Adjuvant Therapy inBreast Cancer: State of the Art

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UCDAVIS COMPREHENSIVE CANCER CENTER

Objectives

1. Chemotherapy benefit in the elderly
2. RCB score in triple negative breast cancer
3. Trastuzumab alone in elderly
4. Omission of radiation therapy using molecular markers

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2022 ASCO ANNUAL MEETING

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Final results from a phase III randomized clinical trial of adjuvant endocrine therapy ± chemotherapy in women ≥ 70 years old with ER+ HER2- breast cancer and a high genomic grade index: the Unicancer ASTER 70s trial

Etienne Brain, Alessandro Viansone, Emmanuelle Bourbouloux, Olivier Rigal, Jean-Marc Ferrero, Sylvie Kirscher, Djelila Allouache, Véronique d'Hondt, Aude-Marie Savoye, Xavier Durando, François Duhoux, Laurence Venat-Bouvet, Emmanuel Blot, Jean-Luc Canon, Florence Rollot, Hervé Bonnefoi, Jérôme Lemonnier, Magali Lacroix-Triki, Aurélien Latouche, Franck Bonnetain, Dewi Vernerey, GERICO & UCBG/Unicancer

ASTER 70s (EudraCT 2011-004744-22/NCT01564056) was supported by the National PHRC 2011, Cephalon/Teva, Amgen, Ipsogen/Qiagen/HalioDx, L'Association d'Aide à la Recherche Cancérologique de Saint-Cloud and La Ligue Contre le Cancer

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Genomic Tools for BC and Older Patients

- Quantification of mRNA or cDNA of genes involved in tumour proliferation
- To identify patients requiring CT despite good standard prognostic factors and to avoid CT in others: better individual risk stratification
- **Constant under-representation** of older patients in randomized clinical trials (RCTs)

Trial	Age limit	Results
MINDACT	≤ 70	0.8% 70+ (56/6,693)
TAILORx	≤ 75	7% 70+ RS 0-10 (111/1,626) 4% 70+ RS 11-25 (300/6,897)
RxPONDER	Any	12% 70-75 yo RS ≤ 25 (581/5,018)

- **Genomic Grade Index (GGI)**
  - 97 genes (cell cycle regulation and proliferation)
  - Transposed onto a qRT-PCR

Origin	Genes
GGI	MYBL2, KPNA2, CDC2, CDC20
Reference	GUS, TBP, RPLPO, TFRC

Cardoso et al. N Engl J Med. 2016; 375:717-729. Kalinsky et al. N Engl J Med. 2021 Dec 16;385(25):2336-2347. Sparano et al. N Engl J Med. 2018 July 12; 379(2): 111–121.

Sotiriou et al. J Natl Cancer Inst. 2006;98:262–272. Toussaint et al. BMC Genomics. 2009 Sep 10;10:424.

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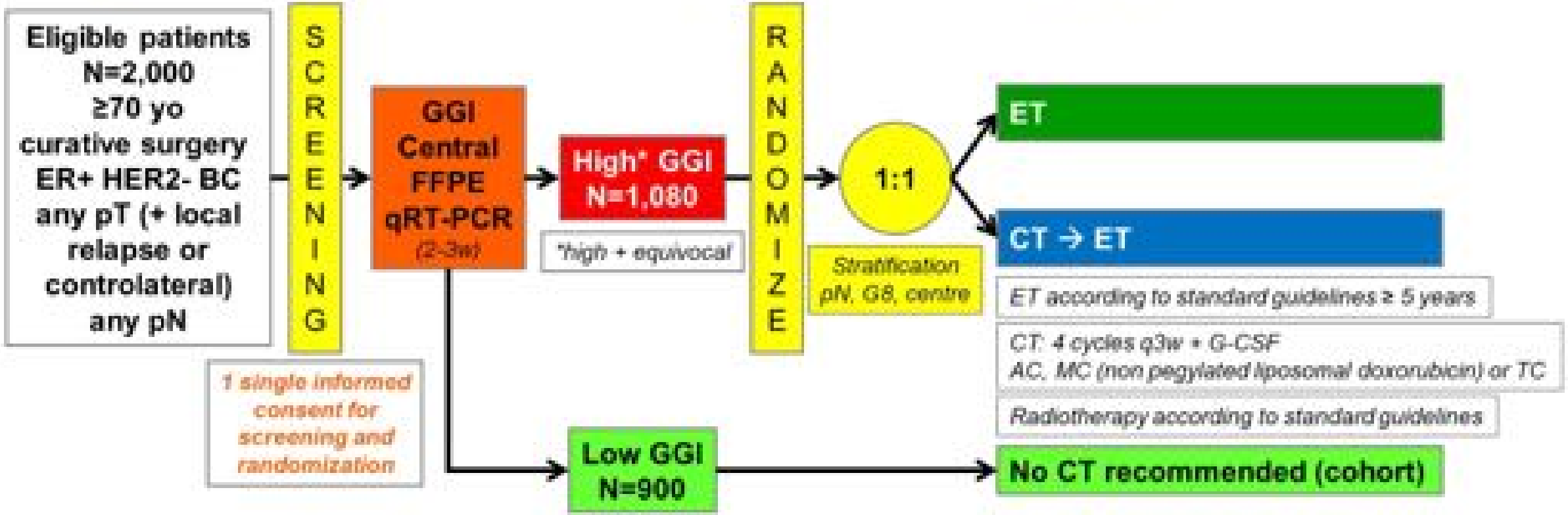
ASTER 70s Study Design

Adjuvant systemic treatment for ER+ HER2- BC in women over 70 according to GGI
Hypothesis: 4-year OS with CT → ET > 4-year OS with ET only if high GGI



All patients — *Lee score, G8, CCI, polypharmacy (baseline, 4 years)*
Randomized patients — *IADL, MMSE, QLQ C30 & ELD15, socioeconomic, willingness, blood & serum (baseline, 3 months, yearly x 4 years)*

Objectives

Primary objective

Overall survival (OS) if high risk of relapse according to GGI (high + equivocal)

Secondary objectives

- Breast cancer specific survival (BCSS)
- Invasive and distant disease-free survival (i/dDFS)
- Event-free survival (EFS), (distant) relapse-free survival [(d)RFS]
- Safety (NCI-CTC v4.0)
- GGI performance (prognostic and predictive)
- Health-related quality of life (HRQoL, QLQ C-30 & ELD-14)
- Treatment acceptability
- Lee score and G8 validation for older patients with early-stage BC
- Q-TWiST and cost-effectiveness

Ancillary

- GGI prognostic value in first 500 patients with 3 years of follow-up
- Ageing biomarkers
- Correlative biomarkers

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Statistical considerations

- Superiority trial, intent to treat (ITT) analysis
- GGI high (+ equivocal) ~ 50-60%
- Primary endpoint: OS with 4 years of minimal follow-up
  - H0: 4-year OS with ET 80.2%
  - H1: 4-year OS with CT → ET 87.5% (HR 0.61)
- Interim analysis using O'Brien Fleming boundaries and α spending function to reject H0 or H1 when 50% events observed (01/2019)

Time point	α type 1 error	β type 2 error (power)	Number of events expected	To randomize + lost to follow up	To screen
Initial	0.05 (2-sided)	0.20 (80%)	129	680/700	1,800-2,000
IDMC 03/09/2014*	0.05 (2-sided)	**0.10 (90%)**	**171**	**864/1080**	**2,000**

**Due to 11% patients not adherent to treatment assigned by randomization [2/128 (1.6%) if ET, 102/128 (20.3%) if CT → ET], increase the number of patients to be randomized in order to minimize OS variability and improve the stability of ITT results*

Jones et al. J Clin Oncol 2009; 27(8):1177-1183. Muss et al. N Engl J Med 2009; 360(20):2055-2065.

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Selected Patients Characteristics

	Randomized N=1,089				Not randomized N=880		p
	ET (N=548)		CT → ET (N=541)				
	N	%	N	%	N	%	
Median age (min-max)	75.8 (70.01-92.4)		76.0 (70-89.9)		75.4 (69.8-92.4)		NS
PS 0	374	**68.6**	340	**63.0**	559	**70.7**	**<0.05**
G8≤14*	210	38.8	222	41.3	318	38.9	NS
Lee>8**	83	15.4	85	15.9	103	12.7	NS
Adjusted CCI# >6	94	17.4	98	18.4	129	16.0	NS
Prior cancer	131	**24.0**	99	**18.3**	144	**17.1**	**0.02**

** G8, screening tool for frailty: if ≤14, it requires the need of a complete geriatric assessment as identifies patients at risk of frailty*
*** Lee, 4-year mortality score: if ≥8 in a person ≥70 yo, 4-year mortality is estimated ~ 50%*
 # CCI, Charlson Comorbidity Index

Randomized patients: median IADL 8 (8-8), median MMSE 28 (26-30)

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Selected Tumour Characteristics

