

# Innovative Research Projects: From Basic Science into Clinical Study and Routine



**Emeritus Professor, Kyoto University**

**Visiting Professor, CCI: Center for Cancer**

**Immunotherapy and Immunobiology, Kyoto University**

**Director, Cancer and Infectious Disease Center, Tokyo  
Metropolitan Komagome Hospital**

**President, Japanese Breast Cancer Society**

**Masakazu Toi MD, PhD**

# COI Disclosure Information

## Masakazu Toi

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I have the following financial relationships to disclose.

- ✓ **Leadership position (no salary):** Japanese Breast Cancer Society, Assoc. JBCRG, Assoc. KBCRN. NPO OOTR
- ✓ **Honoraria (lecture fee) from:** Daiichi-Sankyo, Eli Lilly and companies, AstraZeneca
- ✓ **Research funds under contract from (as department):** Taiho, AstraZeneca, Kyowa-Kirin, Shimadzu, Astellas, Assoc. JBCRG, AFI Technology, Yakult, Luxonus, GL Science, Assoc. KBCRN, Sanwa Shurui
- ✓ **Research funds (incentive) :** Chugai, Eisai, Nippon-Kayaku

# Agenda

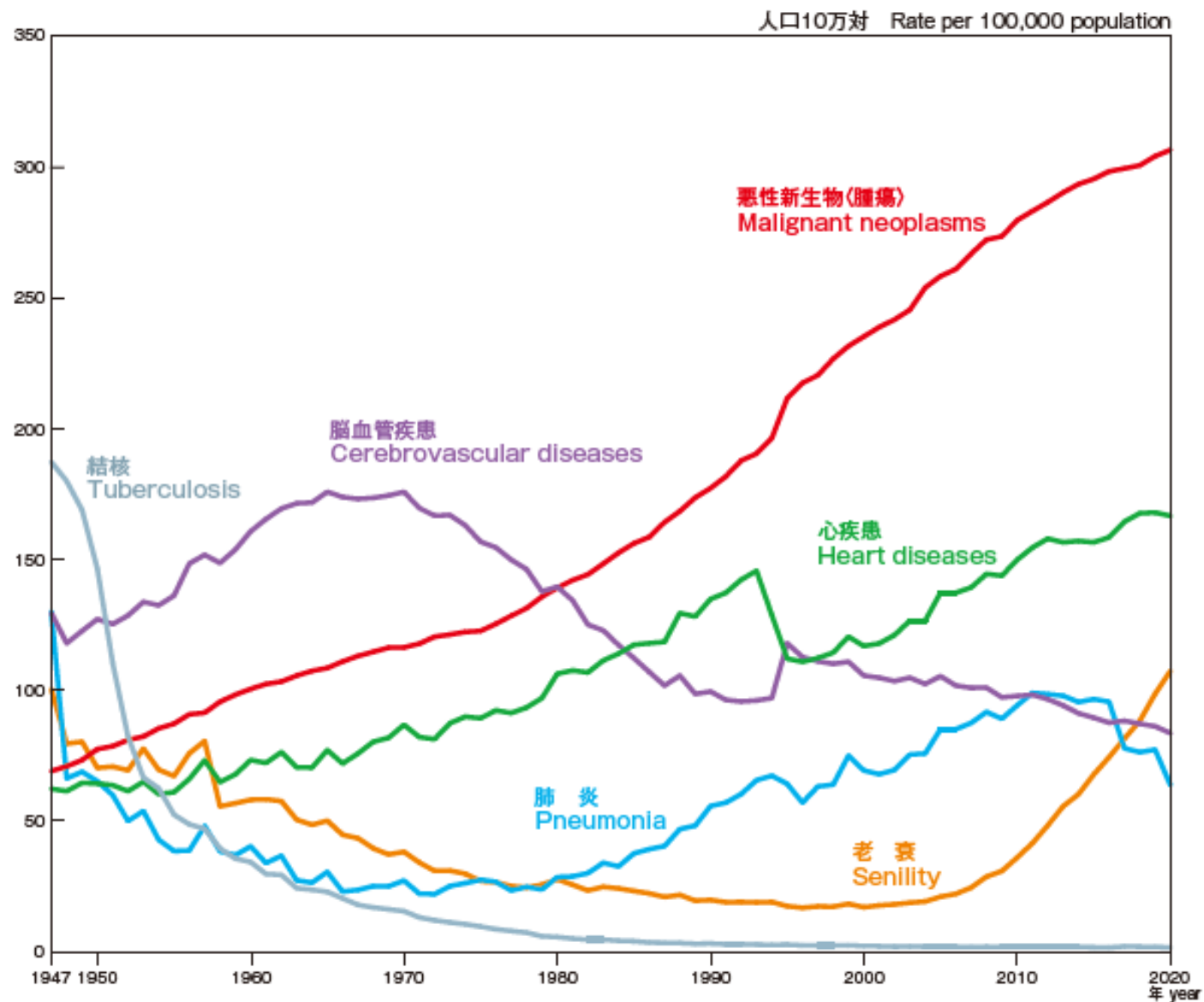
- Epidemiology in Japan
- Radiofrequency ablation therapy
- ADC
- Oral fluoropyrimidines
- A carcinogenesis model

# Cancer Statistics in Japan 2022



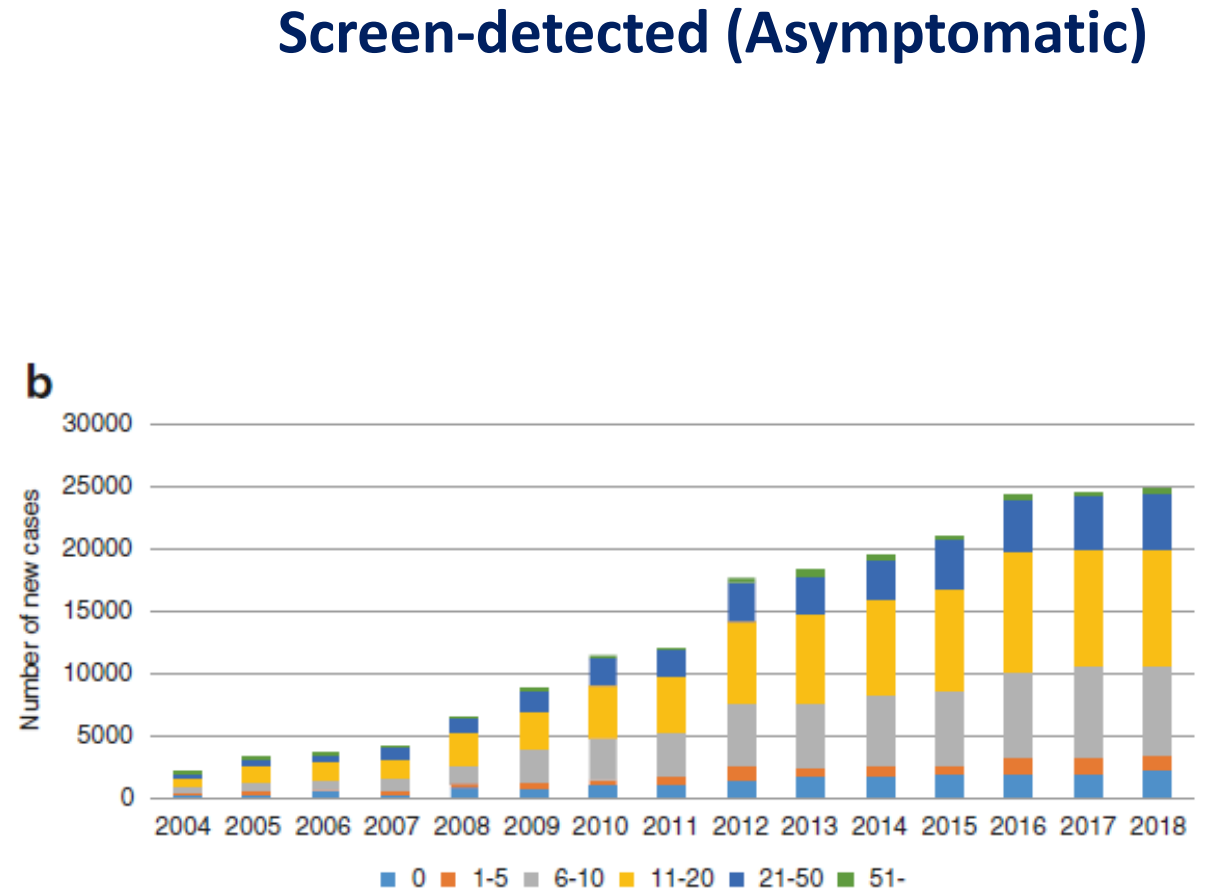
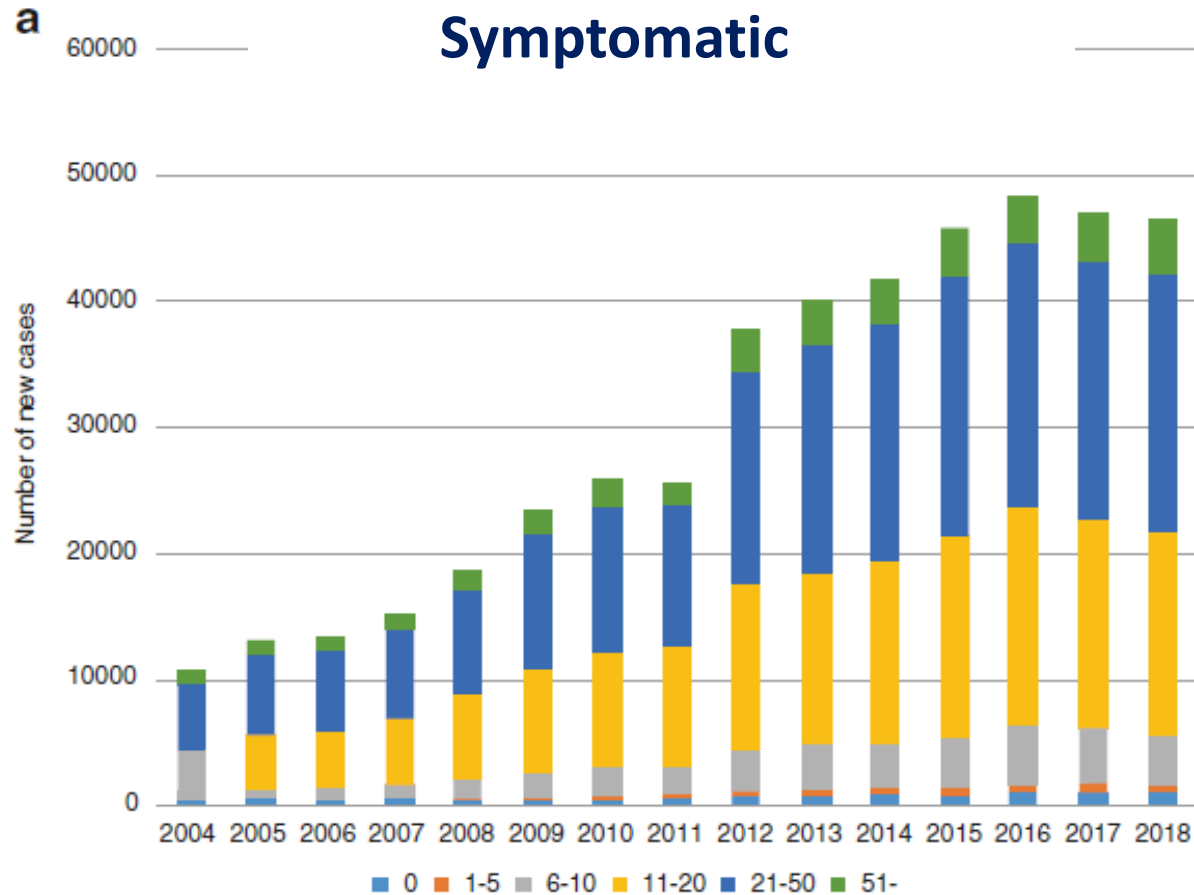
公益財団法人 がん研究振興財団  
Foundation for Promotion of Cancer Research

