

第2回 GRACE Seminar 第1部

Oncotype DXのエビデンスと 当院での適応

がん研有明病院
乳腺センター乳腺内科
原 文 堅

日時：2021年3月7日（火） 13:35－13:55

CQ29.ホルモン受容体陽性HER2陰性乳癌に対して、多遺伝子アッセイの結果によって、術後化学療法を省略することは推奨されるか？

★ HOME » 乳癌診療ガイドライン » 薬物療法【目次】 »

CQ29.ホルモン受容体陽性HER2陰性乳癌に対して、多遺伝子アッセイの結果によって、術後化学療法を省略することは推奨されるか？

1. 初期治療

推 奨

・ホルモン受容体陽性HER2陰性乳癌で、リンパ節転移陰性であれば、OncotypeDXのRSが25以下の場合には術後化学療法を省略することは強く勧められる。

〔推奨の強さ：1，エビデンスの強さ：強，合意率：100%（19／19）〕

・ホルモン受容体陽性HER2陰性乳癌で、MammaPrintのゲノム低リスクの場合には術後化学療法を省略することは弱く勧められる。

〔推奨の強さ：2，エビデンスの強さ：中，合意率：95%（18／19）〕

乳癌診療ガイドライン

(3)その他のアッセイ

PAM50^{5) 6)} やCurebest95GC Breast^{7) 8)} などは、後向き研究でOncotype DXとの比較検討も交えて予後予測因子としての有用性が報告されているが、化学療法の効果予測を検証する前向き比較試験を認めなかったためシステマティックレビューを行わなかった。

手術標本（パラフィンブロック）からRNAを抽出し、遺伝子発現量を定量する

21種の遺伝子

遺伝子発現プロファイル：16種の癌遺伝子と5種の対照遺伝子をRT-PCR法*で解析。

増殖セット	ERセット	浸潤セット	HER2 増殖セット	他の遺伝子	レファレンス
Ki-67 STK15 Survivin Cyclin B1 MYBL2	ER PGR BcL2 SCUBE2	Stromelysin3 Cathepsin L2	GRB7 HER2	GSTM1 CD68 BAG1	Beta-actin GAPDH RPLP0 GUS TFRC

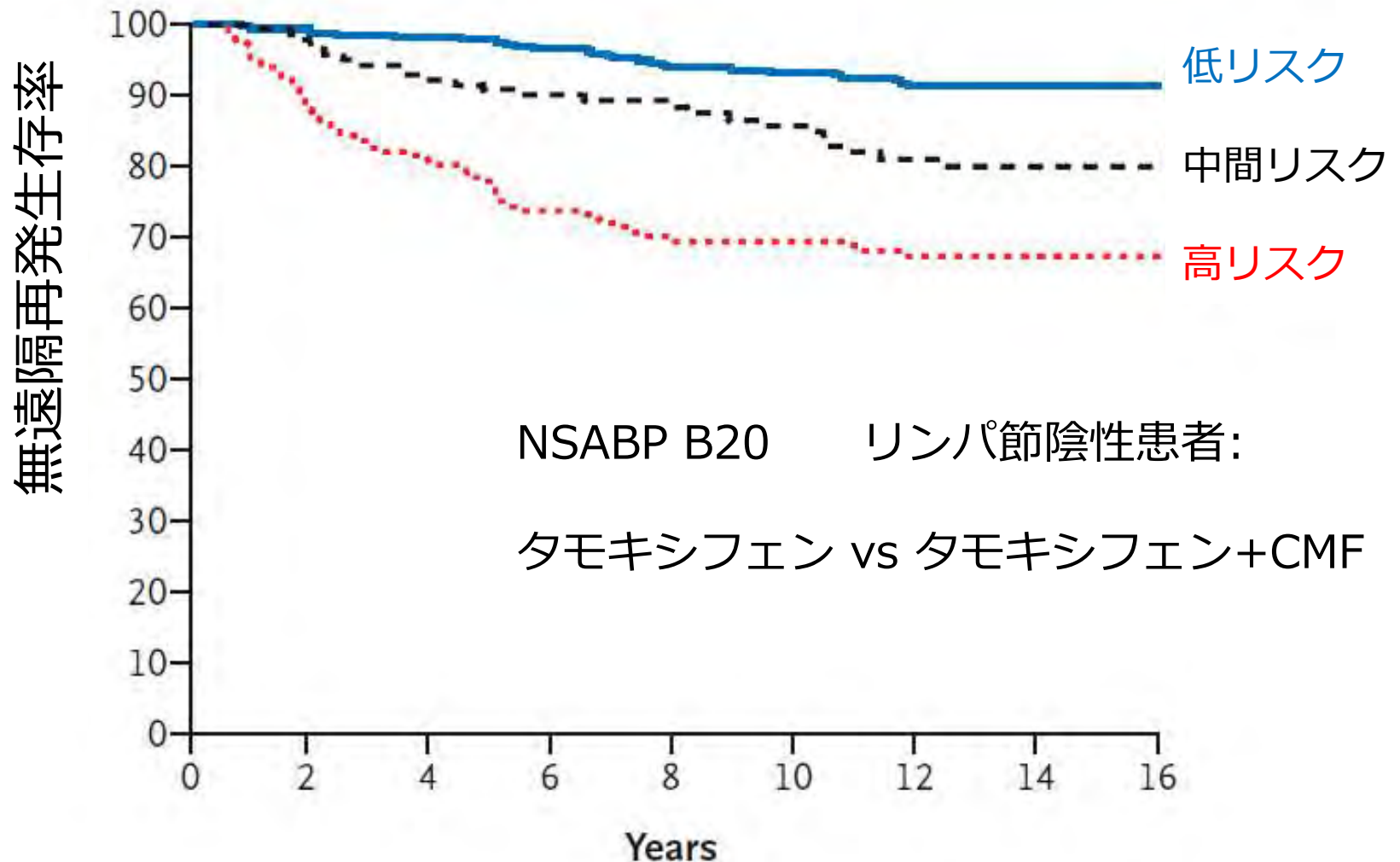
*RT-PCR：Reverse-Transcriptase-Polymerase-Chain-Reaction

再発スコア（Recurrence Score：RS）

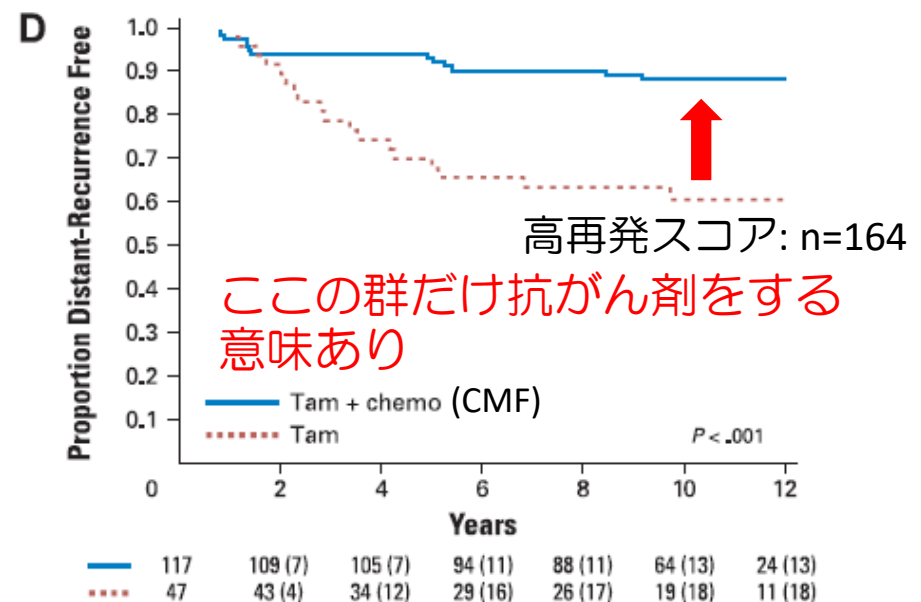
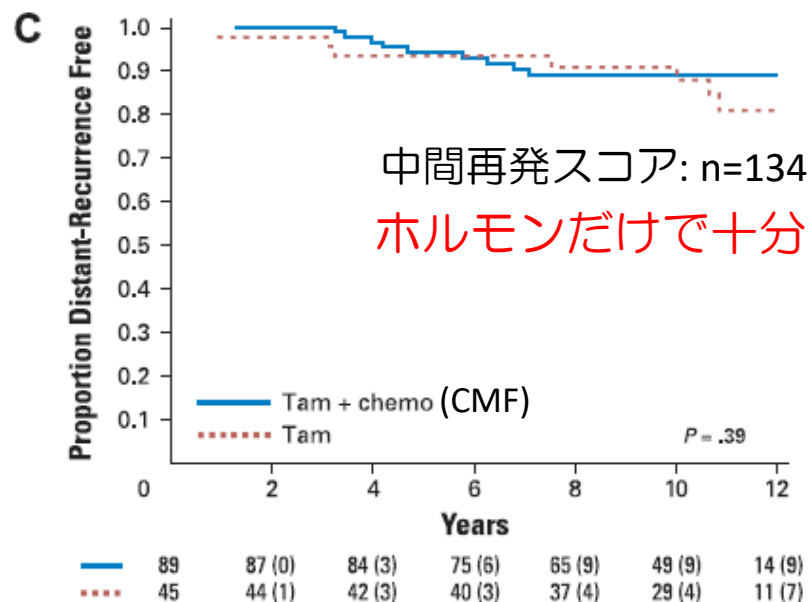
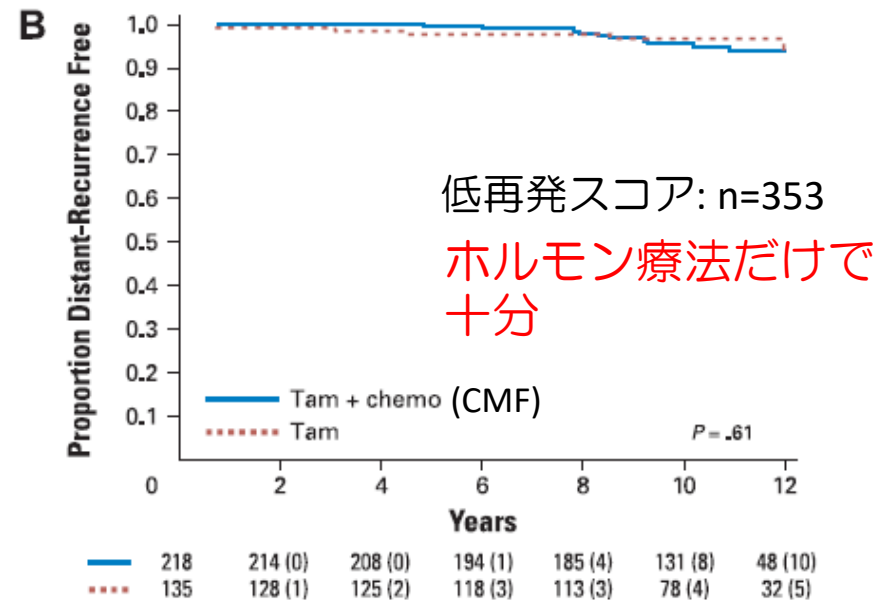
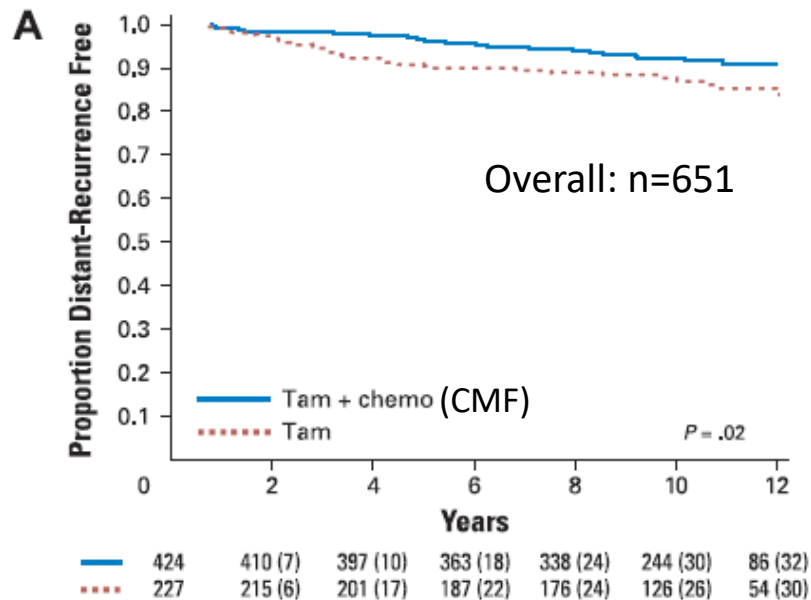
Stage I or II、リンパ節転移－、ER＋、タモキシフェン投与患者400例以上の検討から、OncotypeDX™の21種の遺伝子発現プロファイルと、それに基づくアルゴリズムが得られました。それにより、0～100の数字で表されるRSが計算されます。右表のように668例の症例についての確認研究によりRSが示されました。¹

リスク分類	RS	リスクグループ毎の比率(%) (n=668)
低リスク	<18	51
中間リスク	18≤RS<31	22
高リスク	31≤	27

Oncotype DX: 予後予測として利用可能



Oncotype DX: 抗がん剤効果予測ツールとして利用可能



Who needs chemo?

Oncotype DX
LN(-)

TAILORx

TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010

Preregister - Oncotype DX RS (N=11,232)



Register (N=10,273)

ARM A: Low RS 0-10
(N=1629 evaluable)
ASSIGN
Endocrine Therapy (ET)

Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE
Stratification Factors: Menopausal
Status, Planned Chemotherapy, Planned
Radiation, and RS 11-15, 16-20, 21-25

ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo

ARM B: Experimental Arm
(N=3399)
ET Alone

ARM C: Standard Arm
(N=3312)
ET + Chemo

5y DDFS 97%
Sparano JA, et al. NEJM 2015.

PRESENTED AT: 2018 ASCO
ANNUAL MEETING

#ASCO18
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PRESENTED BY: Joseph A. Sparano, MD

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Reshaping the future of patient care

TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

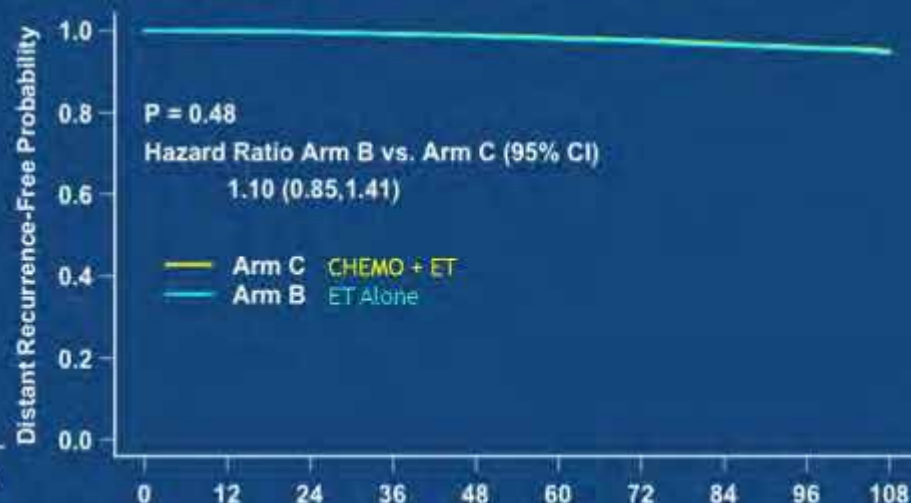
836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as first event, of which 199 (23.8%) were distant

Primary Endpoint Invasive Disease-Free Survival



Number at risk		Months									
—	3312	3204	3104	2993	2849	2645	2335	1781	1130	523	
—	3399	3293	3194	3081	2953	2741	2431	1859	1197	537	

Secondary Endpoint Distant Relapse-Free Interval



Number at risk		Months									
—	3312	3215	3142	3059	2935	2734	2432	1866	1197	554	
—	3399	3318	3239	3147	3033	2833	2537	1947	1267	581	

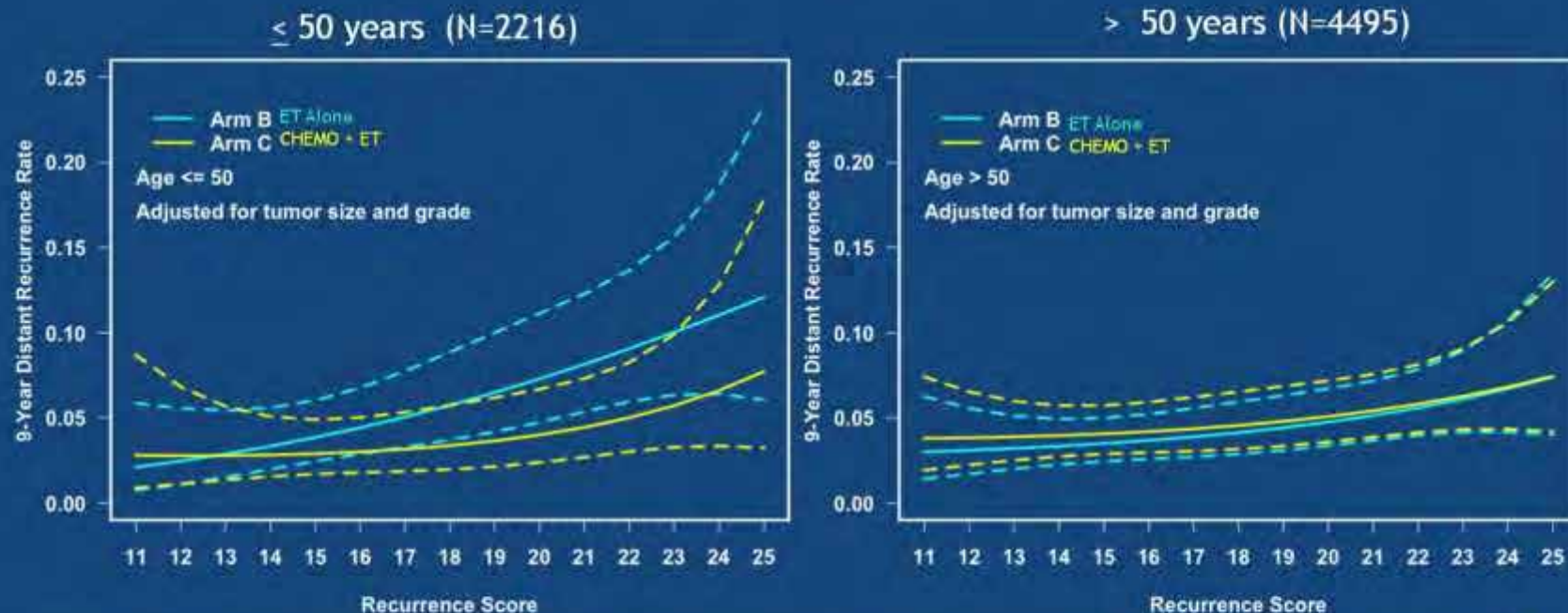
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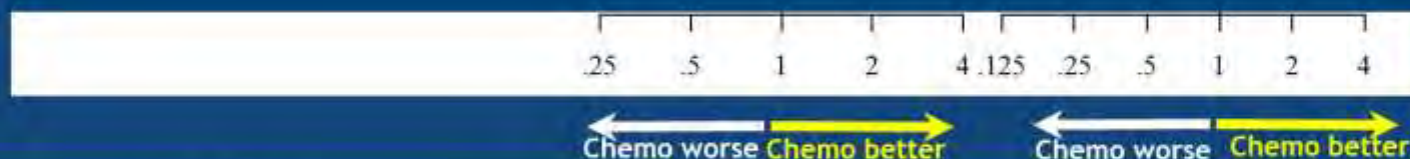
TAILORx Results: Association between Continuous RS 11-25 and 9-Year Distant Recurrence Rate by Treatment Arms Stratified by Age (≤ 50 vs. >50 Years)



RS modeled with a natural spline with 2 degrees of freedom, adjusted for tumor size and grade

Results - Exploratory Analysis: Impact of Age and Menopausal Status on Chemotherapy Benefit for RS 16-25

Age & Menopausal Status	Total #/IDFS/DR Events	IDFS Hazard Ratio	DRFI Hazard Ratio
Age ≤40	203/ 35/12		
Age 41-45	441/ 51/21		
Age 46-50, Pre-Meno	630/ 69/33		
Age 46-50, Post-Meno	141/ 15/ 5		



St. gallen 2019 Voting
リンパ節転移陰性で再発スコア21~25の
50歳未満の女性に対して実施すべき治療は？

1. 化学療法 + 内分泌療法 Chemo + ET



2. OFS + 内分泌療法 OFS + ET



3. 化学療法 + OFS + 内分泌療法 Chemo + OFS + ET



4. TAMのみ Tamoxifen only



5. Abstain



Total patients	RS 0-10	RS 11-15	RS 16-20	RS 21-25	RS 26-100
N=9719	N=1619	N=2373	N=2712	N=1626	N=1389
Age >50 years N=6665 (69%)	No CT Benefit N=1190 (12%)	No CT Benefit N=1572 (16%)	No CT Benefit N=1789 (18%)	No CT Benefit N=1134 (12%)	Substantial CT Benefit N=980 (10%)
Age ≤50 years N=3054 (31%)	No CT Benefit N=429 (4%)	No CT Benefit N=801 (8%)	1.6% CT Benefit N=923 (9%)	6.5% CT Benefit N=492 (5%)	Substantial CT Benefit N=409 (4%)
58% 12% Patients ≤50 years Low clinical risk High clinical risk 7% 7% of all patients No CT benefit 2% of all patients ~6.5% CT benefit 3% of all patients ~6.4% CT benefit 2% of all patients ~8.7% CT benefit					

**Oncotype DXをすれば
ER陽性、N(-)症例の
58+12+7=77%がケモ不要
ということになる!!!**

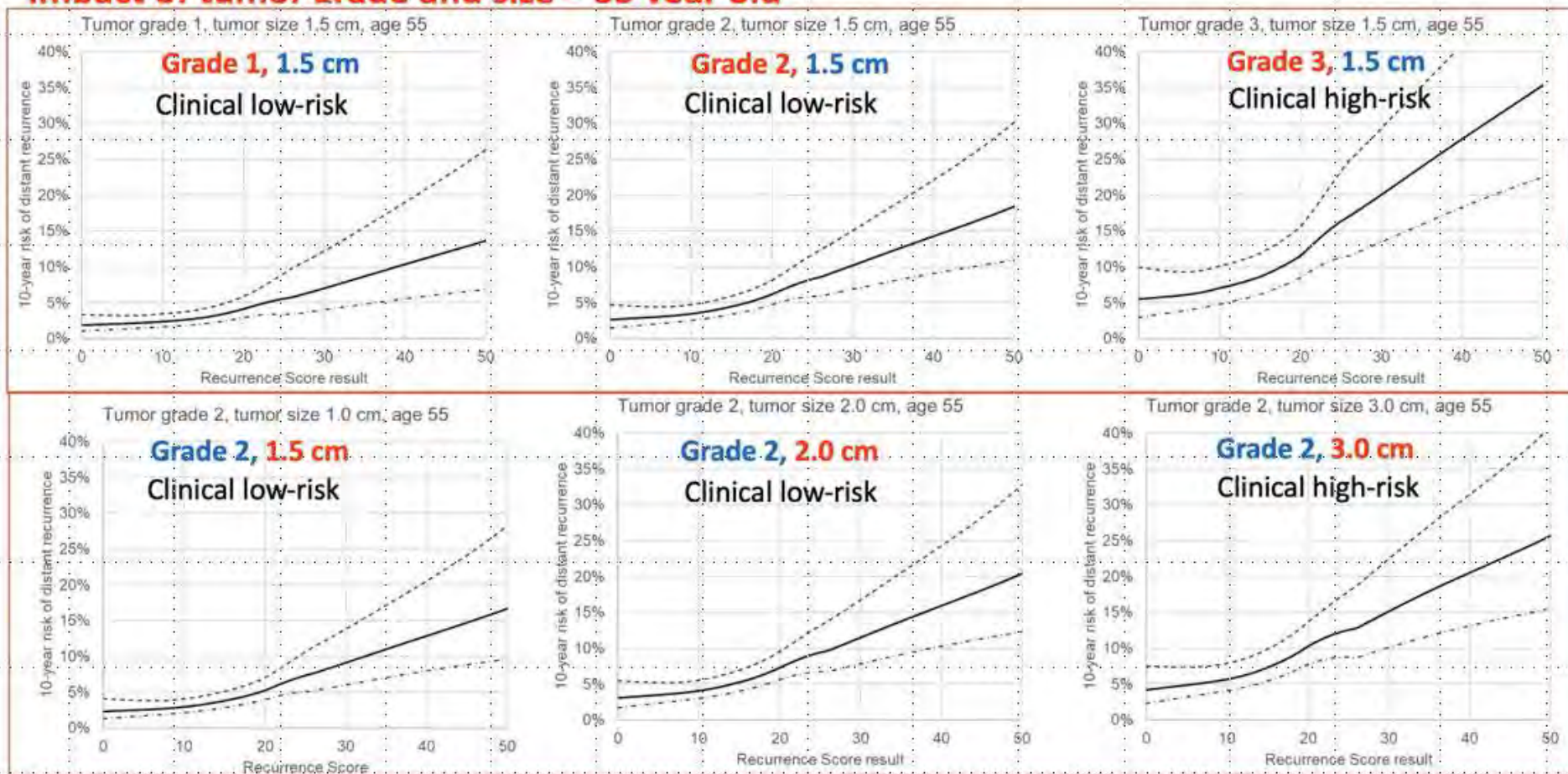
High clinical risk: Grade1 & T>3cm,
Grade2 & T>2cm,
Grade3 & T>1cm

Who needs chemo?

Oncotype DX
LN(-)

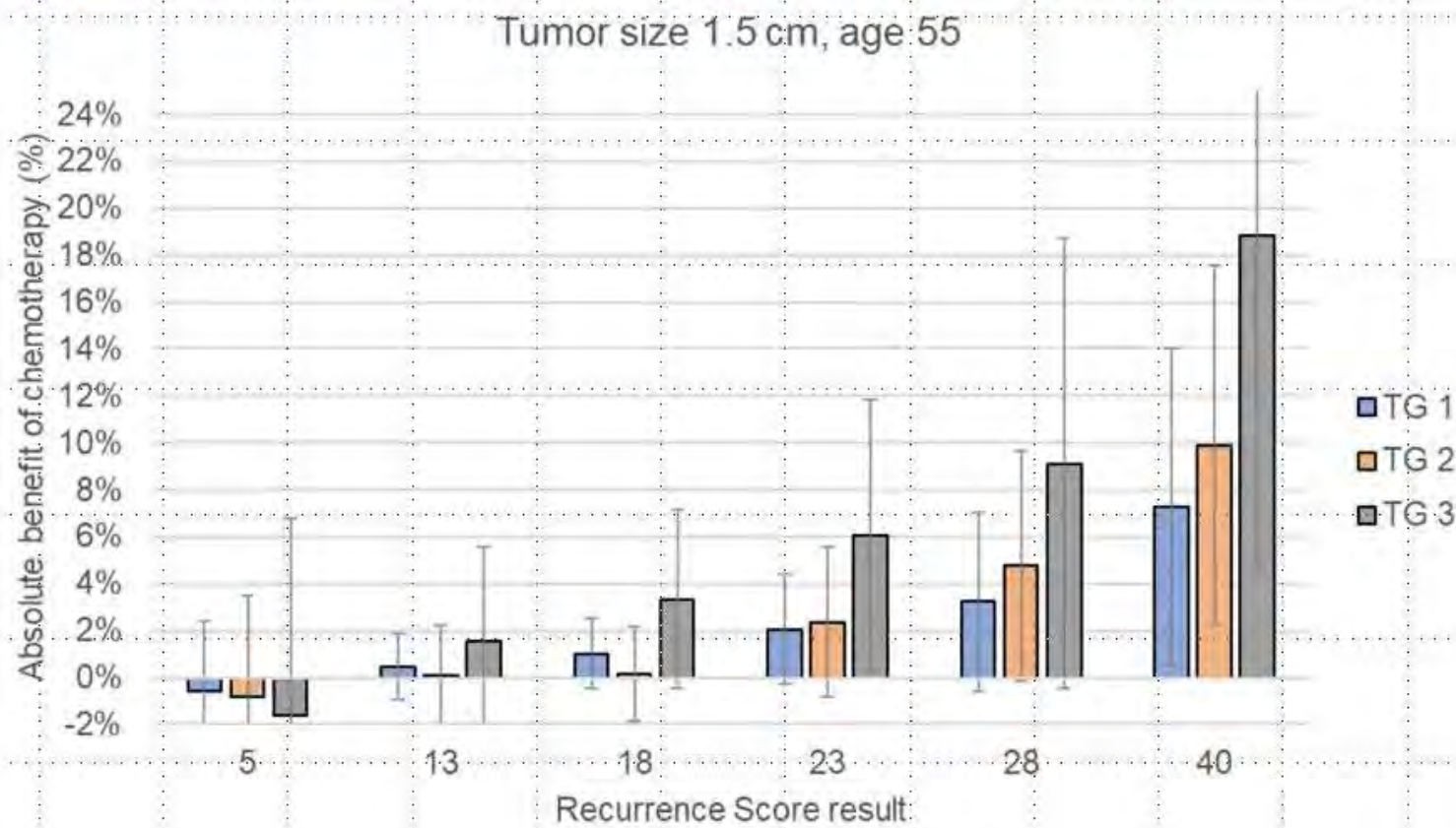
RSCLin

Results – prognosis: RSClin™ 10-year distant recurrence risk estimates (95% CI) Impact of tumor grade and size – 55 year old



Results—prediction: RSClin™ estimate of absolute CT benefit at 10 years (95% CI) Tumor grade series

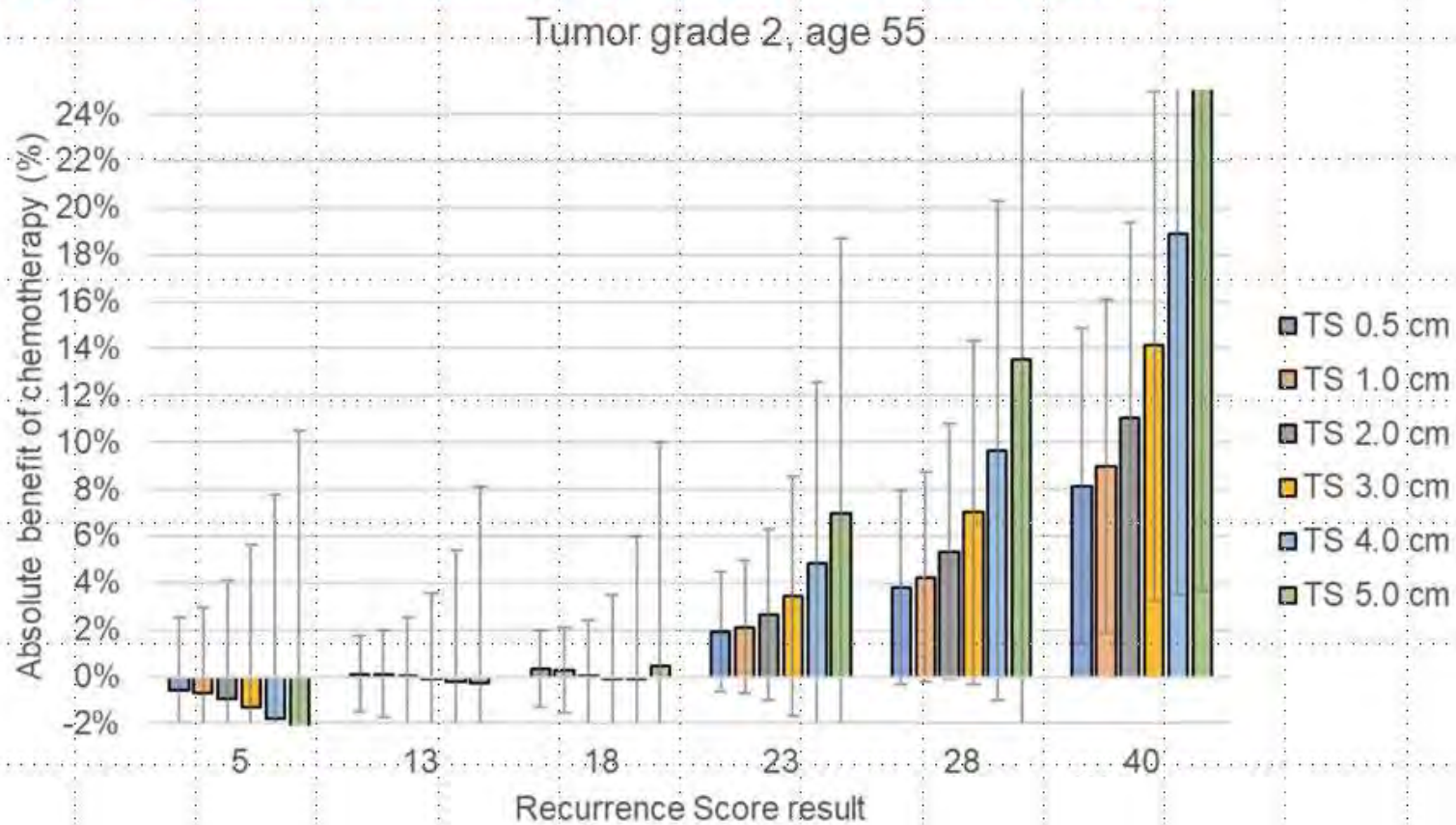
- Greater CT benefit with higher RS irrespective of grade.
- More absolute CT for higher grade tumors due to the higher underlying recurrence risk



Results—prediction: RSClin™ estimate of absolute CT benefit at 10 years (95% CI)

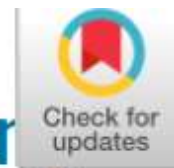
Tumor size series

- Greater CT benefit with higher RS irrespective of size.
- More absolute CT for larger tumors due to the higher underlying recurrence risk



Development and Validation of a Tool Integrating the 21-Gene Recurrence Score and Clinical-Pathological Features to Individualize Prognosis and Prediction of Chemotherapy Benefit in Early Breast Cancer

Joseph A. Sparano, MD¹; Michael R. Crager, PhD²; Gong Tang, PhD³; Robert J. Gray, PhD⁴; Salomon M. Stemmer, MD⁵; and Steven Shak, MD²



Oncotype IQ. Exact Sciences. Physician Portal.
<https://online.genomichealth.com>

Dana-Farber Reflex Criteria for RS Testing

- Designed to provide score at time of medical oncology visit for majority of patients without over ordering. The following parameters must be met:
 - Tumor > 1 cm
 - Age < 66
 - Node negative or 1-3+ nodes
 - Grade II/III
 - Grade I if tumor > 2 cm and/or nodal (1-3) involvement
- Outside of these parameters requires physician to order



9 Year Event Rates by Recurrence Score

RS 0-10 (Arm A)

- 3% distant recurrence with ET alone

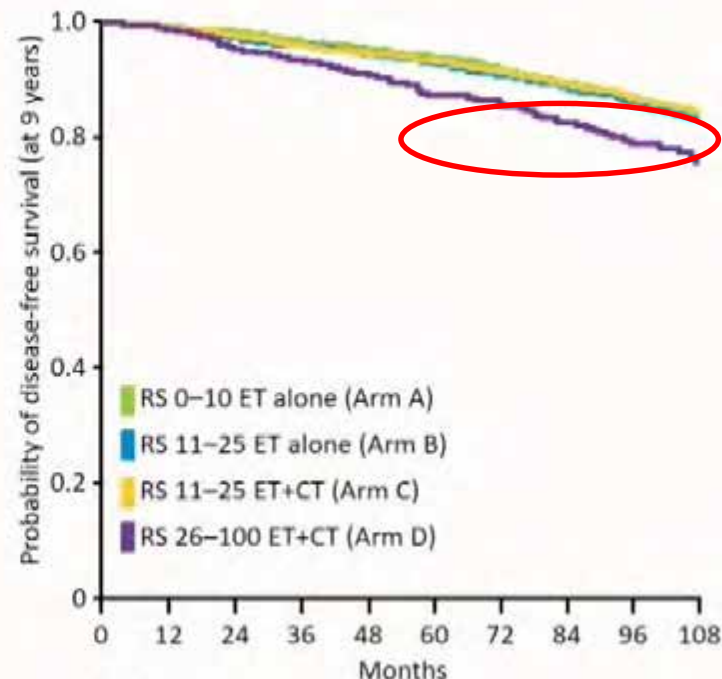
RS 11-25 (Arms B & C)

- 5% distant recurrence rate overall
- $\leq 1\%$ difference for all endpoints
 - IDFS (83.3 vs. 84.3%)
 - DRFI (94.5 vs. 95.0%)
 - RFI (92.2 vs. 92.9%)
 - OS (93.9 vs. 93.8%)

RS 26-100 (Arm D)

- 13% distant recurrence despite chemo

ケモ+ホルモンでも予後不良！
S-1 (POTENT試験：N(-)も対象)

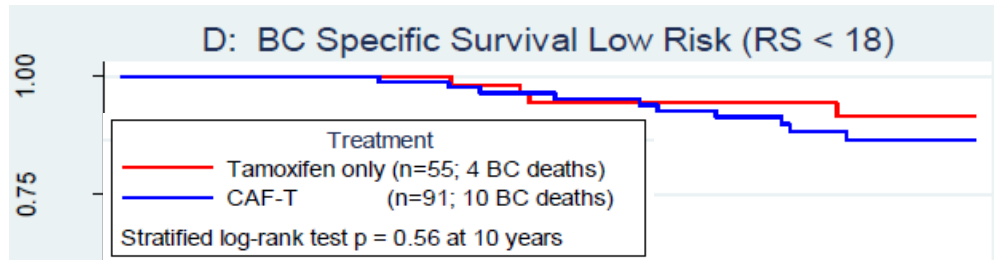


No. at risk

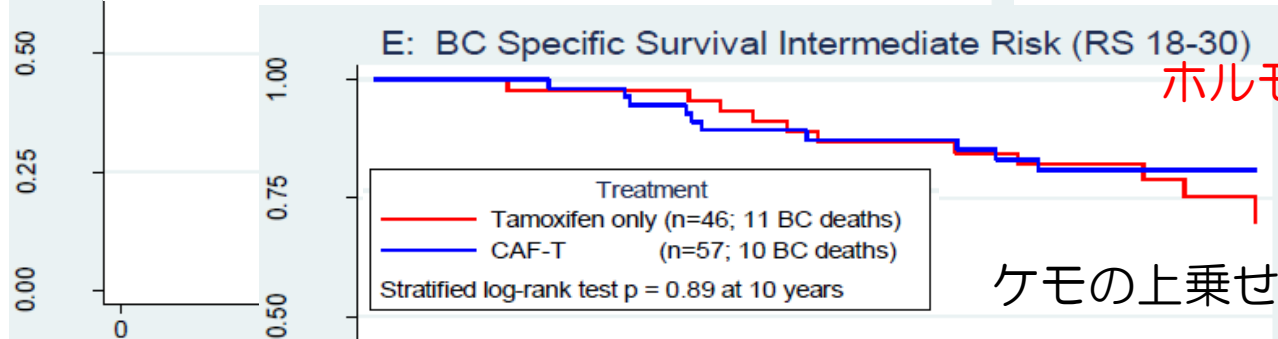
1,619	1,568	1,523	1,470	1,406	1,310	1,153	867	511	213
3,399	3,293	3,194	3,081	2,953	2,741	2,431	1,859	1,197	537
3,312	3,204	3,104	2,993	2,849	2,645	2,335	1,781	1,130	523
1,389	1,291	1,174	1,090	986	617	463	329	187	77

Oncotype DX
LN(+)は？

リンパ節転移のある場合でも同様

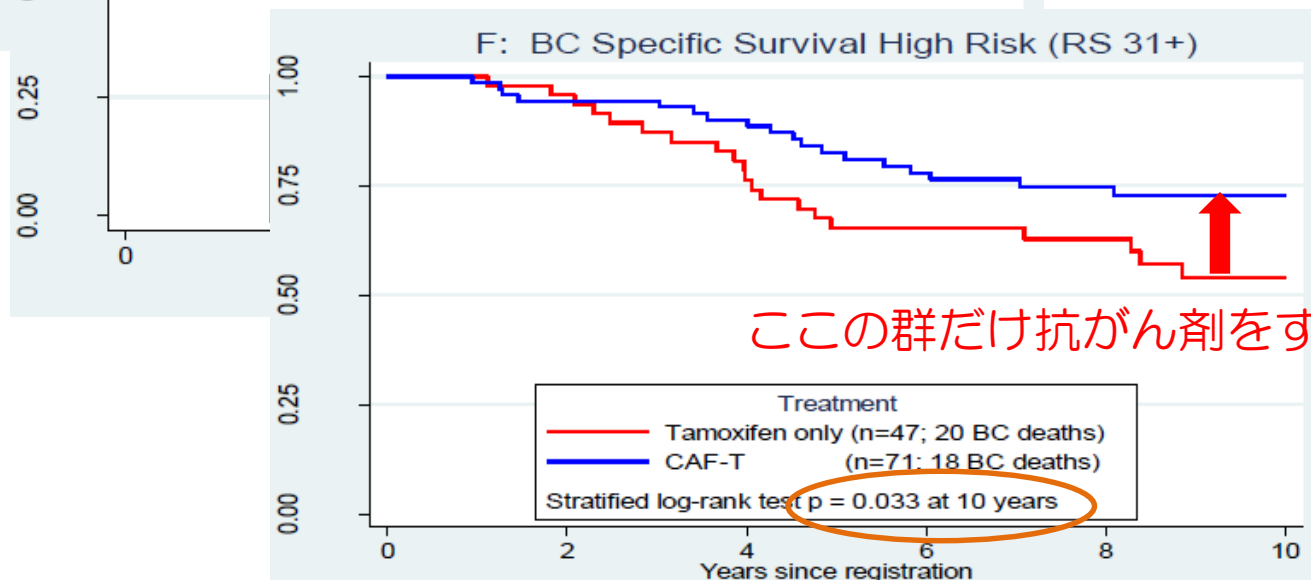


ホルモン療法だけで十分



ホルモン療法だけで十分

ケモの上乗せ効果なし



この群だけ抗がん剤をする意味あり

Who needs chemo?

Oncotype DX
LN(+)

RxPONDER

RxPONDER Schema

Key Entry Criteria

- Women age ≥ 18 yrs
- ER and/or PR $\geq 1\%$, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND

R
E
G
I
S
T
R
A
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I
O
N

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy Recommended

R
A
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N

N = 5,000 pts

Arm 1:
Chemotherapy Followed by
Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

Stratification Factors

Recurrence Score: 0-13 vs. 14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.

** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.

ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

RxPONDER Schema

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Recurrence Score 0-25

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monarchE Study Design

HR+, HER2-, high risk early breast cancer

High risk defined as:

- ≥4 positive axillary lymph nodes (ALN) OR
- 1-3 ALN and at least 1 of the below:
 - Tumor size ≥5 cm
 - Histologic grade 3
 - Centrally tested Ki67 ≥20%

Other criteria:

- Women or men
- Pre-/ postmenopausal
- With or without prior adjuvant/neoadjuvant chemotherapy
- No distant metastases

N = 5637^a

R
1:1

Stratified for:

- Prior chemotherapy
- Menopausal status
- Region

Abemaciclib (150mg twice daily for up to 2 years^b)
+ **Standard of Care Endocrine Therapy**
(5 to 10 years as clinically indicated)

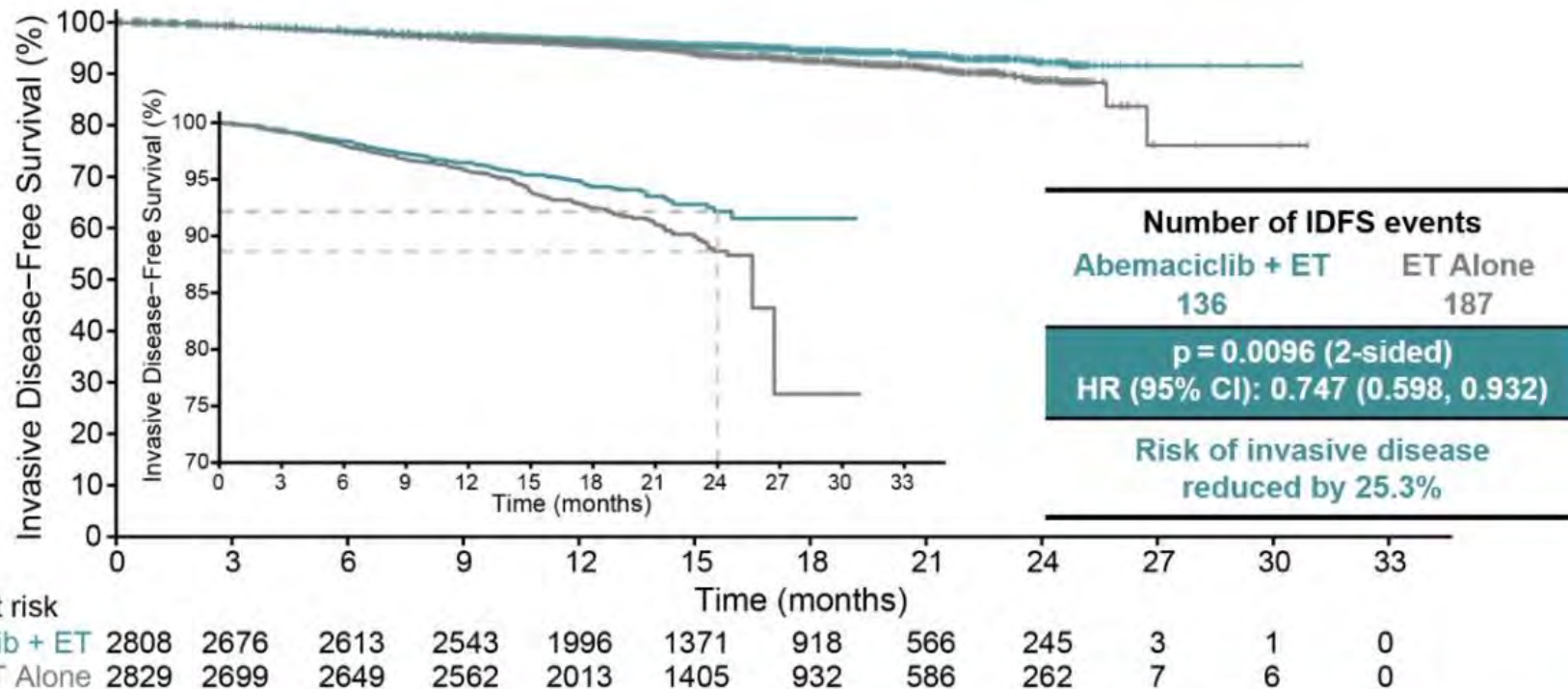
Standard of Care Endocrine Therapy^b
(5 to 10 years as clinically indicated)

Endocrine therapy of physician's choice

Primary Objective: Invasive disease-free survival (STEEP criteria)
Key Secondary Objectives: Distant relapse-free survival, Overall survival, Safety, Patient reported outcomes, and Pharmacokinetics

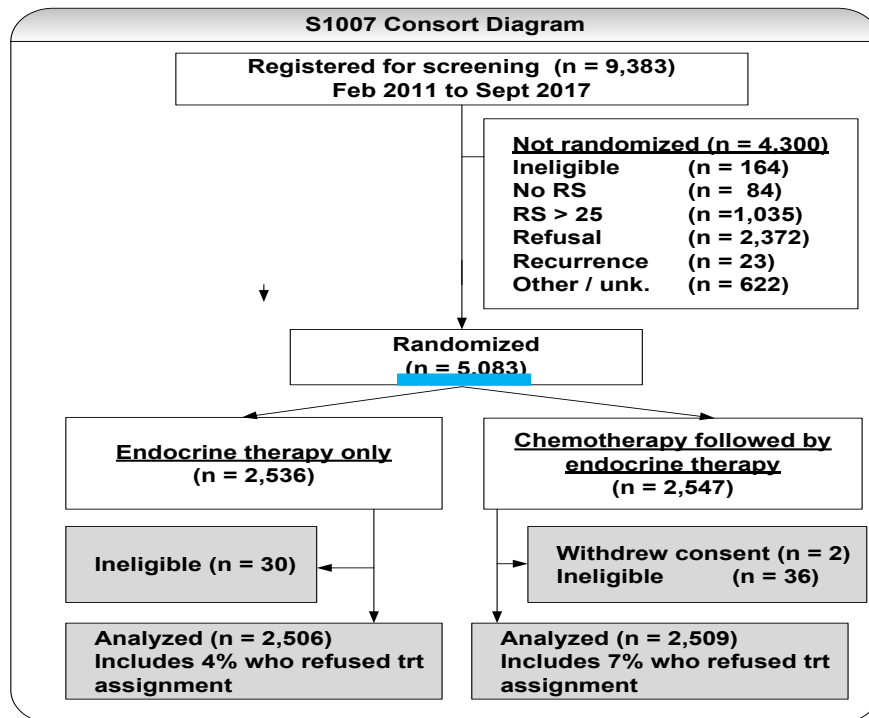
^aRecruitment from July 2017 to August 2019; ^bTreatment period = first 2 years on study treatment after randomization

Invasive Disease-Free Survival



Two-year IDFS rates were 92.2% (abemaciclib + ET arm) and 88.7% (ET arm) – 3.5% absolute difference

RxPONDER Results: Accrual and ITT population



- ✓ 50% randomized to chemotherapy received TC (4 or 6 cycles)
- ✓ Ovarian function suppression use in premenopausal pts (6-month post randomization data)
 - 16% in the ET arm and 3% in Chemotherapy + ET arm
- ✓ 2 treatment-related deaths in ET arm (stroke) and 3 in chemotherapy + ET arm (sepsis, typhlitis, and liver necrosis)

Baseline Characteristics by Treatment Arm

Baseline variable	Endocrine Therapy (n=2,506)	Chemotherapy (n=2,509)	Overall (n=5,015)
Race			
White	64.9%	66.4%	65.7%
Black	4.8%	5.1%	5.0%
Asian	6.8%	6.1%	6.5%
Other/Unknown	23.5%	22.3%	22.9%
Hispanic			
Yes	13.0%	11.9%	12.4%
No	67.6%	68.9%	68.3%
Unknown	19.4%	19.3%	19.3%
Menopausal status			
Premenopausal	33.2%	33.2%	33.2%
Postmenopausal	66.8%	66.8%	66.8%
Recurrence Score			
RS 0-13	42.7%	42.8%	42.8%
RS 14-25	57.3%	57.2%	57.2%
Nodal Dissection			
Full ALND	62.7%	62.5%	62.6%
Sentinel nodes only	37.4%	37.5%	37.4%
Positive Nodes			
1 node	65.9%	65.0%	65.5%
2 nodes	24.9%	25.7%	25.3%
3 nodes	9.2%	9.2%	9.2%
Grade			
Low	24.6%	24.7%	24.7%
Intermediate	64.1%	66.1%	65.1%
High	11.3%	9.2%	10.3%
Tumor size			
T1	58.5%	57.7%	58.1%
T2/T3	41.5%	42.3%	41.9%

閉経前 33%

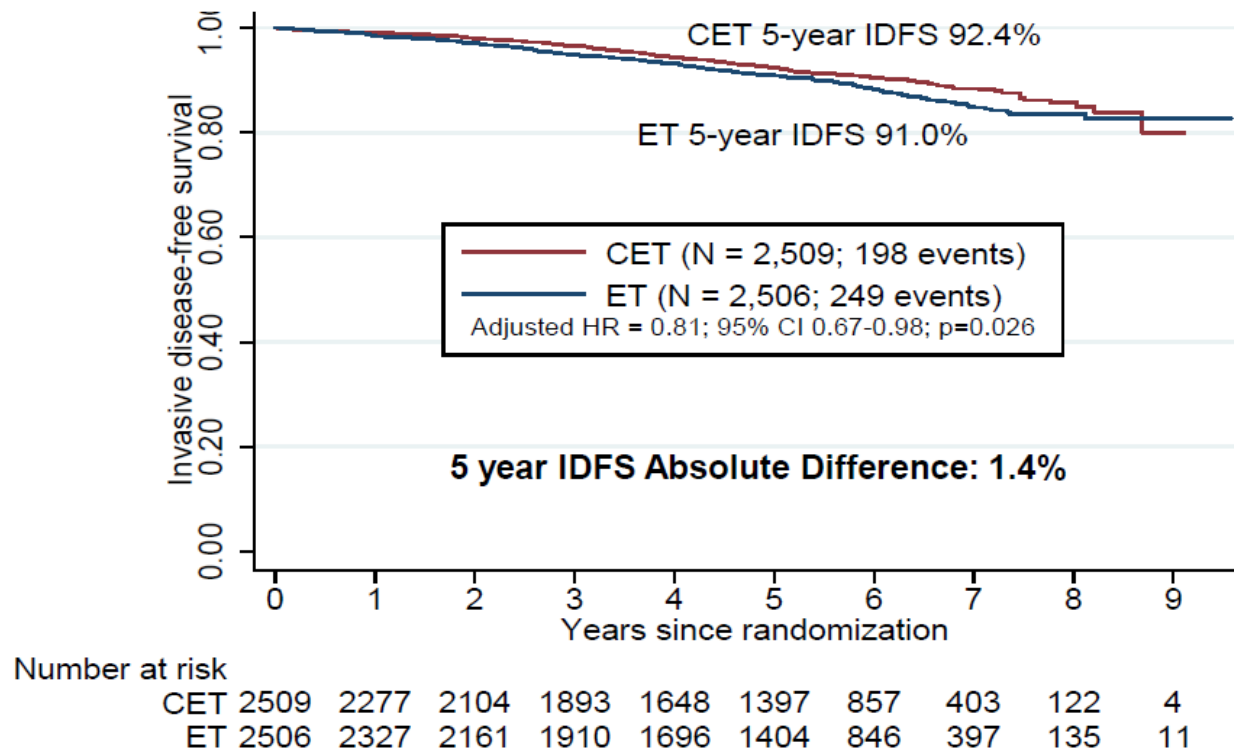
RS 0-13:14-25 ≒
4:6

SN only 37%

n1個 66%
n2個 25%
N3個 10%

Grade 1 25%
Grade 2 66%

IDFS in Overall Population by Treatment Arm

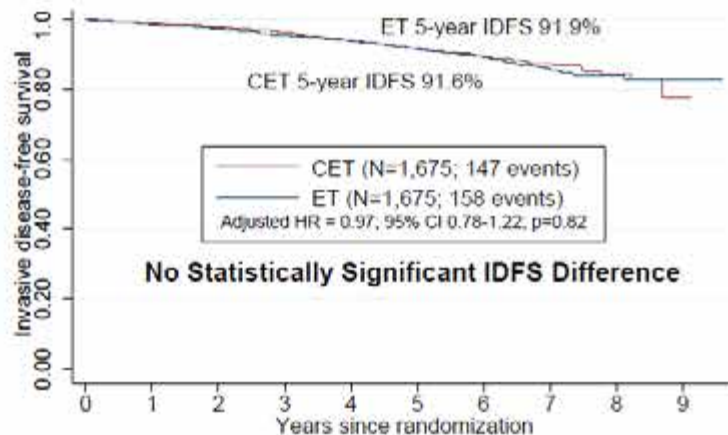


CET = Chemotherapy + Endocrine Therapy; ET = Endocrine Therapy Alone

447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years

IDFS Stratified by Menopausal Status

Postmenopausal



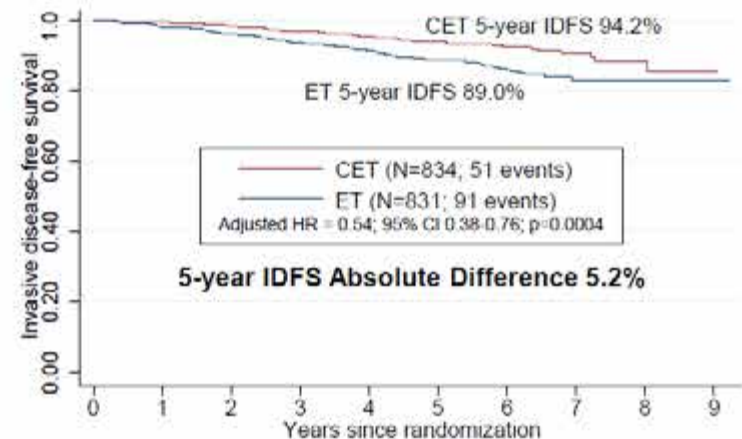
Number at risk

CET	1675	1514	1400	1268	1113	943	585	287	88	3
ET	1675	1567	1462	1308	1167	975	601	298	104	9

IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

Premenopausal



Number at risk

CET	834	763	704	625	535	454	272	116	34	1
ET	831	760	699	602	529	429	245	99	31	2

IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

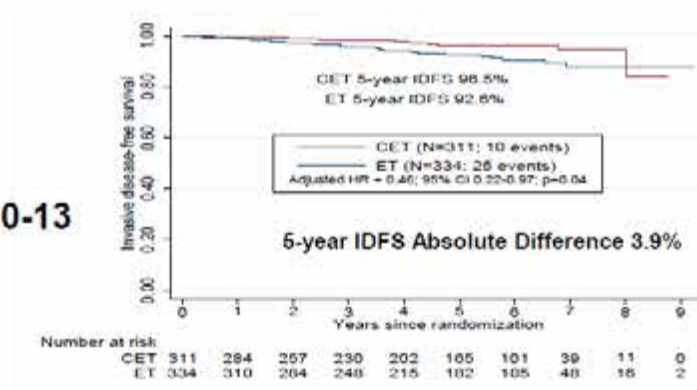
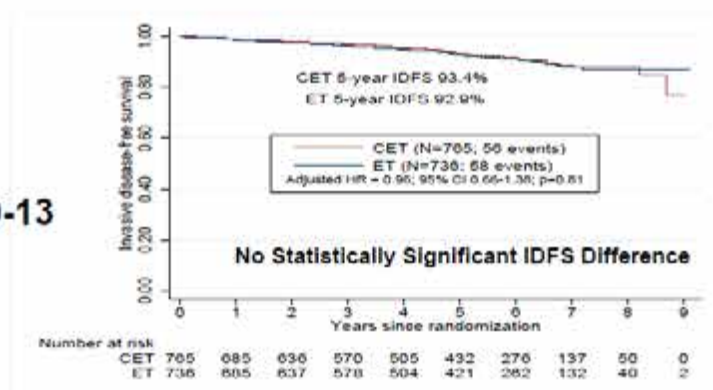
IDFS Stratified by Recurrence Score and Menopausal Status

Postmenopausal

Premenopausal

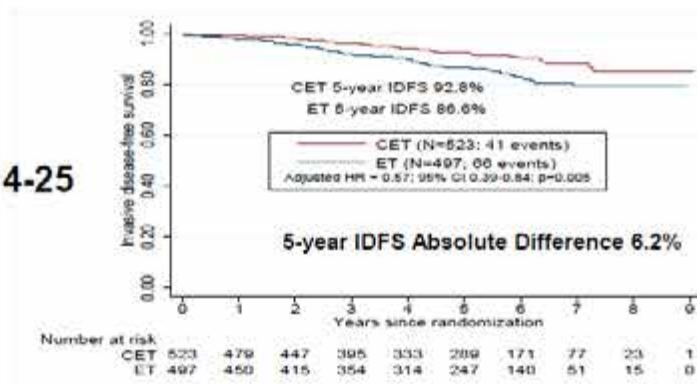
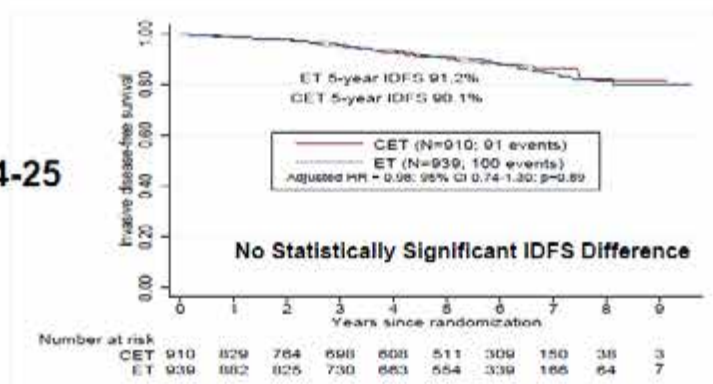
RS 0-13

RS 0-13



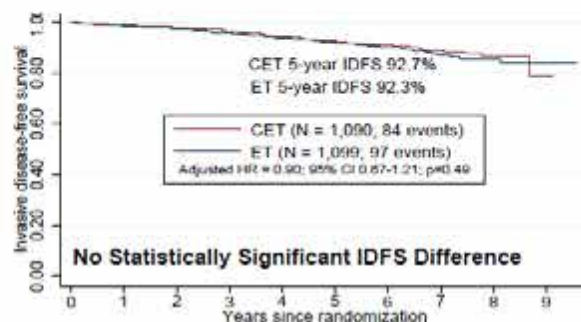
RS 14-25

RS 14-25

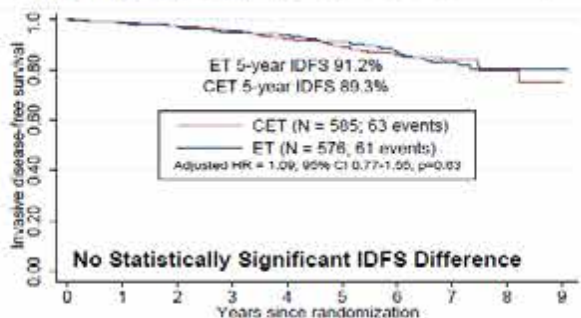


IDFS Stratified by Number of Nodes and Menopausal Status

Postmenopausal

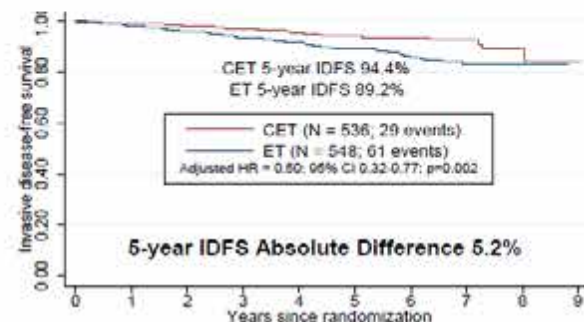


Number at risk										
CET	1090	995	929	851	753	644	406	195	60	2
ET	1099	1028	962	861	785	668	428	213	71	8

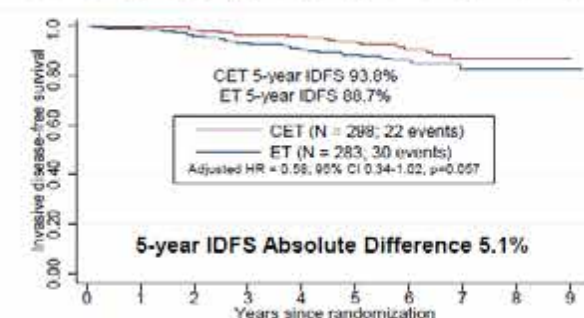


Number at risk										
CET	585	519	471	417	360	299	179	92	28	1
ET	576	539	500	447	382	307	173	85	33	1

Premenopausal



Number at risk										
CET	536	483	440	390	336	286	180	73	20	1
ET	548	506	469	408	360	290	175	68	18	0



Number at risk										
CET	298	280	264	235	199	168	92	43	14	0
ET	283	254	230	194	169	139	70	31	13	2

Oncotypeの適応と解釈

適応	
リンパ節転移陰性	エビデンス的には「ケモを悩んでいる」患者全員、 だが保険適応がないので、下表に従い推奨
リンパ節転移陽性	エビデンス的には閉経後、pN1-3個で「ケモを悩 んでいる」患者全員、 だが保険適応がないので、下表に従い推奨 閉経前の方は現時点では推奨ないが、Case by case (例：T1bN1mic, Ki67<10%など)

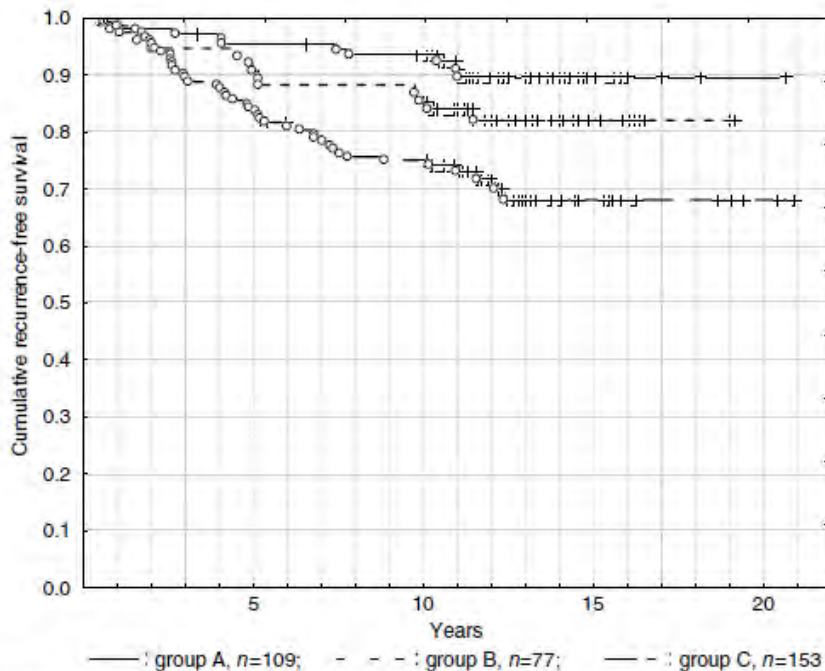
St.Galeen 2005 改変	Low risk	Intermediate risk	High risk
	すべてを満たす ・ T1 ・ NG1 ・ 35歳以上 ・ ly(-) ・ ki67 low	1つ以上満たす場合 ・ T2以上 ・ NG2-3 ・ 35歳未満 ・ ly(+) ・ ki67 intermediate 以上	すべてを満たす場合
pN0	B	A	C
pN1-3個	A	B	C
pN4個	D	D	D

A: 強く推奨する
B: 弱く推奨する
C: 行わないことを弱く推奨する
D: 行わないことを強く推奨する

術後療法TAMのみ時代の予後

がん研1982-1993 n=436

Intermediate-risk patients



Intermediate risk	10yRFS	再発率
A: n0かつ risk factor1	93.5%	6.5%
B: n0かつ risk factor2~5	88.2%	11.8%
C: n+	75.0%	25.0%

Risk factor

pT> 2cm

Grade2,3

脈管侵襲あり

HER2+

35歳未満

Oncotypeの適応と解釈

解釈	
リンパ節転移陰性	50歳より上：RS25以下でケモ省略 50歳以下：Low Clin risk：RS20以下でケモ省略 50歳以下：High Clin risk：RS15以下でケモ省略
リンパ節転移陽性	閉経後：LN1-3個+、RS25以下でケモ省略 閉経前：LN+なら基本的に全例ケモを推奨 (Case by caseで提出可、解釈もRSに応じて)

High clinical risk: Grade1 & T>3cm,
 Grade2 & T>2cm,
 Grade3 & T>1cm



ご清聴ありがとうございました。