	Randomized N=1,089				Not randomized N=880		p
	ET (N=548)		CT → ET (N=541)				
	N	%	N	%	N	%	
Mastectomy	211	38.6	216	39.9	240	27.9	<0.0001
pT0-1	238	43.8	234	43.6	503	58.9	<0.0001
Local relapse*/controlateral	76	13.9	65	12.0	84	9.4	NS
pN0	287	53.5	295	55.0	441	51.7	NS
Lobular	99	18.1	88	16.3	203	23.8	0.003
Multifocal	106	19.4	103	19.0	136	16.1	NS
Histological grade I grade II/III	37 302/202	6.8 55.8/37.3	26 300/215	4.8 55.5/39.7	205 559/91	24.0 65.4/10.6	<0.001
PgR negative	115	21.0	119	22.0	141	16.4	0.004
GGI high/equivocal	355/193	64.8/35.2	354/187	65.4/34.6	0	0	NA

"Local relapse" by convention defined as pN0

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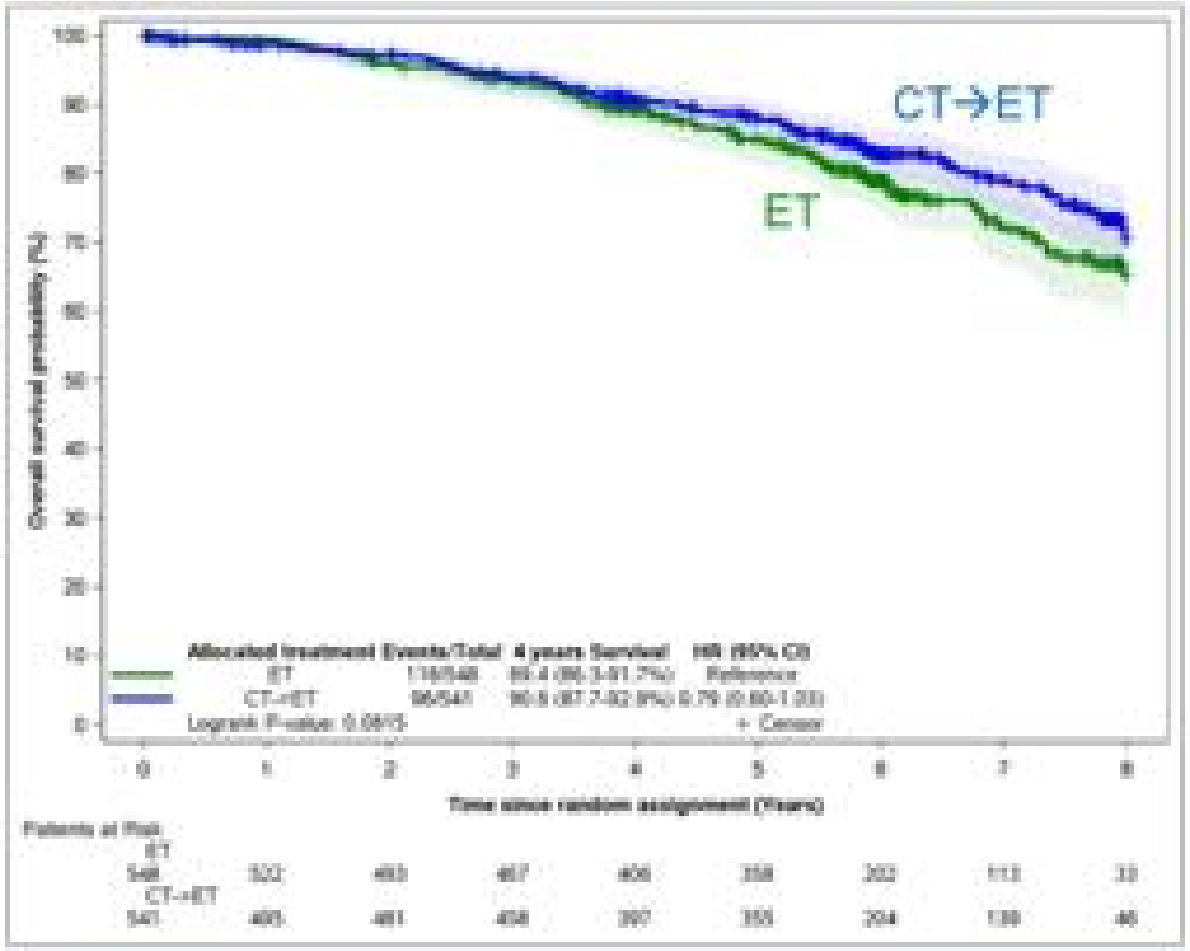
Treatment Realization in Randomized Patients

	ET (N=548)		CT → ET (N=541)		
	N	%	N	%	*p*
Non-adherence to treatment assigned*	3	**0.6**	111	**20.5**	**<0.0001**
Chemotherapy choice	3		430		
Taxane (TC)	2	66.7	281	65.3	NA
Anthracycline (AC, MC)	1	33.3	148	34.4	
Other	0	0	1	0.2	
Treatment stopped					
CT stopped before cycle 4	0	NA	28	6.4	NA
CT stopped for toxicity	0	NA	26	4.8	
ET stopped for toxicity	124	22.6	114	21.1	
≥ 1 AE any grade/grade ≥ 3	445/52	**81.2/9.5**	503/183	**92.9/34.2**	**<0.0001**
≥ 1 SAE	17	**3.1**	88	**16.3**	**<0.0001**
Grade 5	1	0.2	3	0.6	0.3711

**Non-adherence to treatment arm assigned: 114/1,089 patients (10.5%)*

OS: ET — *vs* CT→ET — (intent to treat) (primary endpoint)

median follow-up
5.94 years



4-year OS	89.4 (86.3-91.7)
4-year OS	90.6 (87.7-92.9)
HR	0.79 (0.60-1.03)
p	0.08

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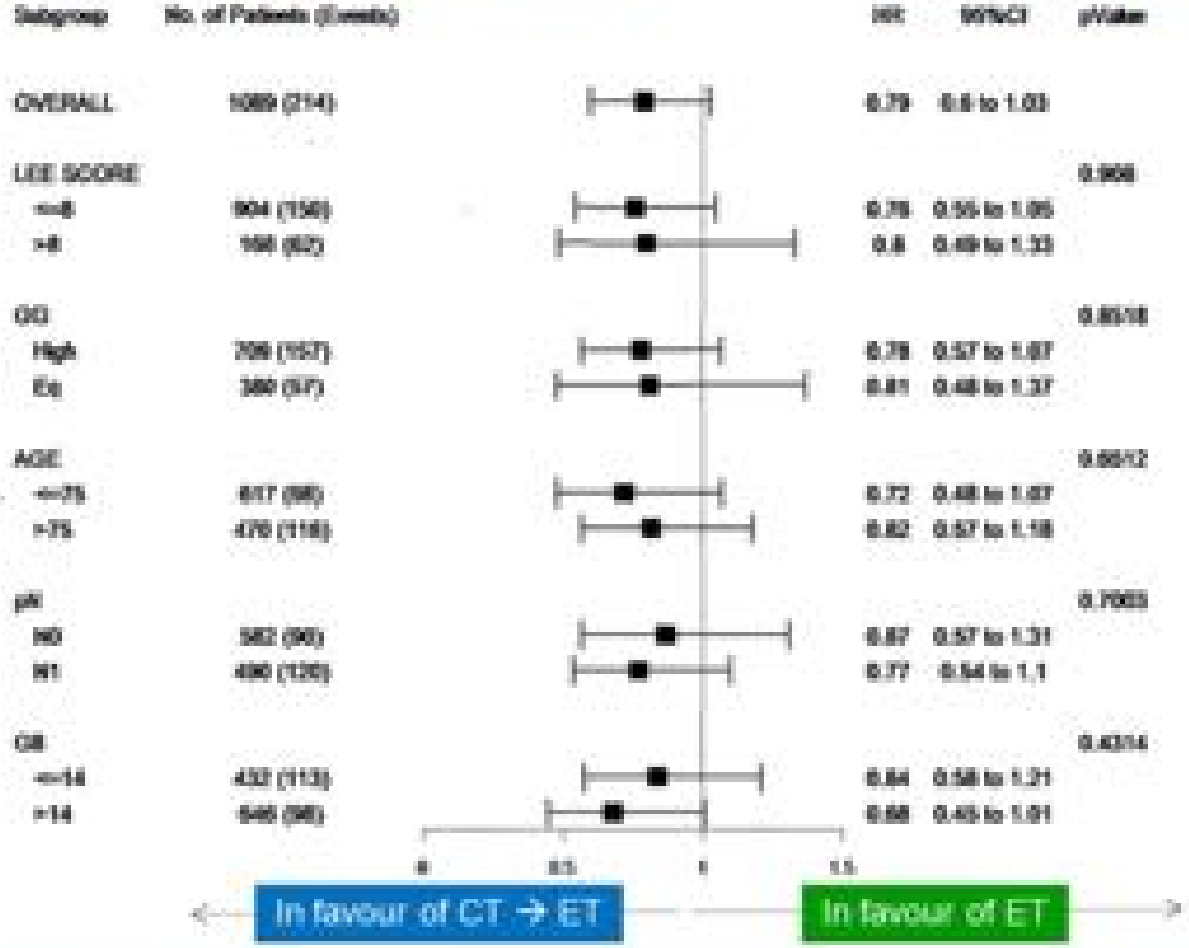
OS: ET —— *vs* CT→ET —— (intent to treat) (primary endpoint)

FOREST PLOT



LCI, UCI: 95% lower and upper confidence interval
**interaction pvalue*

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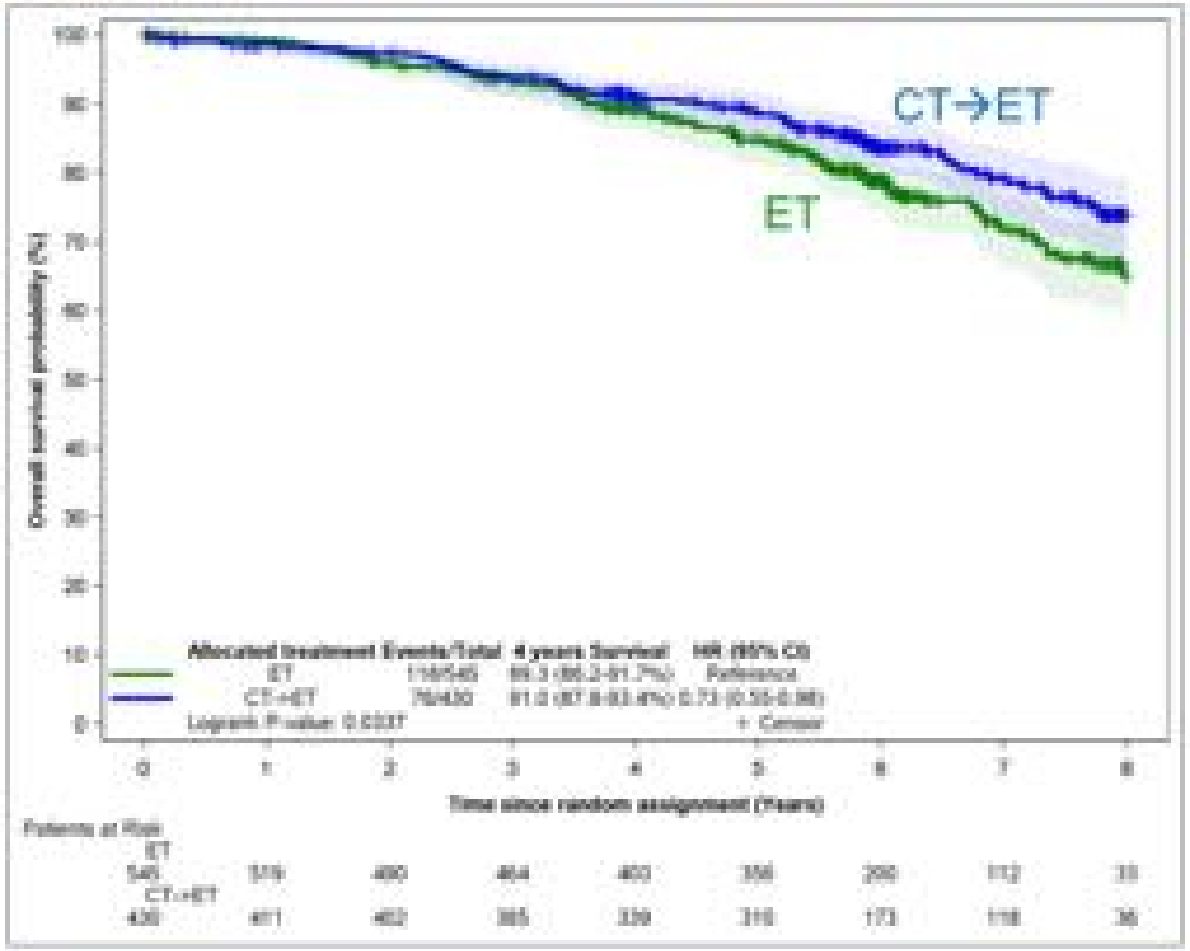
OS: ET —— *vs* CT→ET —— (per protocol)

median follow-up
5.94 years



4-year OS	89.3 (86.2-91.7)
4-year OS	91.0 (87.8-93.4)
HR	0.73 (0.55-0.98)
p	**0.03**

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How does this change clinical practice?

- The Genomic Grade Index (GGI) was prognostic but not predictive in early-stage breast cancer in the elderly
- ASTER 70s trial successfully enrolled representative elderly patients
- The GGI should not be used in clinical care decision making given data on other tumor gene expression assays

Event-free Survival by Residual Cancer Burden After Neoadjuvant Pembrolizumab + Chemotherapy vs Placebo + Chemotherapy for Early-Stage TNBC: Exploratory Analysis From KEYNOTE-522

Lajos Pusztai[1], Carsten Denkert[2], Joyce O'Shaughnessy[3], Javier Cortes[4], Rebecca Dent[5], Heather McArthur[6], Sherko Kümmel[7], Jonas Bergh[8], Yeon Hee Park[9], Rina Hui[10], Nadia Harbeck[11], Masato Takahashi[12], Michael Untch[13], Peter A. Fasching[14], Fatima Cardoso[15], Yalin Zhu[16], Wilbur Pan[16], Konstantinos Tryfonidis[16], Peter Schmid[17]

1. Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; 2. Institute of Pathology, Philipps-University Marburg and University Hospital Marburg, Marburg, Germany; 3. Baylor University Medical Center, Texas Oncology, US Oncology Network, Dallas, TX, USA; 4. International Breast Cancer Center, Quironsalud Group, Barcelona, Spain and Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; 5. National Cancer Center Singapore, Duke – National University of Singapore Medical School, Singapore; 6. University of Texas Southwestern Medical Center, Dallas, TX, USA; 7. Breast Unit, Kliniken Essen-Mitte, Essen, Germany and Charité – Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany; 8. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer Theme, Karolinska University Hospital, Karolinska Comprehensive Cancer Center, Solna, Sweden; 9. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 10. Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; 11. Breast Center, LMU University Hospital, Munich, Germany; 12. Hokkaido Cancer Center, Sapporo, Japan; 13. Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; 14. University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; 15. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 16. Oncology, Merck & Co., Inc., Rahway, NJ, USA; 17. Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK

KEYNOTE-522: Primary Results

- KEYNOTE-522 is the first prospective randomized placebo-controlled phase 3 trial of pembrolizumab in early-stage TNBC in the neoadjuvant and adjuvant settings
- The primary analyses showed:
  - Neoadjuvant pembrolizumab + chemotherapy resulted in a statistically significant and clinically meaningful increase in pCR (ypT0/Tis ypN0)[1]
  - Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab resulted in a statistically significant and clinically meaningful improvement in EFS[2]
- Based on these results, the FDA and EMA have approved pembrolizumab in combination with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery for high-risk early-stage TNBC

1. Schmid P, et al. *N Engl J Med* 2020;382:810-21; 2. Schmid P, et al. *N Engl J Med* 2022;386:556-67.

Residual Cancer Burden (RCB)

Analysis Objective

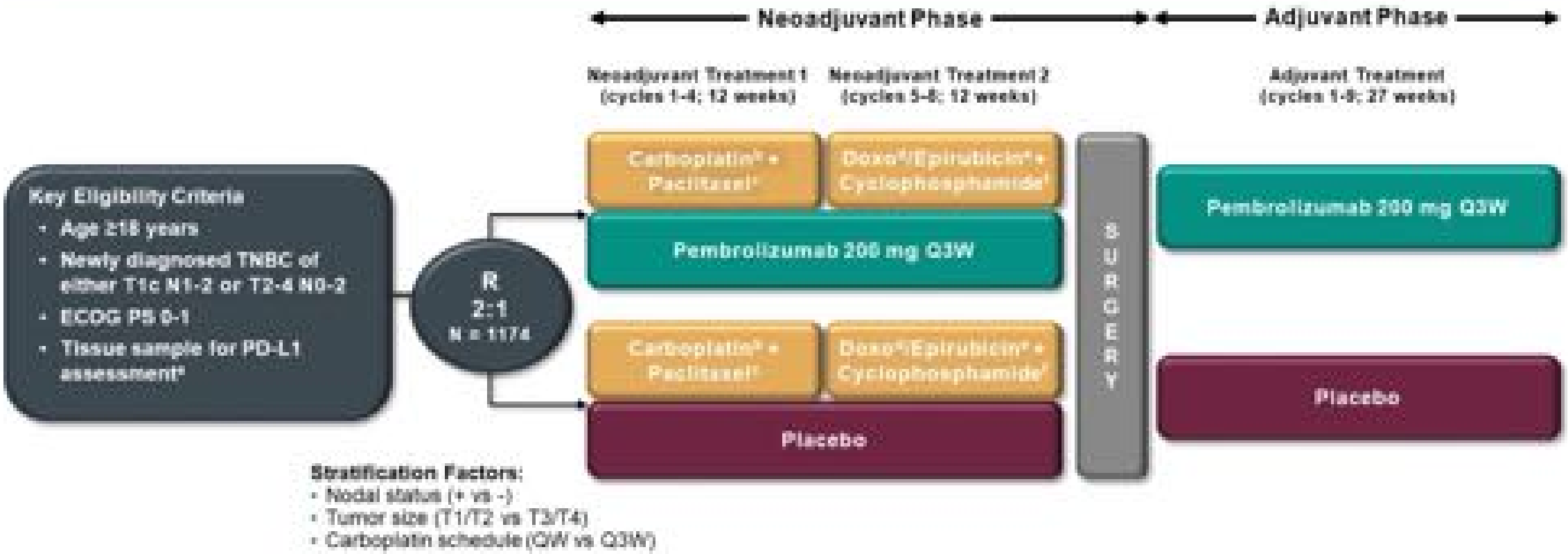
- To evaluate EFS by treatment arm within RCB categories (RCB-0, -1, -2, -3, corresponding to increasingly larger residual cancer)[1] in all patients in KEYNOTE-522

Analysis Considerations

- This was a prespecified exploratory analysis and not controlled for multiplicity
- RCB was assessed by the local pathologist at the time of definitive surgery
- Data cutoff date: March 23, 2021
- Median follow-up duration: 39.1 months (range, 30.0-48.0)

1. Symmans WF, et al. J Clin Oncol 2007;25:4414-22.

KEYNOTE-522 Study Design (NCT03036488)

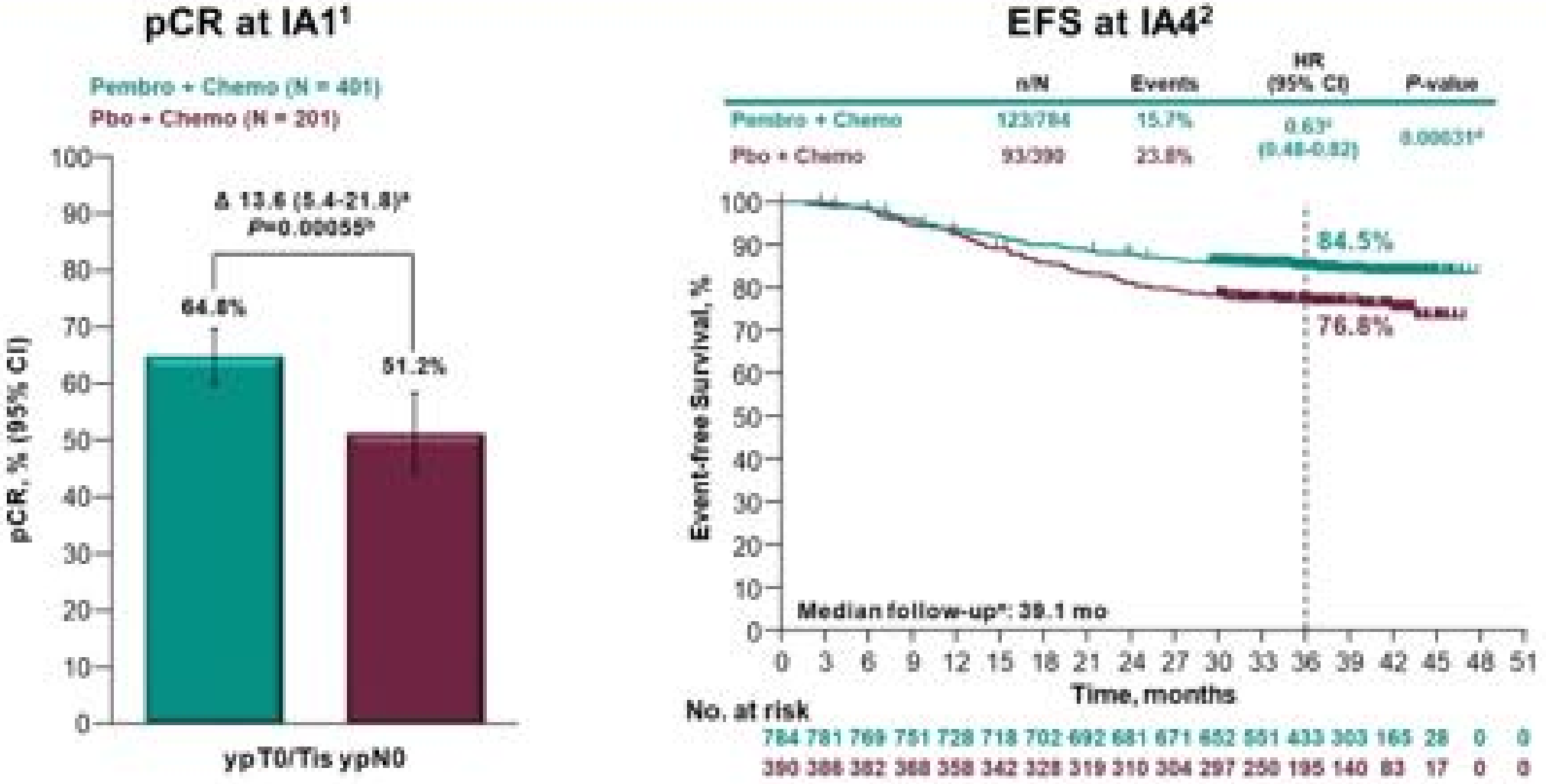


Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

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

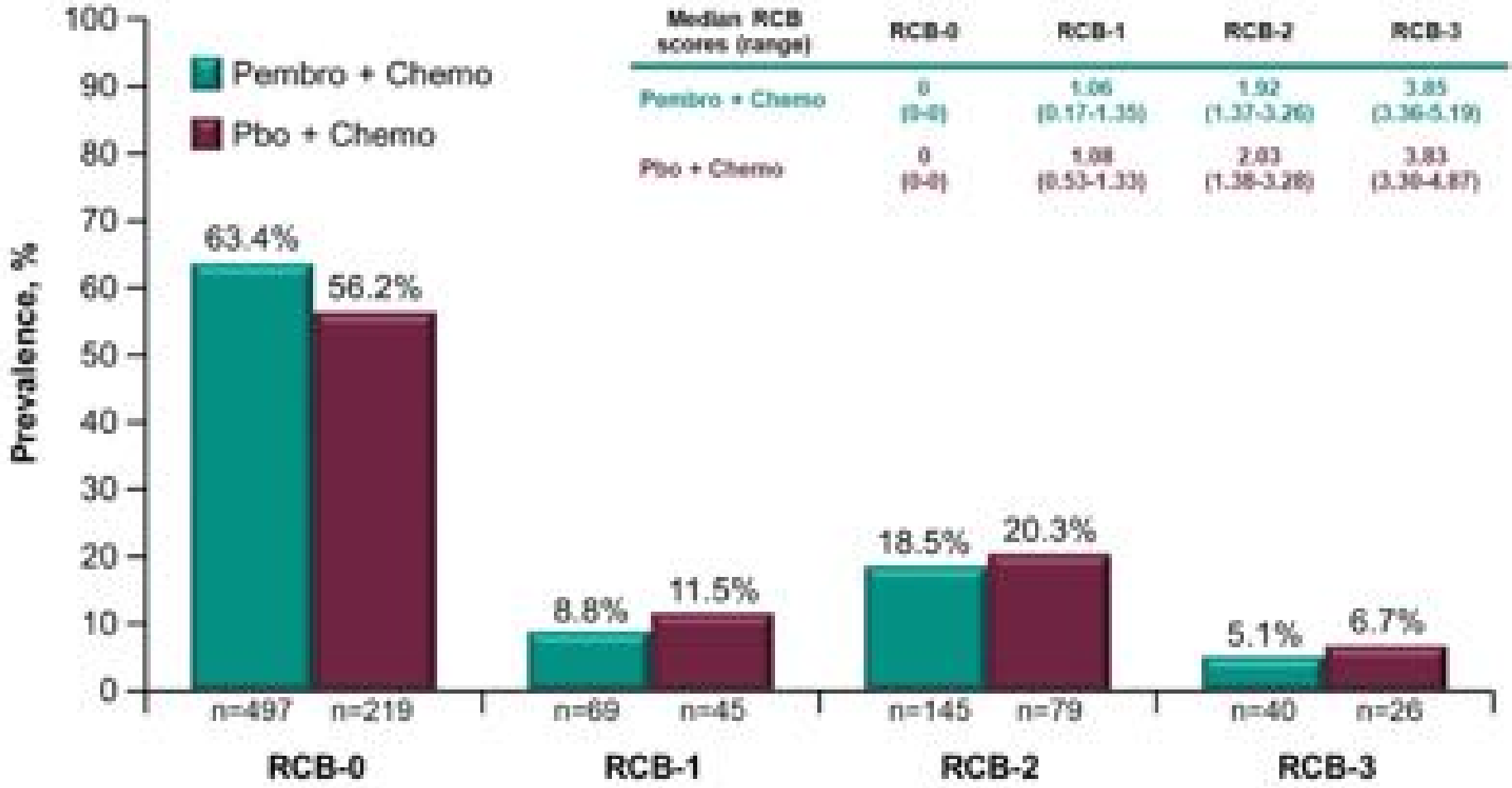
[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m^2 QW. [d]Doxorubicin dose was 60 mg/m^2 Q3W. [e]Epirubicin dose was 90 mg/m^2 Q3W. [f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Primary Analyses of KEYNOTE-522



1. Schmid P, et al. *N Engl J Med* 2020;382:810-21. 2. Schmid P, et al. *N Engl J Med* 2022;386:556-67. [a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]Prespecified *P*-value boundary for significance of 0.003 was crossed; data cutoff date: September 24, 2018. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary of 0.00517 was crossed. [e]Defined as the time from randomization to the data cutoff date of March 23, 2021.

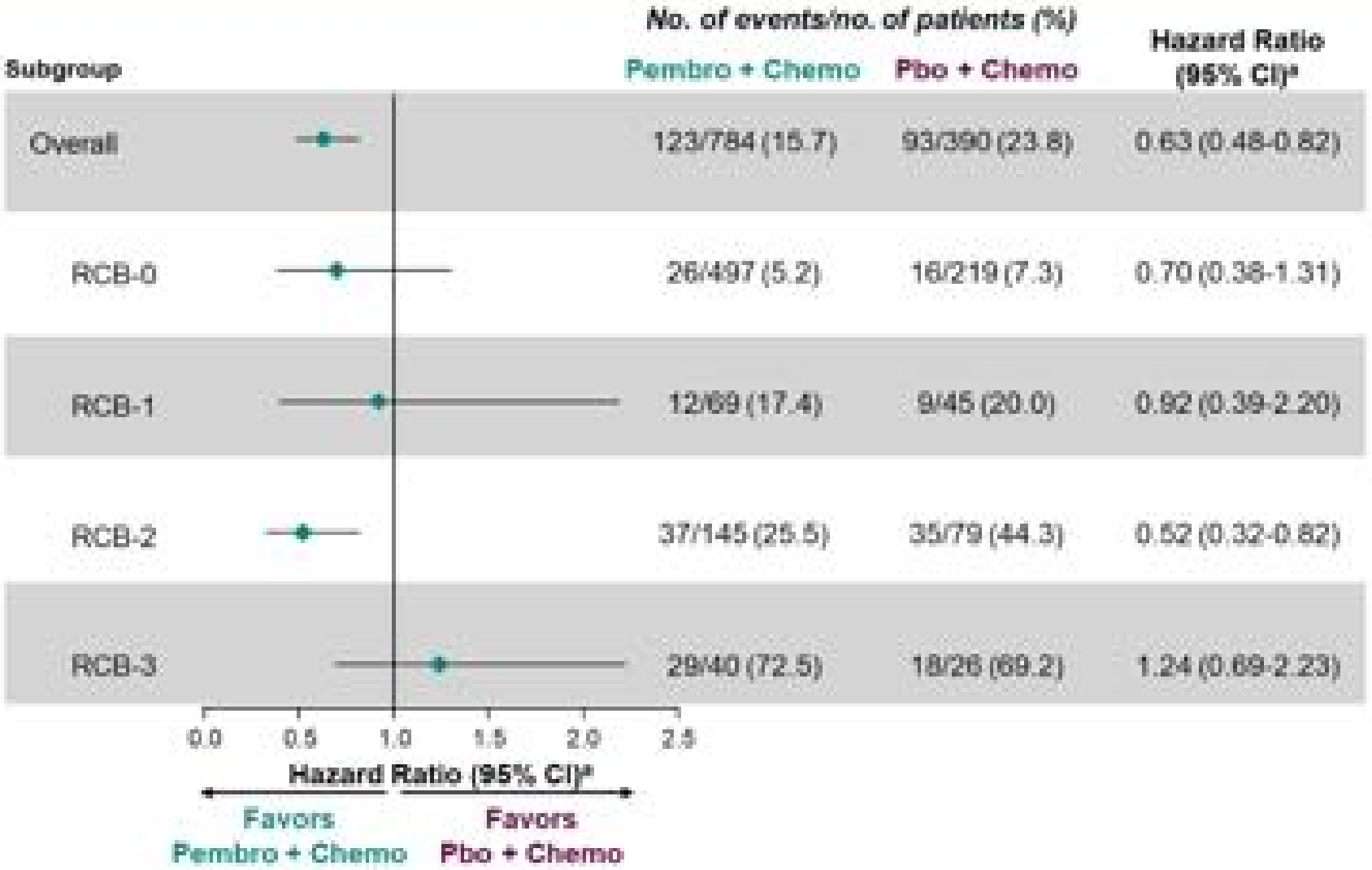
Prevalence of RCB Categories in All Patients



Median RCB scores (range)	RCB-0	RCB-1	RCB-2	RCB-3
Pembro + Chemo	0 (0-0)	1.06 (0.17-1.35)	1.92 (1.37-3.26)	3.83 (3.36-5.19)
Pbo + Chemo	0 (0-0)	1.08 (0.53-1.33)	2.83 (1.38-3.28)	3.83 (3.36-4.87)

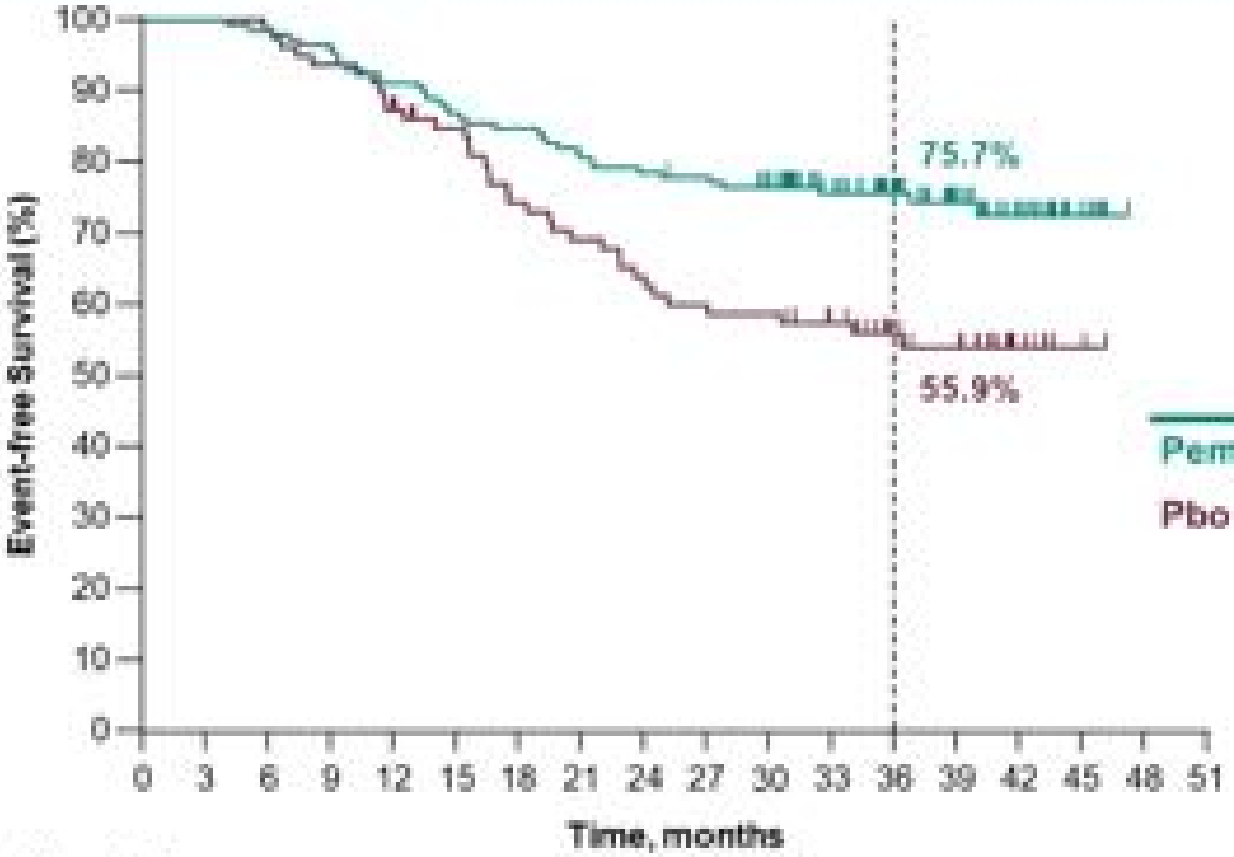
Among all patients (n=1174), 54 patients (4.6%) had missing RCB categorical data: 33 (4.2%) in the pembro + chemo group and 21 (5.4%) in the pbo + chemo group.
Data cutoff date: March 23, 2021.

EFS Analysis by RCB Category



aEFS in overall population is based on a stratified Cox model; EFS by RCB is based on an unstratified Cox model. Data cutoff date: March 23, 2021.

EFS in RCB-2



	n/N	Events	HR (95% CI)
Pembro + Chemo	37/145	25.5%	0.52[a] (0.32-0.82)
Pbo + Chemo	35/79	44.3%	

No. at risk

145	145	143	140	132	126	123	117	114	112	107	90	70	46	26	9	0	0
79	79	78	74	69	65	57	53	49	46	45	40	29	24	7	2	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate. Data cutoff date: March 23, 2021.

Summary of First EFS Events by RCB Category

Event	RCB-0		RCB-1		RCB-2		RCB-3	
	Pembro N = 497	Pbo N = 219	Pembro N = 69	Pbo N = 45	Pembro N = 145	Pbo N = 79	Pembro N = 40	Pbo N = 26
Any EFS event	5.2%	7.3%	17.4%	20.0%	25.5%	44.3%	72.5%	69.2%
Secondary primary malignancy	0.2%	0	1.4%	2.2%	1.4%	3.8%	2.5%	0
PD precluded definitive surgery	0	0	1.4%	2.2%	1.4%	5.1%	10.0%	7.7%
Local recurrence	0.6%	1.4%	4.3%	6.7%	6.9%	8.9%	25.0%	7.7%
Distant recurrence	3.2%	5.5%	8.7%	8.9%	15.2%	22.8%	35.0%	53.8%
Death	1.2%	0.5%	1.4%	0	0.7%	3.8%	0	0

The treatment regimen in each arm included chemo. Among all patients (n=1174), 54 patients (4.6%) had missing RCB categorical data: 33 (4.2%) in the pembro + chemo group and 21 (5.4%) in the pbo + chemo group. Data cutoff date: March 23, 2021.

How does this change clinical practice?

- Pembrolizumab + neoadjuvant chemotherapy is standard for stage II/III TNBC
- This exploratory analysis confirms that RCB is prognostic, but addition of pembrolizumab improved DFS across RCB categories

Randomized controlled trial of trastuzumab with or without chemotherapy for HER2-positive early breast cancer in older patients

- Women 70-80 years
- Early stage HER2-positive breast cancer

Sawaki, et al, JCO 2020

TABLE 1. Baseline Characteristics of the Full Analysis Set (N = 266)

Characteristic	Trastuzumab Monotherapy (n = 135)	Trastuzumab + Chemotherapy (n = 131)	*P*
Mean age, years (SD)	73.9 (2.8)	73.9 (3.0)	.79
Performance status			.76
0	126 (93.3)	121 (92.4)	
1	9 (6.7)	10 (7.6)	
Pathologic tumor size			.57
T1b	10 (7.4)	11 (8.4)	
T1c	55 (40.7)	54 (41.2)	
T2	64 (47.4)	64 (48.9)	
T3	6 (4.4)	2 (1.5)	
Lymph node metastasis			.39
Negative	111 (82.2)	103 (78.6)	
Positive	23 (17.0)	24 (18.4)	
Unknown	1 (0.7)	4 (3.1)	
Stage			.8
I	58 (43.0)	58 (44.3)	
IIA	56 (41.5)	55 (42.0)	
IIB	20 (14.8)	16 (12.2)	
IIIA	1 (0.7)	2 (1.5)	
Surgery			.2
Mastectomy	97 (71.9)	87 (66.4)	
Partial mastectomy	36 (26.7)	44 (33.6)	
Others	2 (1.5)	0 (0.0)	
Hormone receptor status			.55
ER+ and/or PgR+	62 (45.9)	65 (49.6)	
ER− and PgR−	73 (54.1)	66 (50.4)	

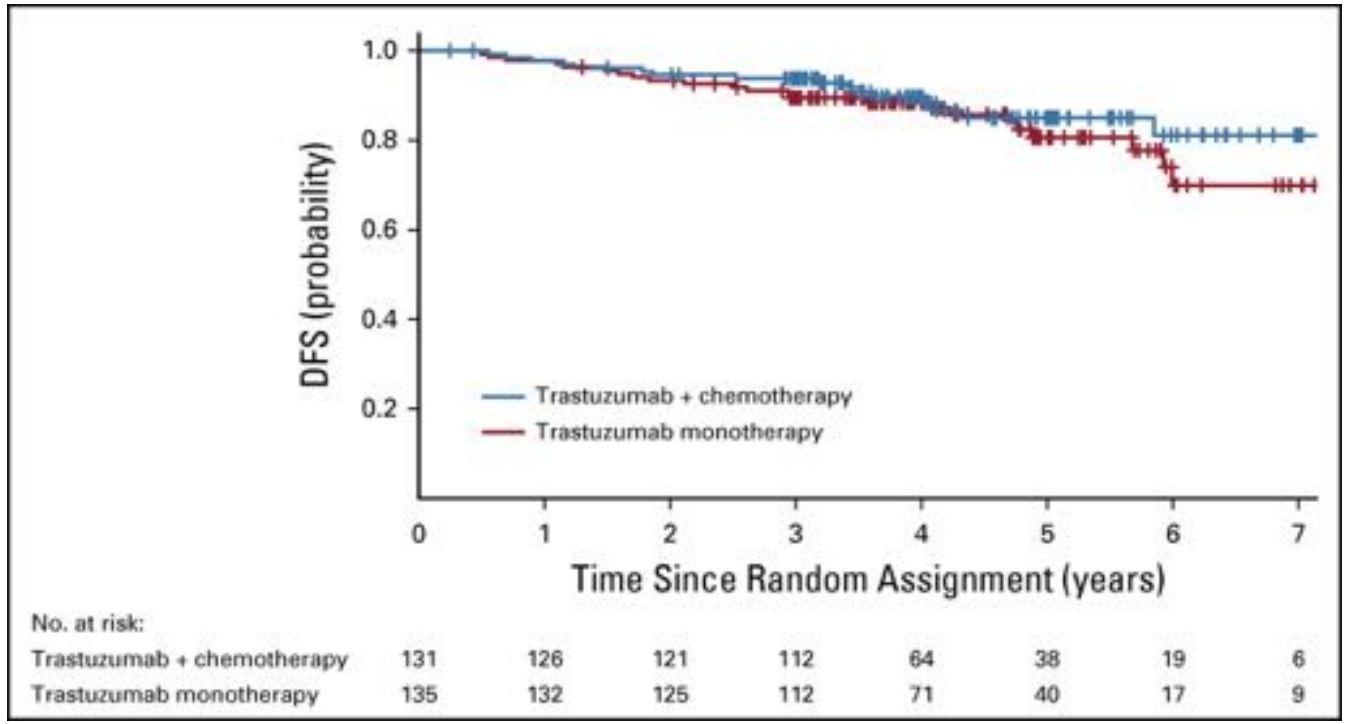


FIG 2. Kaplan-Meier estimates of disease-free survival (DFS). DFS at 3 years was 89.5% (95% CI, 82.9 to 93.6) in the trastuzumab monotherapy group versus 93.8% (95% CI, 87.9 to 96.8) in the trastuzumab + chemotherapy group (HR, 1.36; 95% CI, 0.72 to 2.58; P = .51). The difference in restricted mean survival time for DFS between the study arms at 3 years was −0.39 months (95% CI, −1.71 to 0.93; P = .56). Tick marks indicate censored data.

Published in: Masataka Sawaki; Naruto Taira; Yukari Uemura; Tsuyoshi Saito; Shinichi Baba; Kokoro Kobayashi; Hiroaki Kawashima; Michiko Tsuneizumi; Noriko Sagawa; Hiroko Bando; Masato Takahashi; Miki Yamaguchi; Tsutomu Takashima; Takahiro Nakayama; Masahiro Kashiwaba; Toshiro Mizuno; Yutaka Yamamoto; Hiroji Iwata; Takuya Kawahara; Yasuo Ohashi; Hirofumi Mukai; *Journal of Clinical Oncology* 2020 383743-3752.
DOI: 10.1200/JCO.20.00184

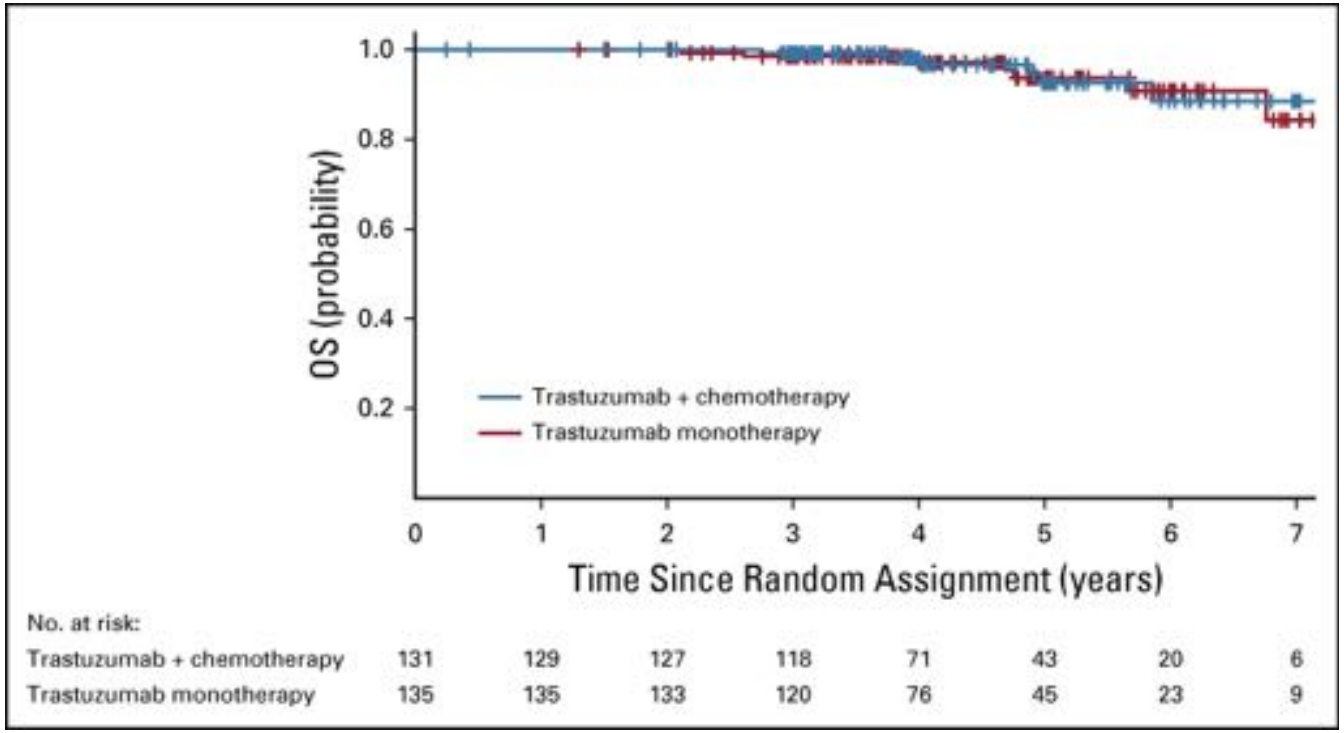


FIG 4. Kaplan-Meier estimates of overall survival (OS). OS at 3 years was 97.2% (95% CI, 91.2 to 99.1) in the trastuzumab monotherapy group versus 96.6% (95% CI, 89.53 to 98.9) in the trastuzumab + chemotherapy group (HR, 1.07; 95% CI, 0.36 to 3.19). Tick marks indicate censored data.

Published in: Masataka Sawaki; Naruto Taira; Yukari Uemura; Tsuyoshi Saito; Shinichi Baba; Kokoro Kobayashi; Hiroaki Kawashima; Michiko Tsuneizumi; Noriko Sagawa; Hiroko Bando; Masato Takahashi; Miki Yamaguchi; Tsutomu Takashima; Takahiro Nakayama; Masahiro Kashiwaba; Toshiro Mizuno; Yutaka Yamamoto; Hiroji Iwata; Takuya Kawahara; Yasuo Ohashi; Hirofumi Mukai; *Journal of Clinical Oncology* 2020 383743-3752.
DOI: 10.1200/JCO.20.00184

TABLE A2. Events in Disease-Free Survival

Variable	Trastuzumab, No. of Events (n = 135)	Trastuzumab + Chemotherapy, No. of Events (n = 131)
Recurrence	18	15
Ipsilateral breast	1	1
Regional lymph node	4	3
Distant	9	8
Second malignancy	9	4
Death	7	6
Breast cancer specific	1	5
Others	6	1

How does this change clinical practice?

- Trastuzumab alone did not meet non-inferiority for DFS in women >70 years
- However, OS differences were small (< 1 mo at 3 years) and QOL worsened with chemotherapy and trastuzumab
- Adjuvant trastuzumab alone can be considered in select patients
- Trastuzumab + weekly paclitaxel also an option

2022 ASCO ANNUAL MEETING

LUMINA: A Prospective Trial Omitting Radiotherapy following Breast Conserving Surgery in T1N0 Luminal A Breast Cancer

T Whelan, S Smith, T Nielsen, S Parpia, A Fyles, A Bane, F Liu, L Grimard, C Stevens, J Bowen, S Provencher, E Rakovitch, V Théberge, A Mulligan, M Akra, D Voduc, T Hijal, I Dayes, G Pond, and M Levine

For the Ontario Clinical Oncology Group

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Background – Adjuvant Breast Radiotherapy (RT)

- Commonly given following breast conserving surgery (BCS)
- Reduces the risk of local recurrence by 67%
- Inconvenient for the patient (and costly)
- Associated with significant toxicity
  - Acute: skin erythema, irritation, and fatigue
  - Late: breast pain, induration, and distortion affecting cosmesis and quality of life
  - Rare life threatening side effects: cardiac disease and second cancers

Background – Molecular Biomarkers

- Genomic era provided unique opportunity to understand the molecular biology of breast cancer
- Perou et al. used ~ 500 genes to classify breast cancer into intrinsic subtypes*

Luminal A:	estrogen pathway; non-proliferative
Luminal B:	estrogen pathway; proliferative
Her2 enriched:	ER-ve, Her2 amplicon; proliferative
Basal:	ER-ve, cell cycle control/DNA repair; proliferative

- Subtype prognostic for distant recurrence

*Perou et al. *Nature* 2000; 406: 747

Background – Intrinsic Subtypes

- Parker et al. developed a technique to classify intrinsic subtypes using 50 genes (Pam-50)*
- Nielsen et al. developed an approach to classify intrinsic subtypes using immunohistochemistry (IHC) analysis of 6 biomarkers (ER, PR, Her2, Ki67, CK5/6 and EGFR)**
  - Luminal A defined as: ER≥1%, PR>20%, Her2 -ve, Ki67≤13.25%

*Parker et al. *JCO* 2009; 27: 1160; **Nielsen et al. *Clin Cancer Res* 2010; 16: 5222

Background – Intrinsic Subtypes

- Voduc et al. evaluated 1,416 patients treated with breast conserving surgery and RT
- Intrinsic subtype was shown to be prognostic for local recurrence (LR)*

Subtype	5 yr LR rate
luminal A	2.8%
luminal B	5.7%
HER2	14.0%
basal	10.3%

*Voduc et al. *JCO* 2010; 28: 1684

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General Objective - LUMINA

- To determine the clinical utility of combining clinical pathological factors and luminal A subtype to identify women with a very low risk of LR following BCS treated with endocrine therapy alone where RT could be omitted

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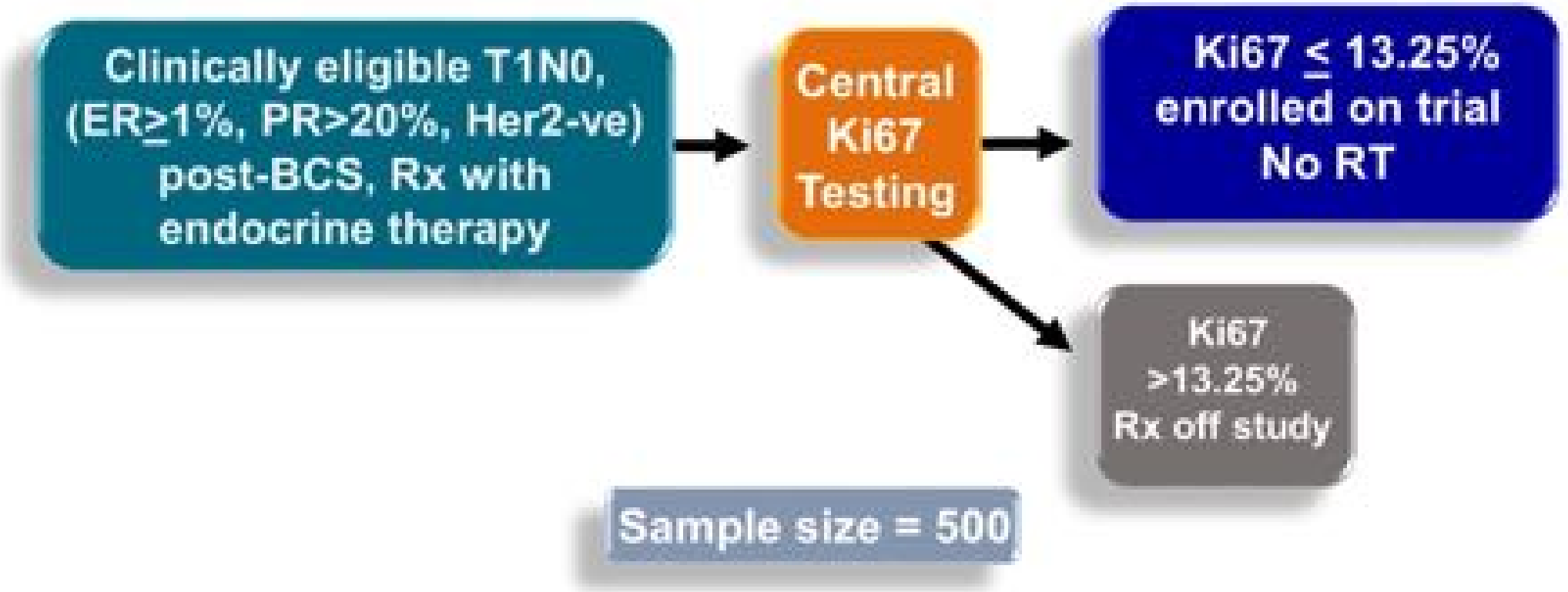
Trial Design - LUMINA



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Patient Population

Inclusion Criteria:

- Age ≥55 yrs
- Invasive ductal T1N0 post-BCS and SLNB
- Margins ≥1mm
- Grade 1-2
- ER≥1%, PR>20%, Her2-ve
- Endocrine therapy

Exclusion Criteria:

- Multifocal or multicentric
- Extensive intraductal component (>25% of tumor DCIS)
- Lymphatic vascular invasion

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Central Ki67 Testing

- 3 laboratories: Hamilton, Toronto and Vancouver
- International Ki67 Working Group methods*
- 4 micron slide stained for Ki67 MIB1 antibody
  - Slide imaged with Aperio Scanscope
  - 500 nuclei counted from 5 random areas using key stroke data capture
- Reliability testing performed between labs yearly
  - Intra class coefficient was high (range 0.90-0.98)

*Nielsen et al. *JNCI* 2021; 113: 808

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Outcomes

Primary:

- Local recurrence (LR, any invasive or non-invasive event)

Secondary:

- Contralateral breast cancer
- Any recurrence
- Disease-free survival
- Overall survival

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Statistical Considerations

- Sample size based on precision of estimate of 5-year LR
- Assuming LR of 3.5% and an upper bound of 2-sided 90% (one sided 95%) CI to be <5%, required 500 patients
- Probability of LR estimated using cumulative incidence function with death as a competing risk
- Intention to treat analysis planned at a median follow-up of 5 years

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Baseline Characteristics

Characteristics	All Patients n=500 (%)
Age (years): mean	67
55 - <65	200 (40)
65 - <75	242 (48)
≥75	58 (12)
Tumor Size (cm): mean	1.1
<0.5	40 (8)
0.51 – 1.0	216 (43)
1.1 – 2.0	244 (49)
Tumor: Grade 1	330 (66)
Grade 2	170 (34)
Endocrine Therapy:	
Tamoxifen	200 (41)
Aromatase inhibitor	292 (59)

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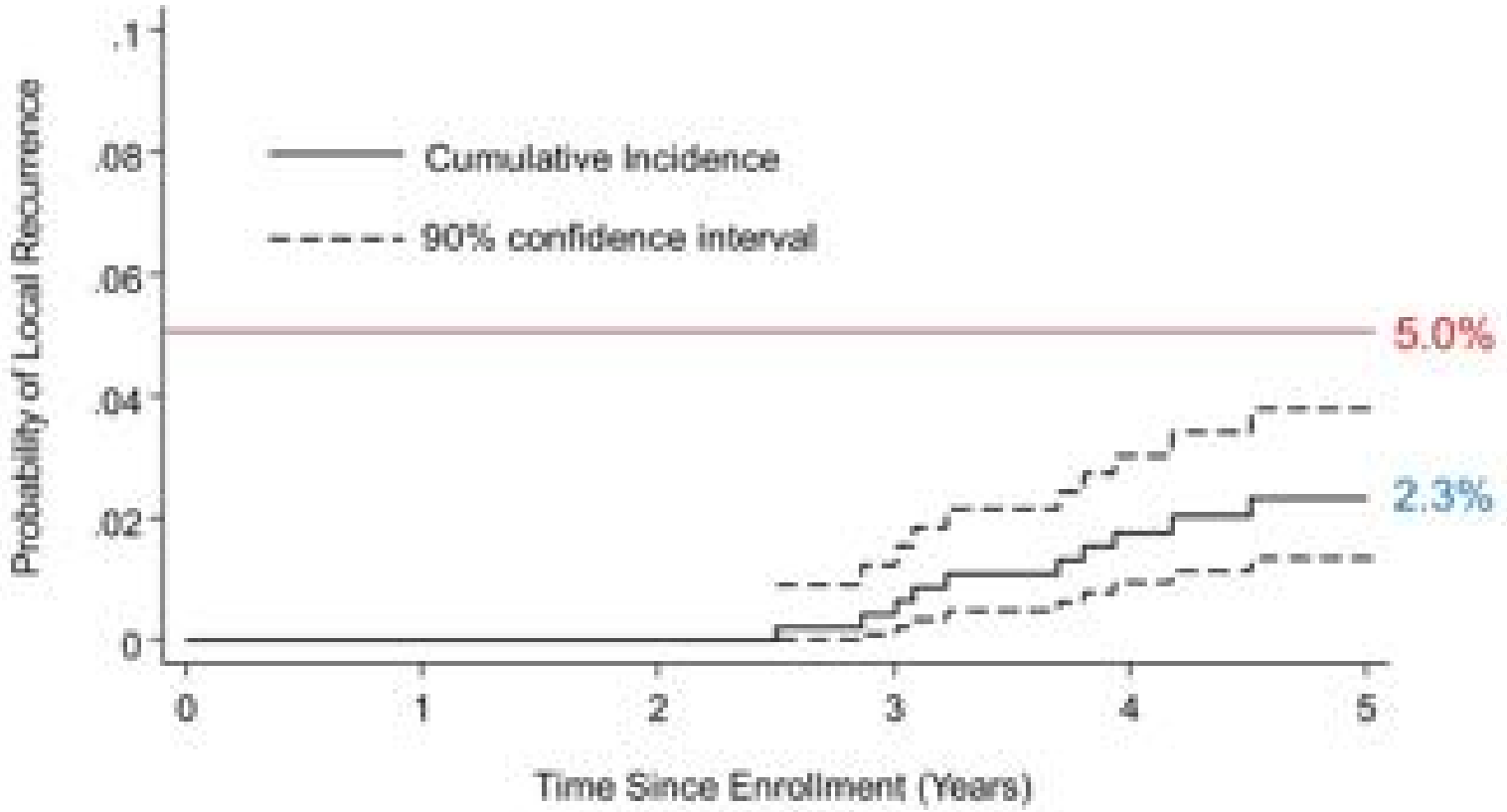
Local Recurrence



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Results

Outcome	Events at 5 Years (total events)	5-Year Rate (90% CI)
Local Recurrence	**10**	**2.3 (1.3, 3.8)**
Contralateral Breast Cancer	8	1.9 (1.1, 3.2)
Any Recurrence	12	2.7 (1.6, 4.1)
Disease Free Survival	47 (23 second primary non-BCs)	89.9 (87.5, 92.2)
Overall Survival	13 (1 BC death)	97.2 (95.9, 98.4)

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Conclusions

- Women ≥55 years with T1N0, G1-2 luminal A breast cancer following BCS treated with endocrine therapy alone had a very low rate of LR at 5 years
- The rate satisfied our pre-specified boundary
- Prospective and controlled nature of this multicentre study supports that such patients are candidates for omission of RT

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Omission of post-lumpectomy radiation therapy

2014 meta-analysis* identified women >65 years with:

- clinical node negative, ER+, HER2- breast cancer < 3cm
- willing to take endocrine therapy

- Need to consider other risk factors like grade, LVI, low ER expression and patient comorbidities

*Van de Water, et al, Ann Sur Onc 2014

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How does this change clinical practice?

- Omitting post-lumpectomy radiation should be individualized
- Incorporating molecular signatures is a step towards identifying patients in which local therapy can be further de-escalated

Thank you.

Questions?

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ASTER 70s ~ 2,000 patients enrolled in 4 years

Keys to success	ASTER 70s
Specific to the older population	Women with early-stage BC **70+**
Main question **frequent** **meaningful** to patients & HCP	**Adjuvant CT** for luminal BC **De-escalation** (optimization)
Design **non-restrictive** inclusion criteria **simplicity** **increased retention** list of **adjusted intervention** **meaningful** endpoints	**Allow G8 ≤14, prior cancer, local relapse** **Single** informed consent for screening and randomization **Cohort as second internal control** **3-month** CT regimens (4 TC, 4 AC or 4 MC) **OS, HRQoL, treatment acceptability**
Education of patients & HCP	Changes in **institutions** (MDTs, guidelines) Collaboration with **geriatrician** (geriatric oncology consultations) Research **nurse** practioner Acknowledgement of specific **time** needed
Interest for **developers**	**Biotech** (GGI), **drugs** (liposomal doxorubicin, G-CSF)
Translational research (biobank)	**Ageing & cancer** (GGI, telomeres, inflammageing, epigenetic clock)
Funding	**Mixed**: public, private, charities
Network	**Unicancer & Units of Coordination in Geriatric Oncology (UCOG)**

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Conclusion 1: In older patients w/ ER+ HER2- BC

- GGI does not predict a significant OS benefit from CT→ET vs ET alone (ITT)
- GGI is prognostic
- 20% non adherence rate to assigned chemotherapy
  - Close to other large RCTs (MINDACT, TAILORx, RxPONDER)
  - Per protocol analysis: high GGI could predict at 4 year of follow-up some absolute benefit with CT (OS +1.7%, iDFS +4.4%)
- Treatment discontinuation

  CT 6% before cycle 4 (*i.e.* CT feasible **with relevant 3-month regimen**)

  ET 22%

Conclusion 2: In older patients w/ ER+ HER2- BC

- The value of any age-agnostic prognostic signatures would require:
  - To factor in specific geriatric data (e.g. PORTRET > PREDICT)
  - A better selection of the right endpoint (composite, reflecting HRQoL/independence and survival)
- ASTER 70s
  - 1,969 patients enrolled & 1,089 patients randomized in 4 years
  - 4-year span prospective large collection (geriatric, HRQoL, biobank, etc.)

Running successfully large trials investigating equitable cancer care through innovation in older patients is possible and provide evidence-based information

Brain. Lancet Healthy Longev. 2021; 2: e680. de Glas et al. Br J Cancer. 2018; 118: 390–400. van der Plas-Krijgsman et al. Lancet Healthy Longev. 2021; 2: e734–11.

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Summary and Conclusions

- Prespecified exploratory analyses of EFS by RCB category show an association of increased RCB score with worse EFS, independent of treatment group
- Among patients with residual disease at surgery, there was a lower percentage of patients in each RCB category in the pembrolizumab group than in the placebo group, indicating that the addition of pembrolizumab not only increased the pCR (RCB-0) rate, but also shifted RCB to lower categories across the entire spectrum of residual disease.
- Addition of pembrolizumab resulted in fewer EFS events in the RCB-0, RCB-1, and RCB-2 categories
  - Benefit was most pronounced in the RCB-2 category
- Taken together, these results indicate that the EFS benefit from pembrolizumab extends to patients who do not achieve a pCR and suggest a contribution from the adjuvant pembrolizumab component