## 18 主要死因別死亡率年次推移 (1947年~2020年) Trends in Crude Mortality Rate for Leading Causes of Death (1947-2020)

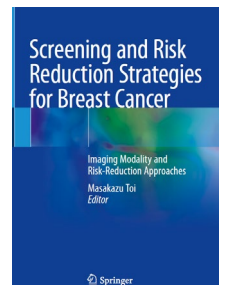
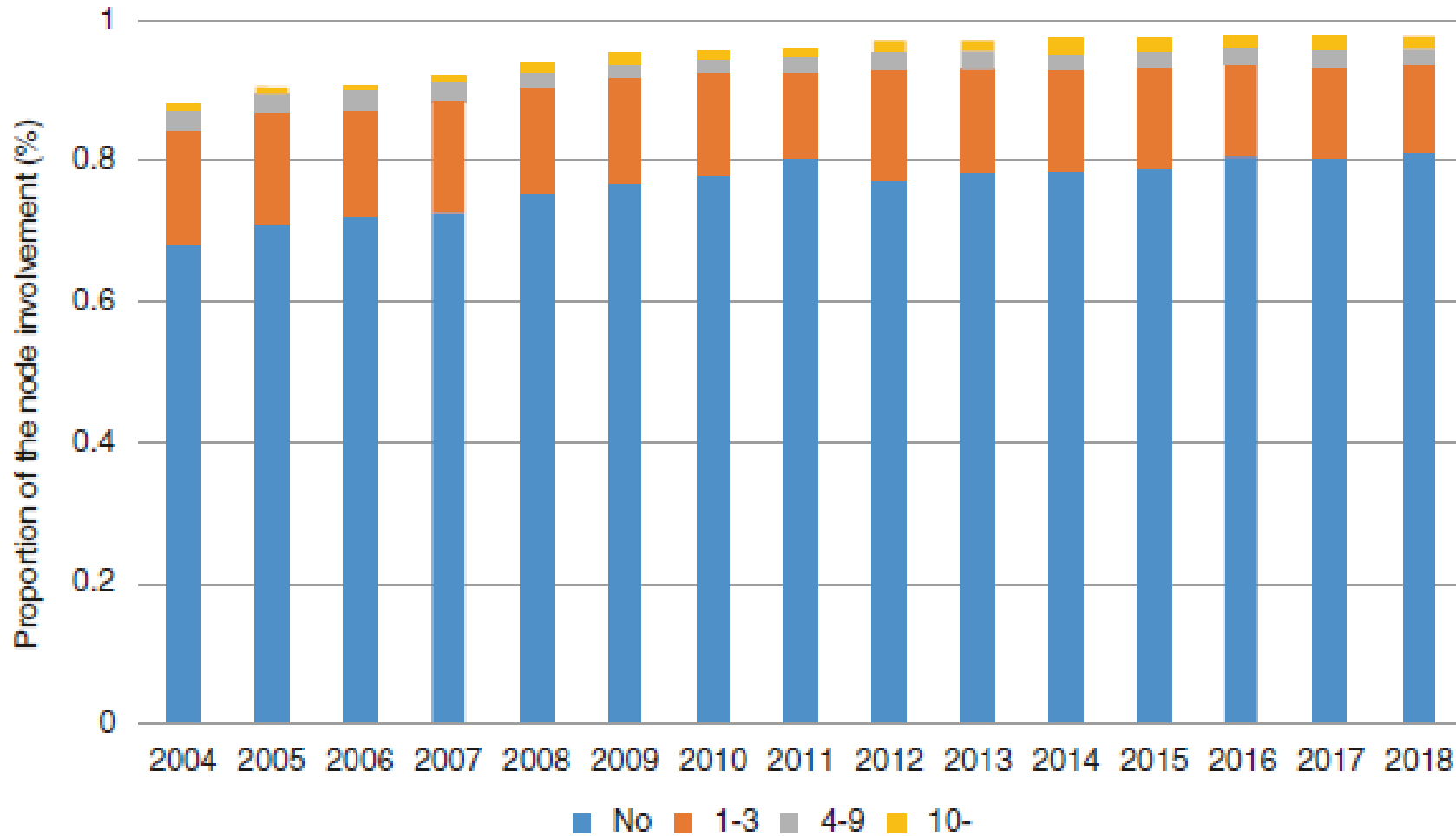




# Size of detected tumours



# Nodal status of detected tumours



# Non-surgical ablation for breast cancer: an emerging therapeutic option



Lancet Oncol 2024 March

*Masakazu Toi, Takayuki Kinoshita, John R Benson, Ismail Jatoi, Masako Kataoka, Wonshik Han, Chikako Yamauchi, Takashi Inamoto, Masahiro Takada*

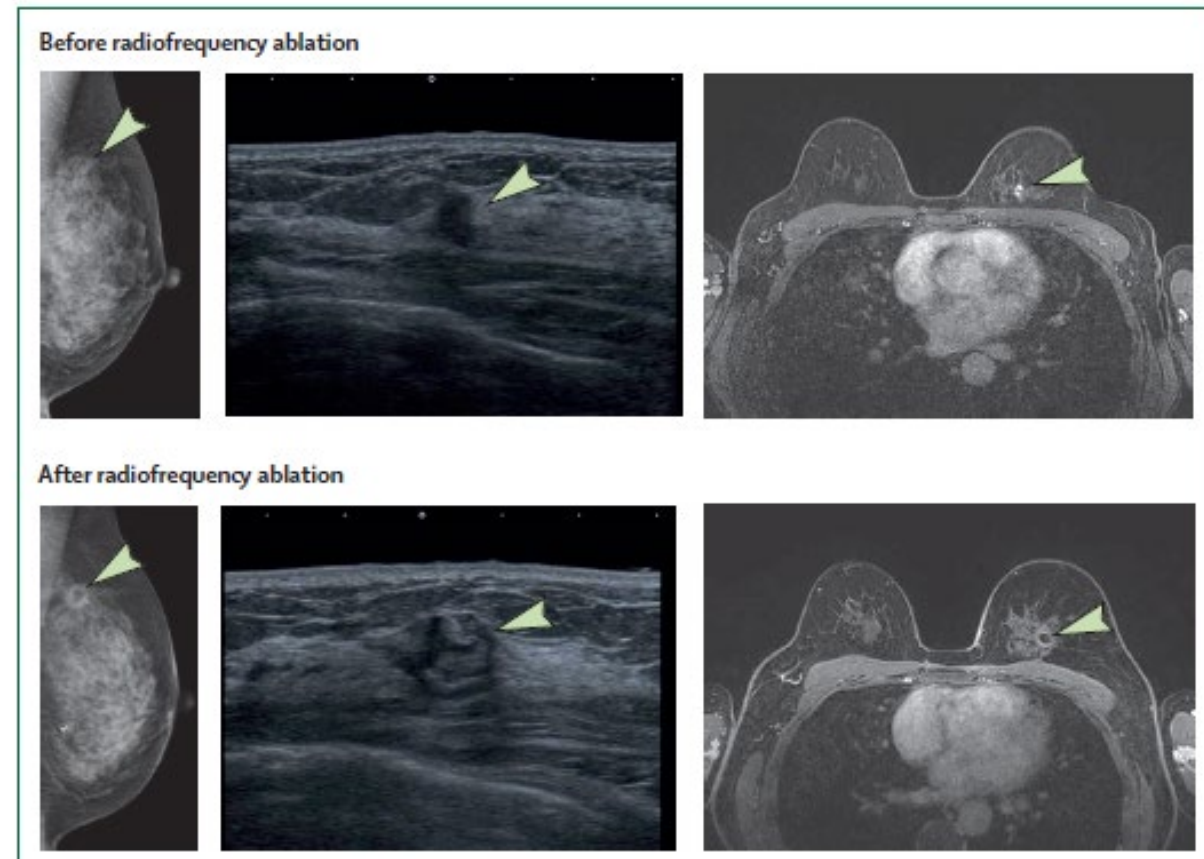
## Indication criteria

**Less than 15mm**

**Well localized**

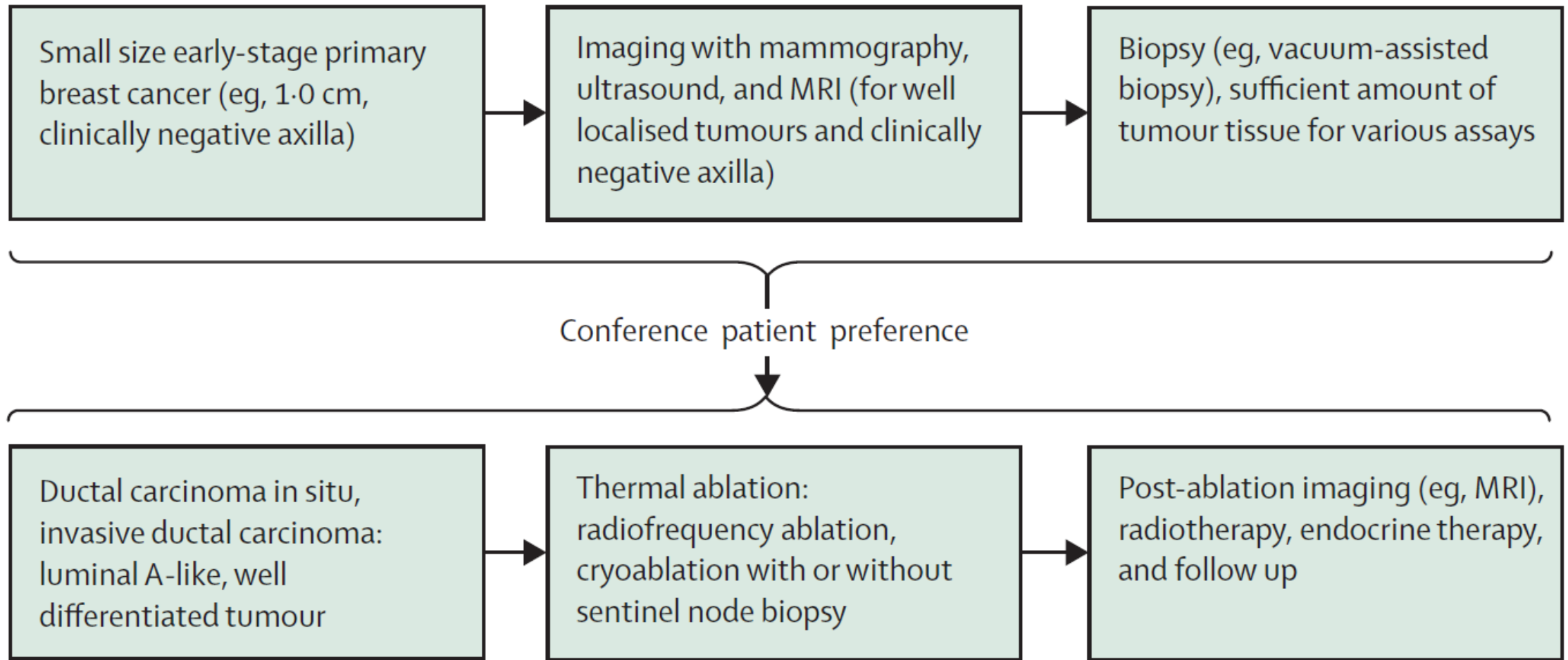
**Luminal A-like**

**Node-negative**

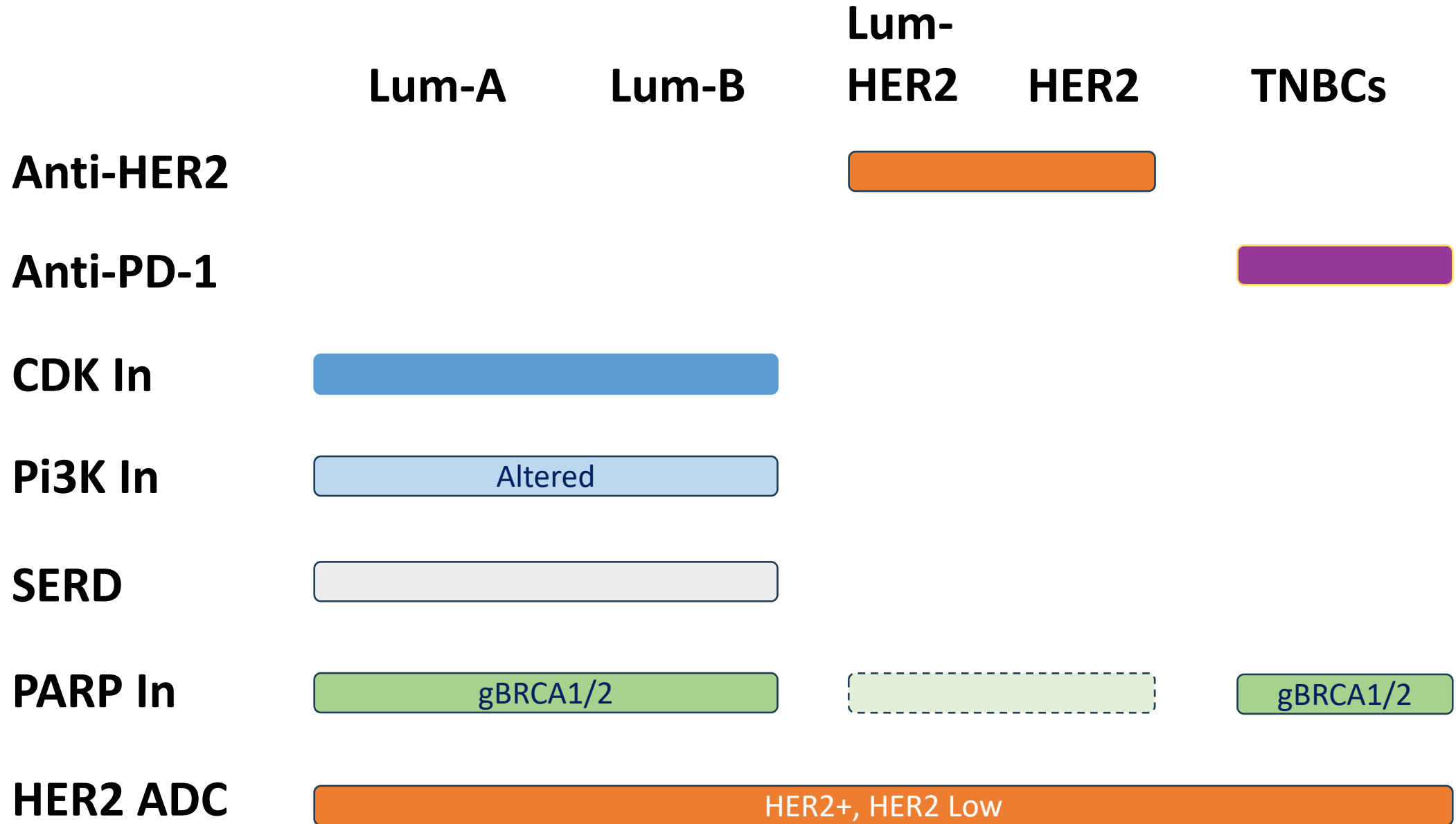


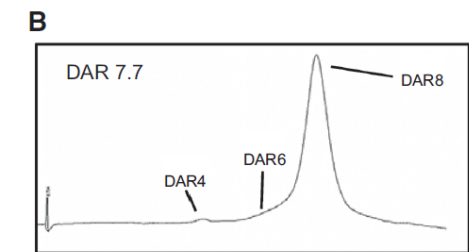
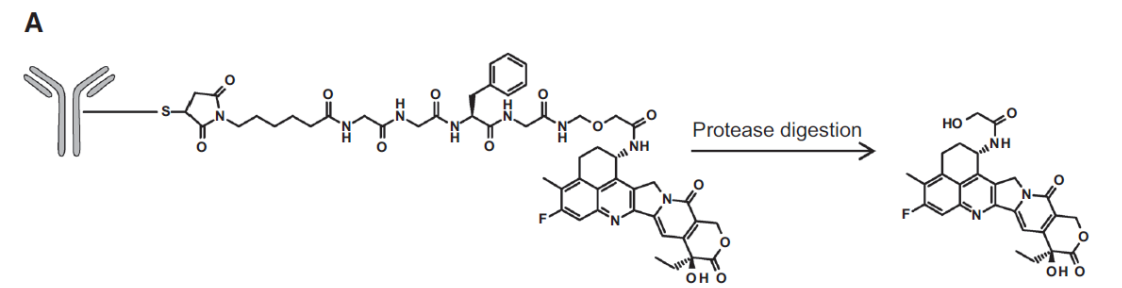
PMDA approved 2023 December.





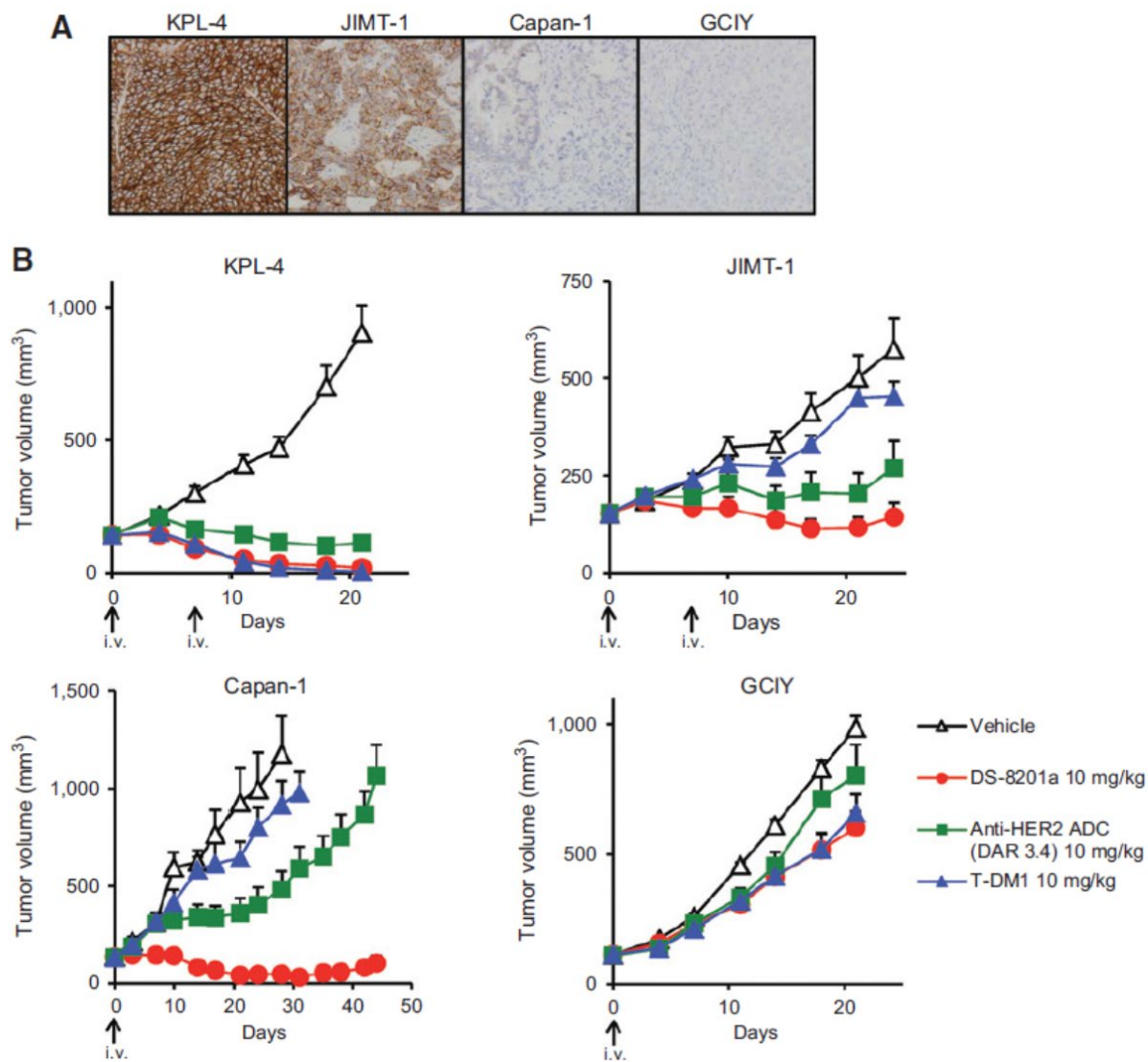
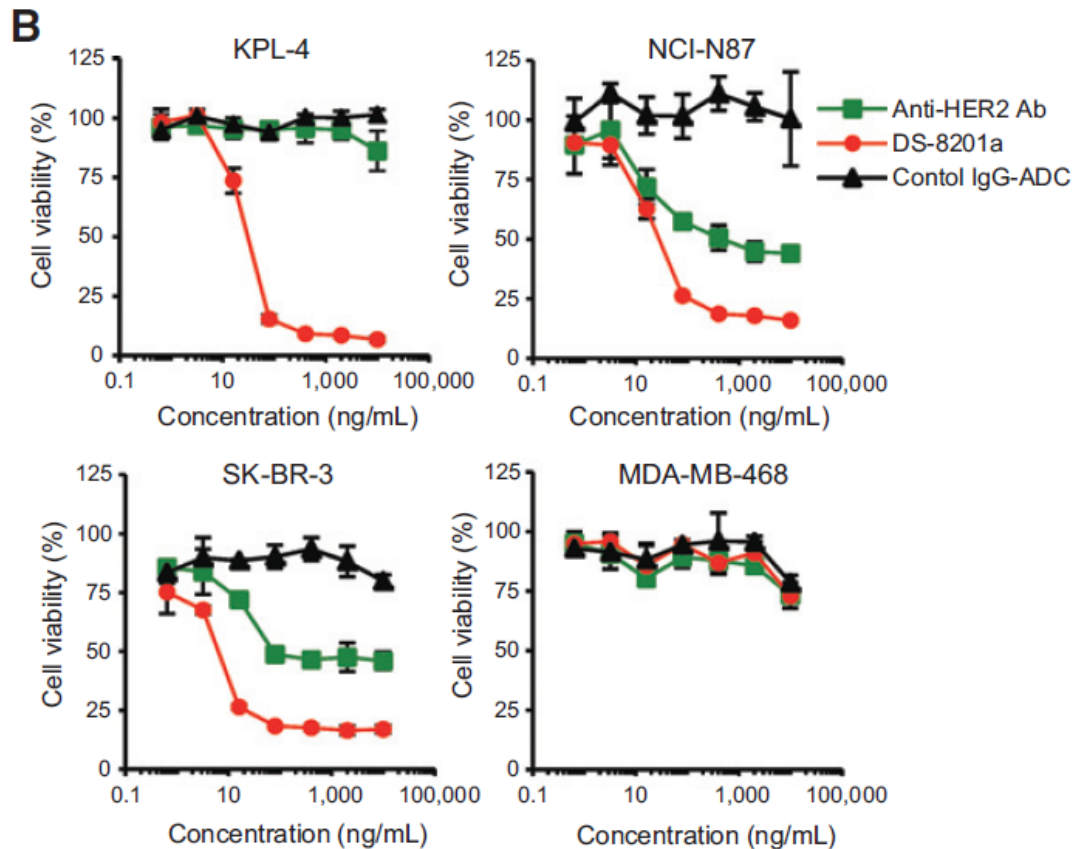
# Recent drugs and tumour subtypes





**C**

DNA topoisomerase I inhibition	
(IC <sub>50</sub> , μmol/L)	
SN-38	2.78
DX-8951f	0.25
DXd	0.31



T-DXd

# Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial

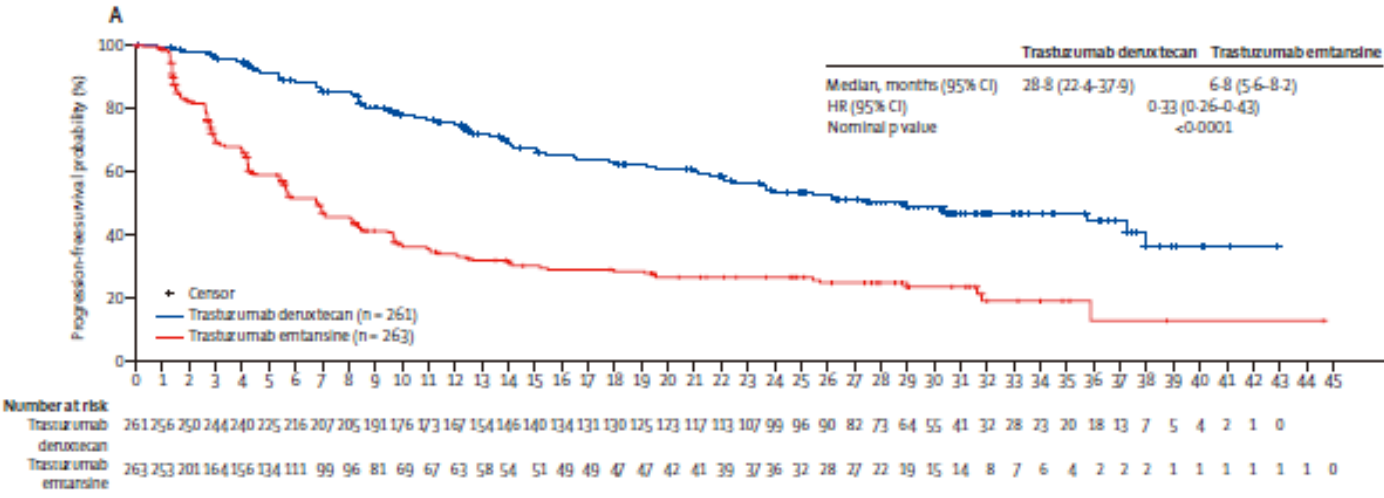


Sara A Hurvitz, Roberto Hegg, Wei-Pang Chung, Seock-Ah Im, William Jacot, Vinod Ganju, Joanne Wing Yan Chiu, Binghe Xu, Erika Hamilton, Srinivasan Madhusudan, Hiroji Iwata, Sevily Altintas, Jan-Willem Henning, Giuseppe Curigliano, José Manuel Perez-Garcia, Sung-Bae Kim, Vanessa Petry, Chiun-Sheng Huang, Wei Li, Jean-Sebastien Frenel, Silvia Antolin, Winnie Yeo, Giampaolo Bianchini, Sherene Loi, