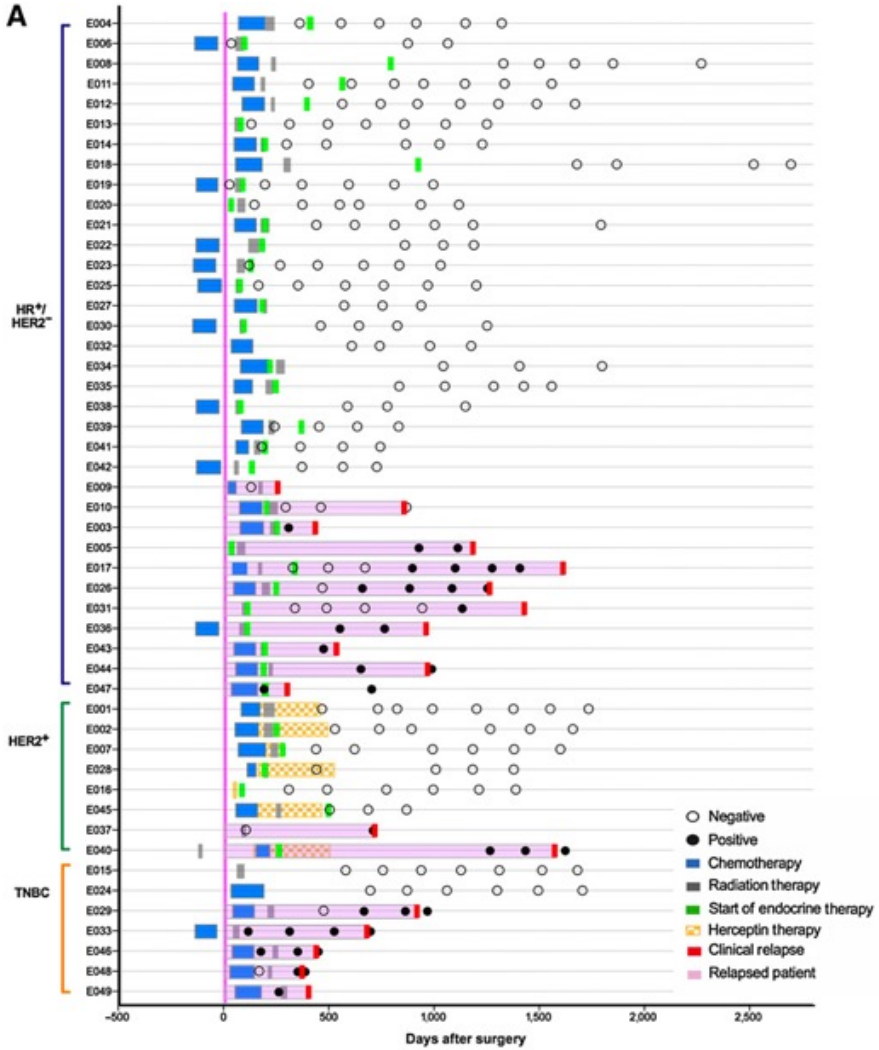
4 Cell-free DNA extraction and patient-specific multiplex PCR followed by NGS



5 Analyze ultra-deep NGS data in plasma to detect presence of ctDNA

natera®

Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence: EBLIS



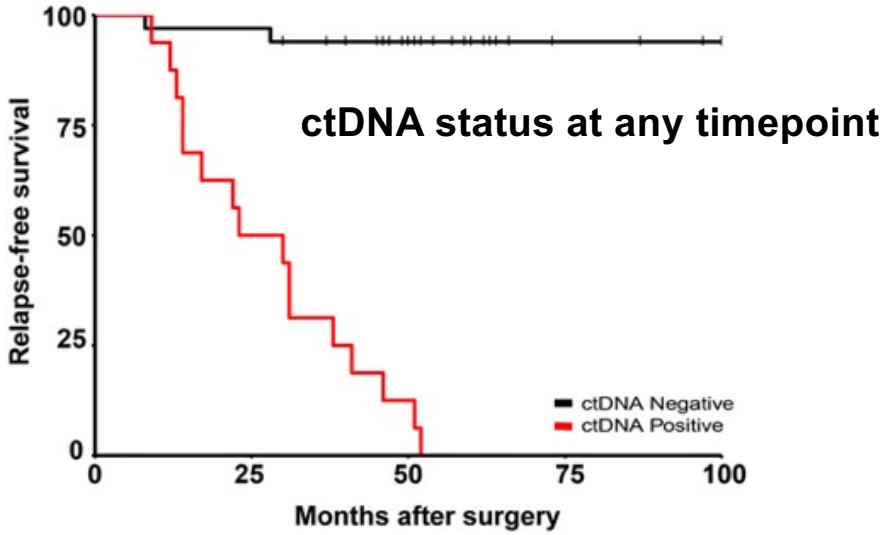
✓ 49例と少数例

✓ Lead time 8.9 months

✓ HR+HER2−で2例がctDNA陰性のまま再発

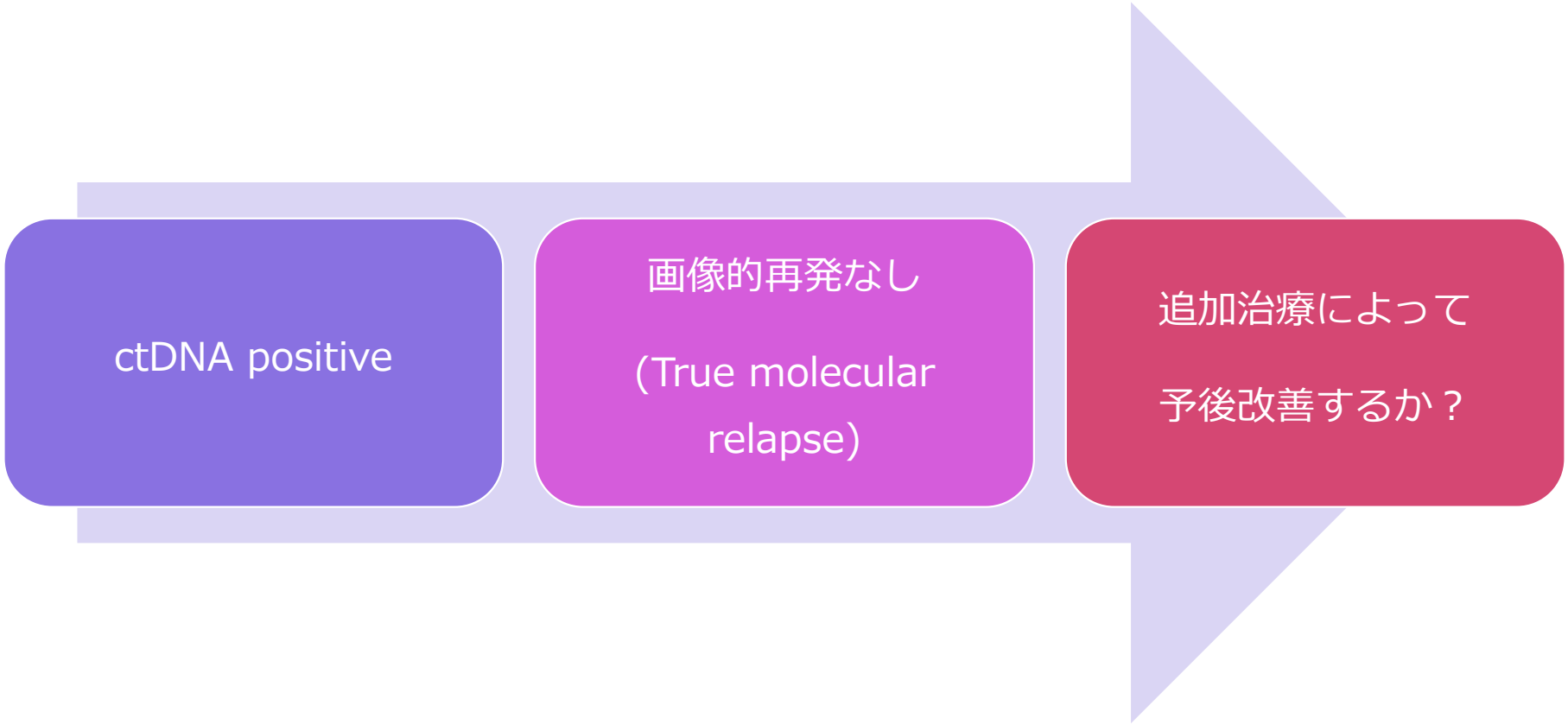
B

Breast cancer subtypes	Total patients	Relapses	% Detected	PPV	NPV	Median lead time (days)
HR+/HER2−	34	11	82%	100%	92%	301
HER2+	8	2	100%	100%	100%	164
TNBC	7	5	100%	100%	100%	258
TOTAL	49	18	89%	100%	94%	285



Clin Cancer Res 2019;25:4255–63

MRD ctDNAモニタリングが目指す方向



CDK 4/6 Inhibitor, Ribociclib, With Adjuvant Endocrine Therapy for ER-positive Breast Cancer (LEADER)

natera

Randomized Phase 2

- ER+(>10%) HER2- IDC
- Stage I-III
- Receiving adjuvant endocrine therapy
- **ctDNA-positive** (pre-screening)
- Adjuvant chemotherapy allowed

R

N=126

Ribociclib 1y + Endocrine therapy (continuous or intermittent)

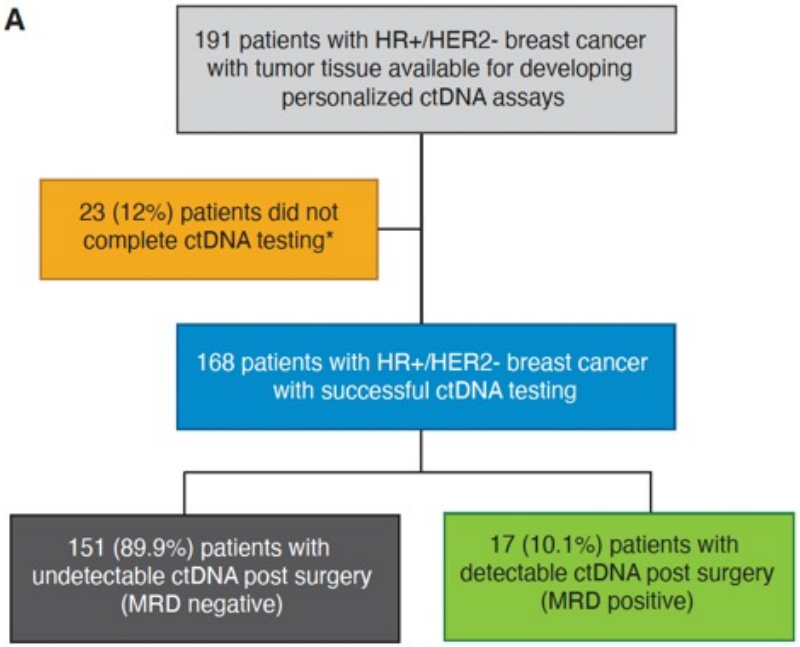
Endocrine therapy

Primary endpoint: ctDNA clearance

NCT03285412

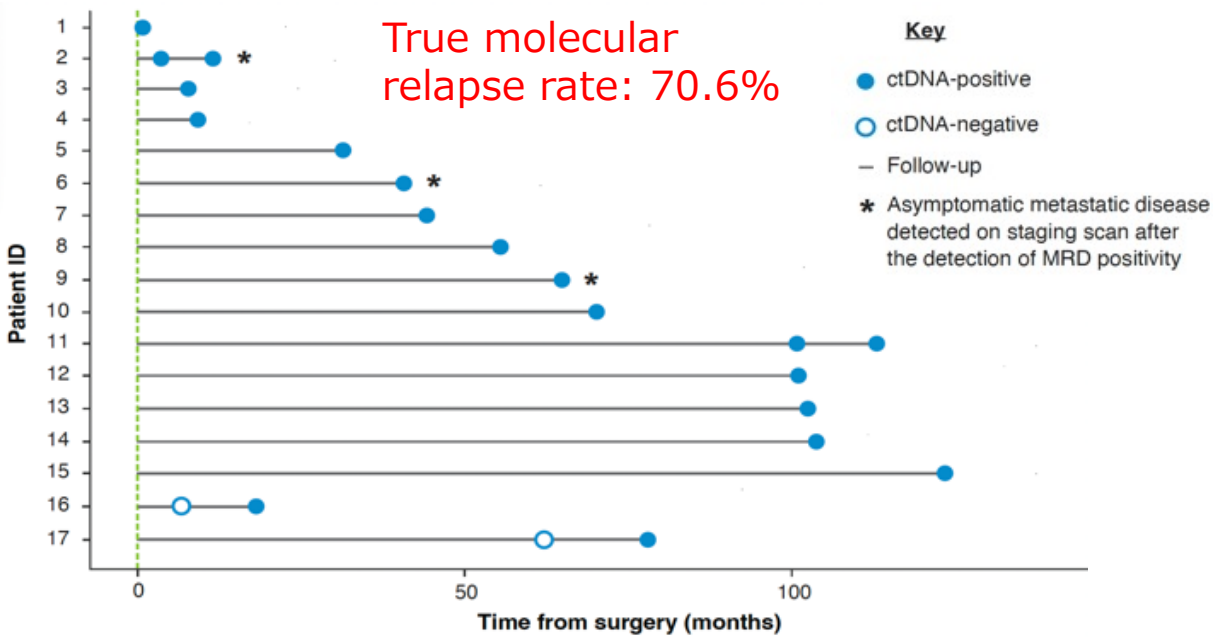
※国内未承認薬含む

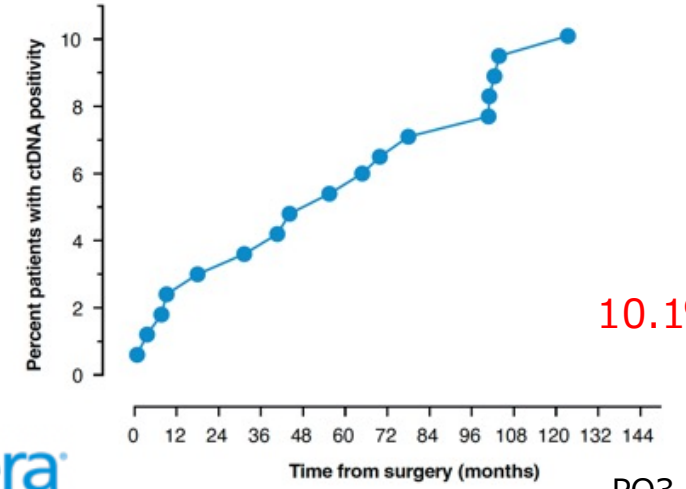
LEADER trial
ctDNA detection rate



ctDNA detection rate: 10.1%

True molecular relapse rate: 70.6%



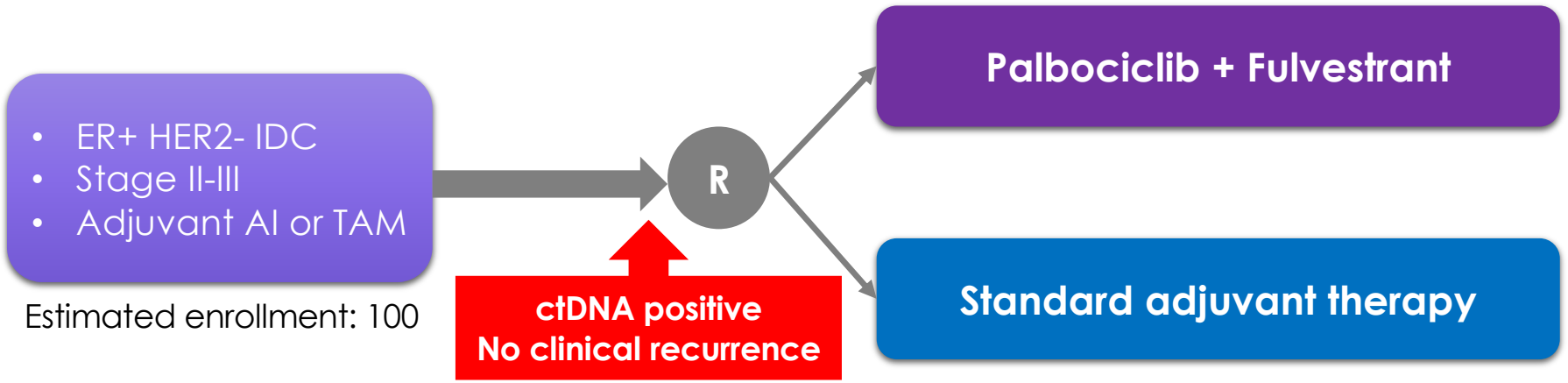


10.1% / 10 year

natera

PO3-13-09 SABCS2023

DNA-Guided Second Line Adjuvant Therapy For High Residual Risk, Stage II-III, Hormone Receptor Positive, HER2 Negative Breast Cancer (DARE)



Screening phase
Primary endpoint: ctDNA positivity

Therapeutic phase
Primary endpoint: Relapse-free survival

NCT04567420

SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM®
DECEMBER 5-9, 2023 | @SABCSSanAntonio

ctDNA monitoring of ER+/HER2- high risk breast cancer during adjuvant endocrine therapy. Interim analysis of the DARE trial (NCT04567420)

Lajos Pusztai, Ekaterina Kalashnikova, Evie Hobbs, Ursa Brown-Glaberman, Monica Mita, Paula Klein, Fengting Yan, Sima Ehsani, Wajeeha Razaq, Alison Stopeck, Manali Bhave, Michelle Loch, Sagar Sardesai, Evanthia T. Roussos-Torres, Mark Burkard, Femi Okubanjo, Eric Gauthier, Angel Rodriguez, Minetta C. Liu, Peter Kabos

Lajos Pusztai, MD, DPhil

Yale Cancer Center, Yale School of Medicine

Conflict of Interest Statement:

Consulting fees/Honoraria: Pfizer, Astra Zeneca, Merck, Novartis, Bristol-Myers Squibb, Stemline-Menarini, GlaxoSmithKline, Genentech/Roche, Personalis, Daiichi, Natera, Exact Sciences

Institutional Research Funding: Seagen, GlaxoSmithKline, AstraZeneca, Merck, Pfizer and Bristol Myers Squibb.

Acknowledgments: This multicenter trial is conducted through the Academic Breast Cancer Consortium (ABRCC) / CRITERIUM with support from Pfizer Pharmaceuticals and Natera Inc.

Hypothesis / Objectives / Methods

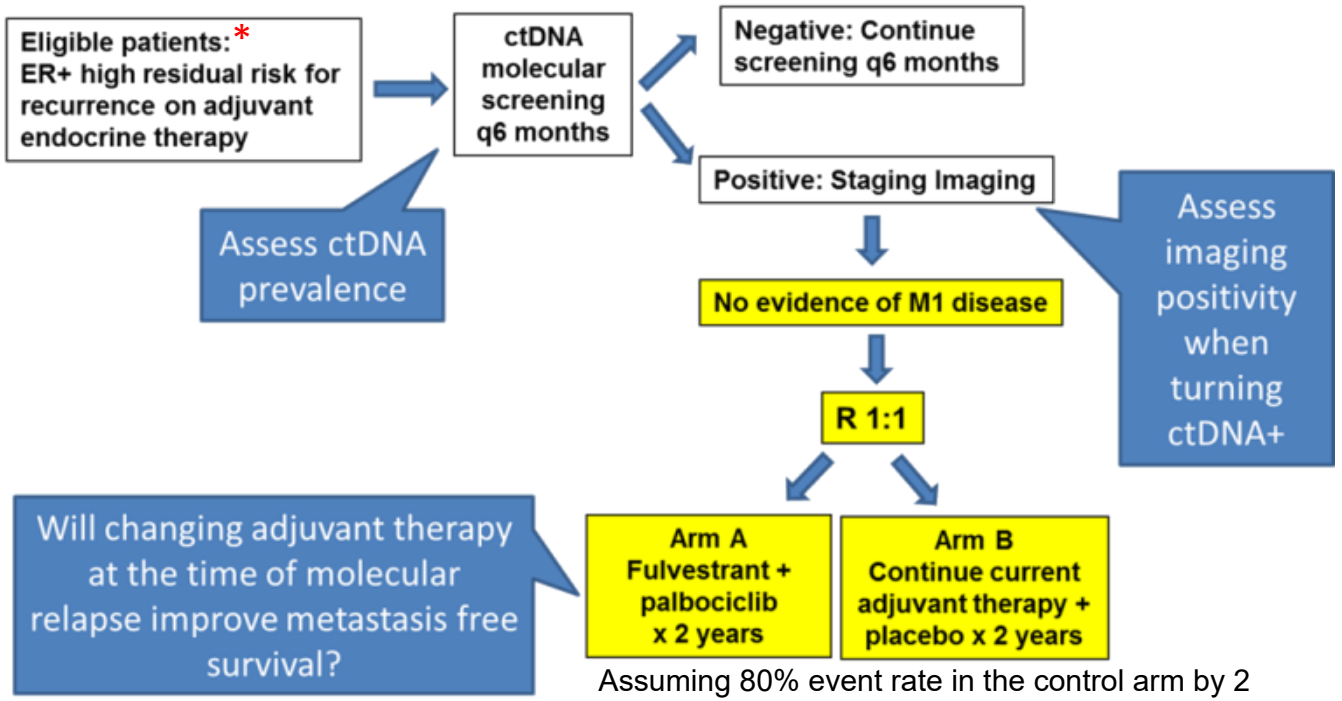
Background:

- The prevalence of stage I-II breast cancers increased in the past 20 years, and despite excellent overall prognosis, stage I-II cancers account for over 60% of annual breast cancer specific death (**Kahn AM et al J Clin Oncol 41 (16_suppl) e18855-e18855, 2023**).

- ctDNA monitoring during adjuvant endocrine therapy provides an opportunity to detect molecular relapse before clinically apparent recurrence on imaging.

Hypothesis: Change of therapy at the time of molecular relapse might delay or prevent metastatic recurrence.

Trial Schema



Assuming 80% event rate in the control arm by 2 years, and HR =0.5 with fulvestrant + palbociclib **N=100** patients randomized will provide 80% power with two-sided alpha of 0.05

*adjuvant ET > 6 months t <7 years, risk of recurrence > 15% calculated by PREDICT, RSPC, or CTS5, or > 4 +LN, or T > 5 cm, or 1-3 +LN/gr3, or > 3 cm tumor, RS > 26, MP high, EndoPredict > 4, Prosigna score > 60

Results

Planned interim analysis: After the first 200 Signatera screening tests, ctDNA positivity rate assessed to determine if screening eligibility criteria needs to be adjusted to keep randomization rate at ≥15%.

Updated results: 15 active sites, **542 patients** accrued between Feb 2021- Oct 2022, **474 tests**, and **417 ctDNA results**

1120 assay results → **37 ctDNA+**(3.3% of assays, 8.9% of patients with results) → **22 randomized**

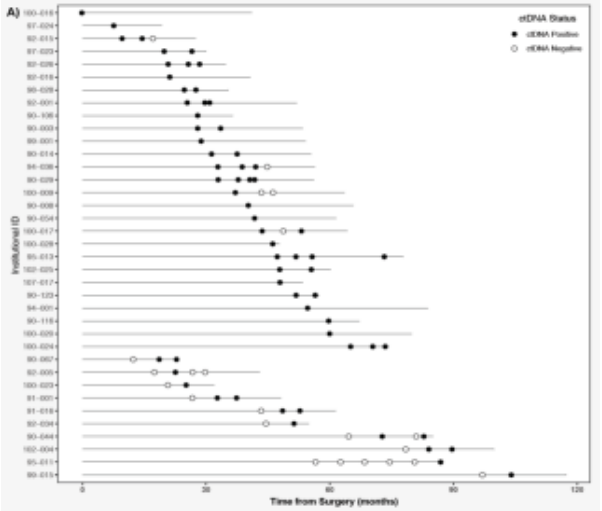
WES failure rate:12% (57/474)
60 % WES failure due to insufficient cancer tissue (57/95)

≥4+LN **(47%)**
≥T3 (**31%**)
Gr 3 (**47%**)

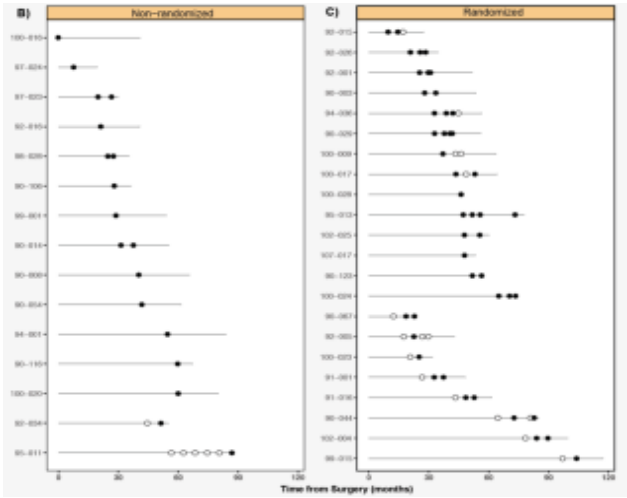
True molecular relapse rate: 73%

Not-randomized:
10 metastases **(27%)**
2 withdraw, 1 died, 2 pending

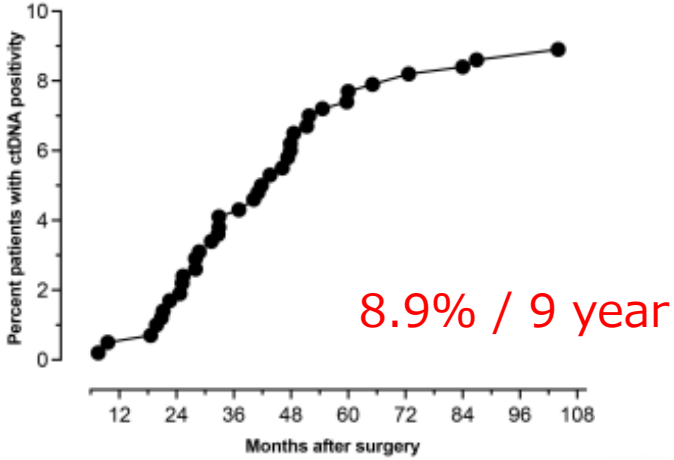
ctDNA detection during follow up (n=37)



ctDNA dynamics in non- randomized (N=15) and randomized patients (N=22)

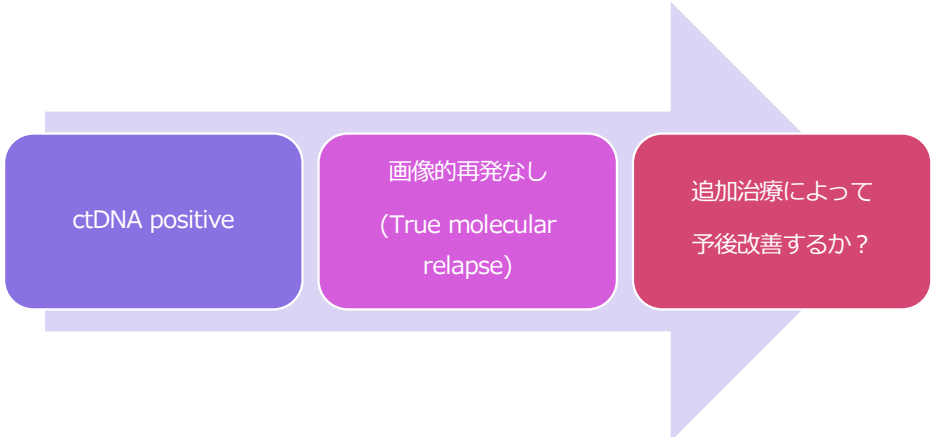


ctDNA detection time relative to time of surgery



LEADERとDAREでわかったこと

- ルミナル乳がん術後のSignateraを用いたctDNA positive rateは約10%
- ctDNA positive の増加率は約1%/年
- ctDNA positiveになった時点でのTrue molecular relapse rateは約70%
- 100人のランダム化比較試験を行うためには1400人を10年かけてスクリーニングする必要がある

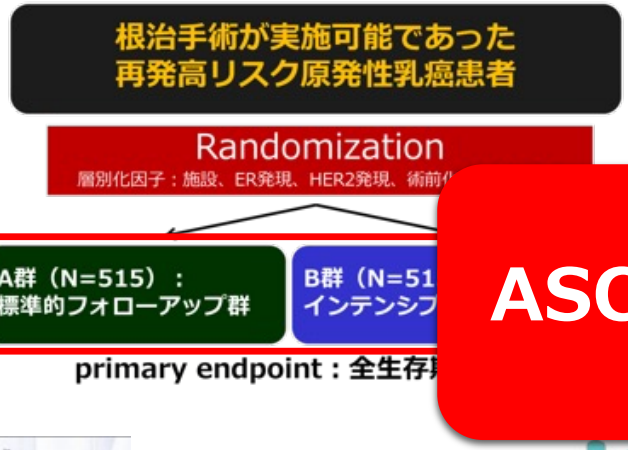


JCOG1204A1

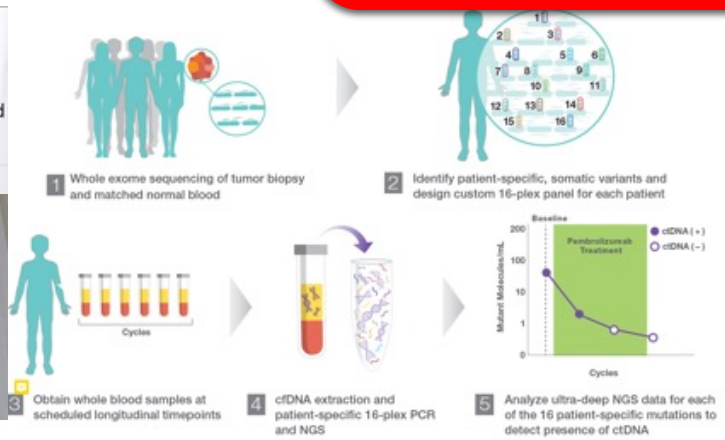
JCOG1204
A randomized controlled trial comparing post-operative intensive follow-up with standard follow-up in High-Risk Breast Cancer Patients
(JCOG1204 INSPIRE Trial)

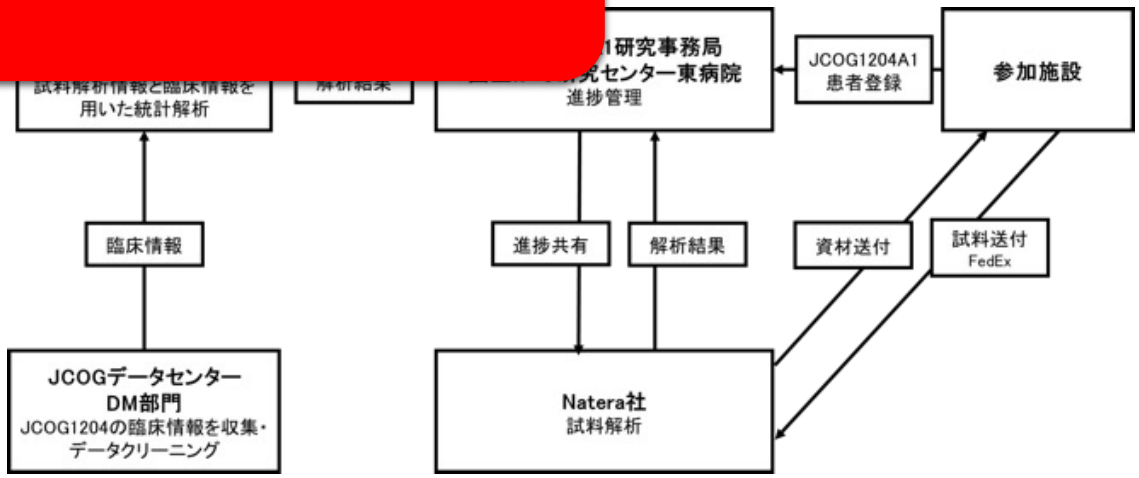
目的
JCOG1204「再発高リスク乳癌術後患者の標準的フォローアップとインテンシブフォローアップの比較第III相試験」の登録患者のうち本附随研究の適格規準をすべて満たす患者において、**血液中のctDNAを測定し、再発の有無や再発時期、再発部位、全生存期間との関連を探索的に検討**する。

対象
1）**JCOG1204のに登録された患者**である。
2）本附随研究への参加について本人より文書による同意が得られている。
3）**同意取得の時期が、手術日を起算日として4年以内**である（手術日の4年後の同一の月日は可）。
期間（DFS：Disease-free survival）」 に規定する
本の提出が可能である。



ASCO2024にて発表予定！





April 2022

ASCO special articles

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update

Fabrice Andre, MD[1]; Nofisat Ismaila, MD, MSc[2]; Kimberly H. Allison, PhD[3]; William E. Barlow, PhD[4]; Deborah E. Collyar, BSc[5]; Senthil Damodaran, MD, PhD[6]; N. Lynn Henry, MD, PhD[7]; Komal Jhaveri, MD[8,9]; Kevin Kalinsky, MD, MS[10]; Nicole M. Kuderer, MD[11]; Anya Litvak, MD[12]; Erica L. Mayer, MD, MPH[13]; Lajos Pusztai, MD[14]; Rachel Raab, MD[15]; Antonio C. Wolff, MD[16]; and Vered Stearns, MD[16]

Circulating tumor DNA.

Recommendation 1.31.
If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician **should not use ctDNA test** to guide decisions for adjuvant endocrine and chemotherapy.

(Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

J Clin Oncol 40:1816-1837. 2022

Whole-genome sequencing ctDNA

Myriad Genetics and MSK to assess MRD testing in breast cancer patients

The study will initially focus on patients with metastatic cancer who received CDK4/6 inhibitors.

September 19, 2023

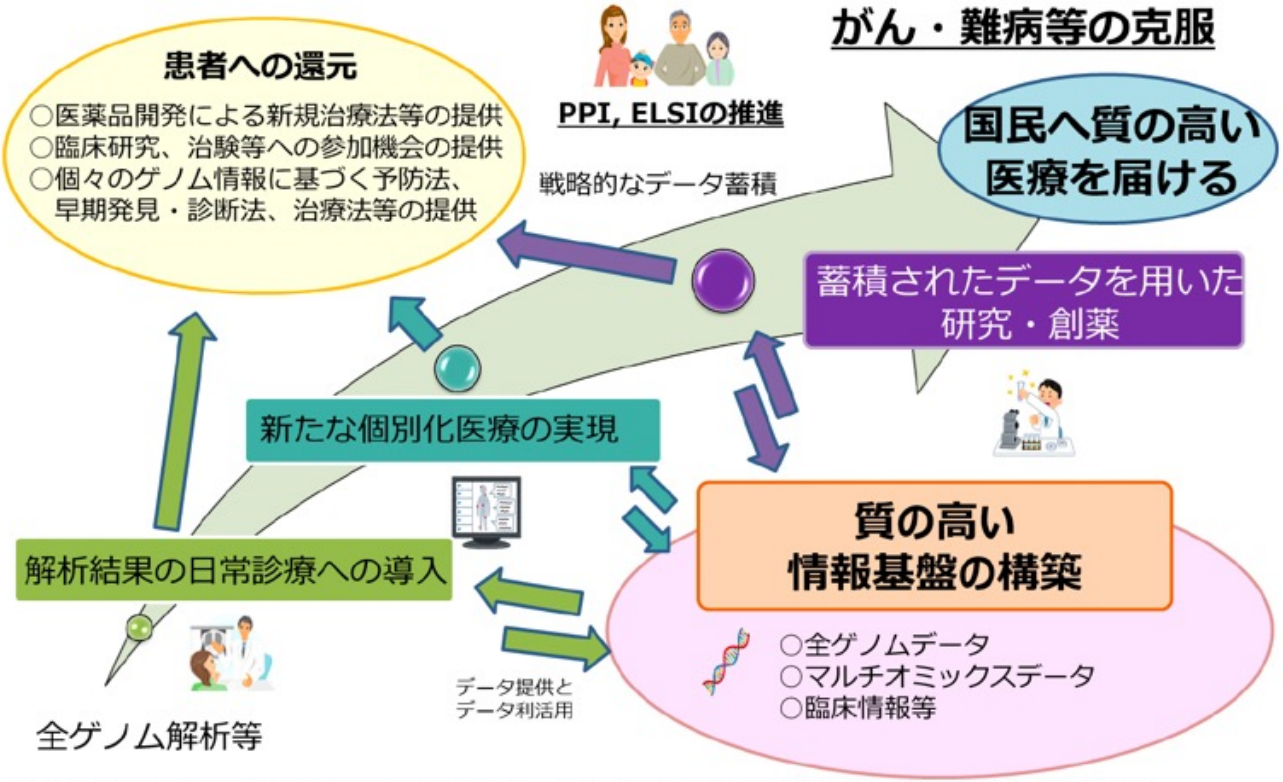
https://www.medicaldevice-network.com/news/myriad-genetics-msk-mrd-testing/?cf-view&cf-closed

「全ゲノム解析等実行計画2022」

（令和４年9月30日策定）

全ゲノム解析等の推進によって目指す医療の姿

国民へ質の高い医療を届けるために、戦略的なデータの蓄積を進め、それらを用いた研究・創薬などを促進することで、将来的な「がん・難病等の克服」を目指すことが、全ゲノム解析等の推進によって目指す医療の姿である。
また、解析結果の日常診療への早期導入や、新たな個別化医療の実現についても更に推進する。

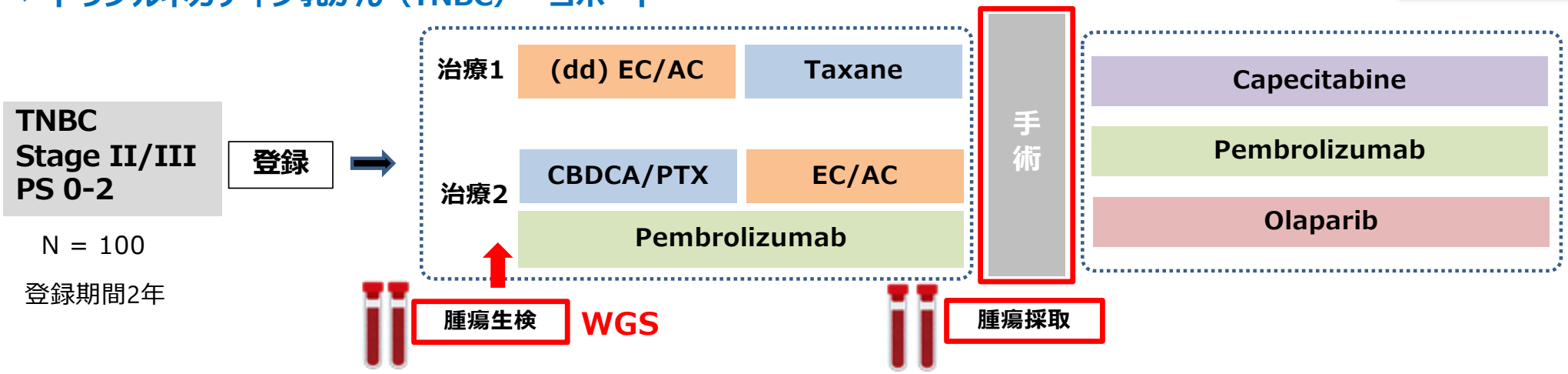


※ 患者・市民参画（Patient and Public Involvement, PPI）、倫理的・法的・社会的課題（Ethical, Legal and Social Issues, ELSI）
※ 本実行計画における「がん」とは、難治性がん、稀少がん、小児がん、遺伝性がん等の全ゲノム解析等による一定の効果が見込まれるが民間だけでは研究・創薬等が困難ながん種を想定。

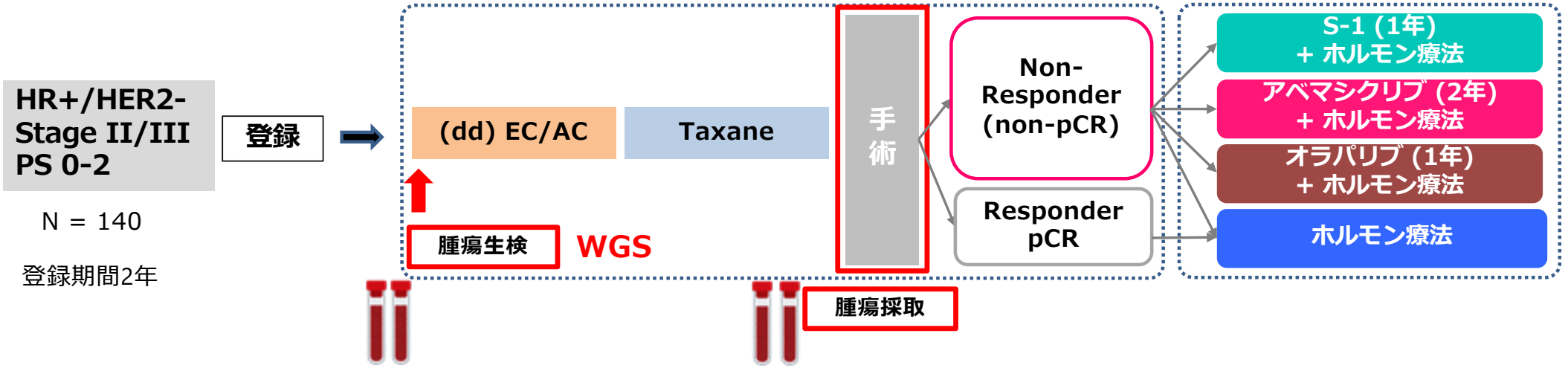
がん全ゲノム解析を用いた乳癌術前化学療法の最適化
-pCR予測およびnon-pCRの新規Target探索- WJOG16822B

登録中

✓ トリプルネガティブ乳がん（TNBC） コホート

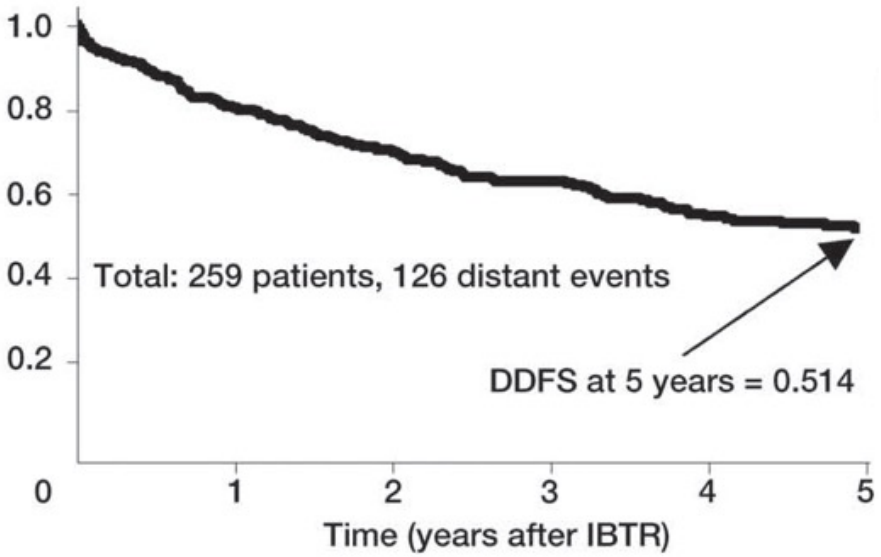


✓ ルミナール乳がん コホート



Background

- Locoregional recurrence (LRR; ipsilateral breast reconstruction [IBTR], chest wall/skin recurrence, regional LN recurrence) has poor prognosis



J Clin Oncol 24:2028-2037.2006.

CALOR study did not show benefit of chemotherapy after LRR of HR+HER2- BC

POLAR trial is evaluating the addition of **Palbociclib** after LRR of HR+HER2- BC

Abemaciclib is the most promising treatment after LRR of locoregional therapy based on **monarchE** results

- More effective adjuvant therapy after LRR of HR+HER2- BC needs to be established

乳がん領域におけるMRD ctDNAの課題と展望 (私見)

MRD精度

- 陽性になったらほぼ確実に再発 （得異度は高い）
- 陰性のまま再発する人は少なくない（感度の課題）

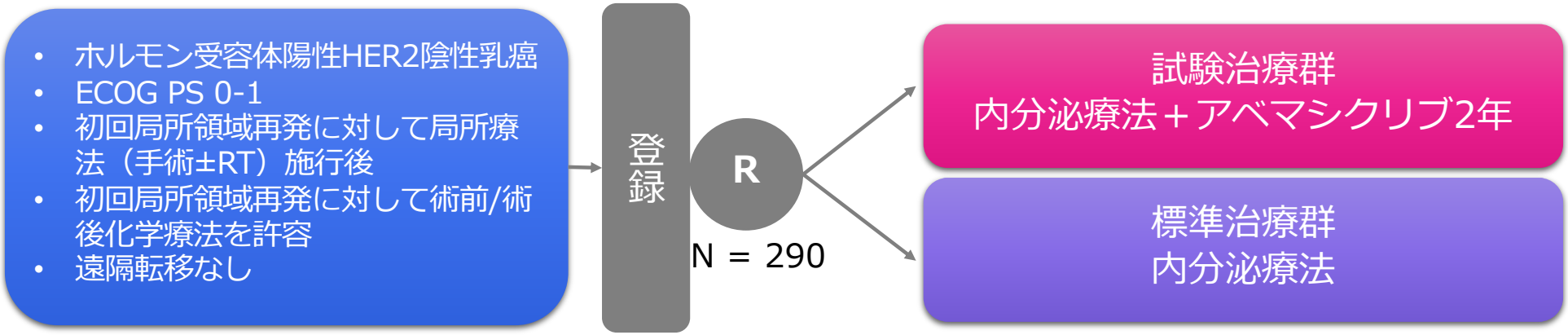
WESとWGS

- WGSで感度が改善するか？

苦手な対象

- 脳転移のみ再発　→髄液ctDNA？
- 局所領域再発のみ再発

JCOG2313：HR陽性HER2陰性乳癌局所領域再発に対する術後アベマシクリブの有効性を評価するランダム比較試験



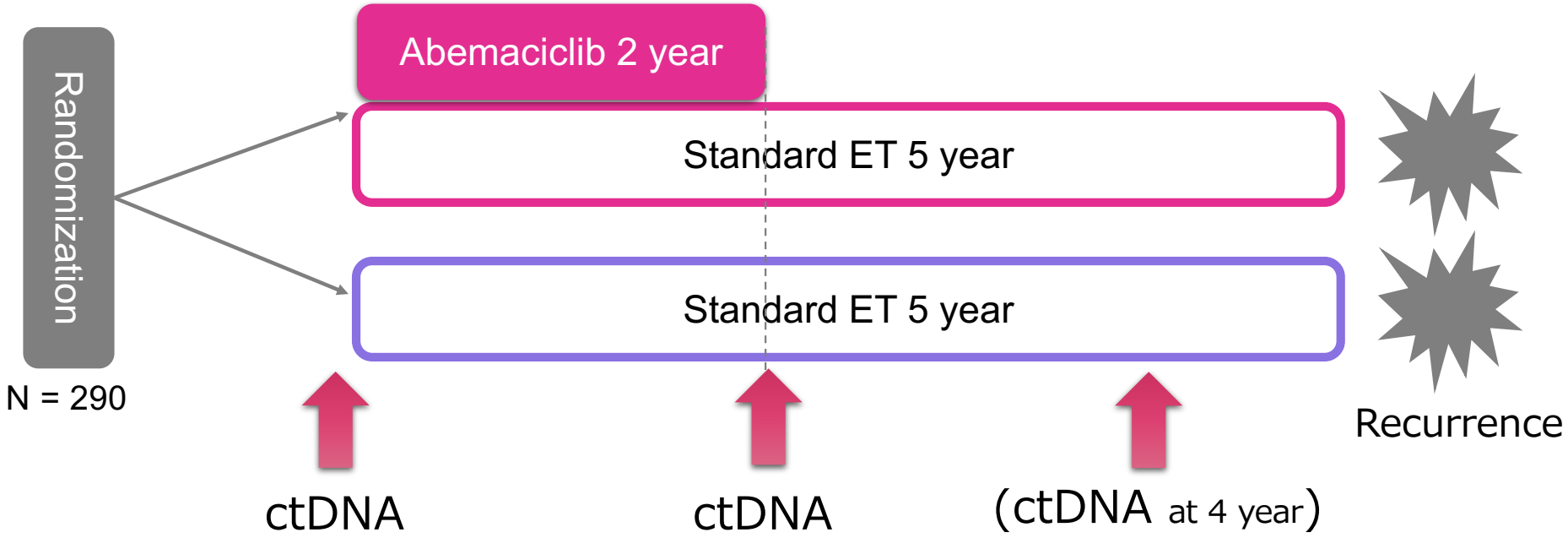
割付調整因子:

- 内分泌療法抵抗性 (内分泌療法歴なし or 術後内分泌療法開始2年以内再発 or 術後内分泌療法開始2年以降再発)
- 同側乳房内再発または他の局所領域再発
- 施設
- 局所領域再発に対する術前/術後化学療法の有無

- **主要評価項目：無浸潤疾患生存期間**
- **副次評価項目：無遠隔再発生存期間、乳癌特異的生存期間、全生存期間、有害事象発生割合**

Yukinori Ozaki

JCOG2313 ctDNA



Yukinori Ozaki

まとめ

- ルミナル乳がんに対する術前ICIによるpCR改善は得られたが、EFSデータ待ち
- 術後Ribociclibは欧米で承認予定で、S-1 vs. Abemaと同じ議論が今後想定される
- ctDNAによるMRD検出はさまざまなアッセイのデータがでてきているが、予後の改善につながるか、より感度を高められるか、苦手な対象を克服できるか、に今後注目した

ご清聴いただきありがとうございました。
2024年もご指導のほど、
どうぞよろしくお願いいたします。

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Department of Breast Medical Oncology, Breast Center
The Cancer Institute Hospital of Japanese Foundation for Cancer Research

B.M.ONCOLOGY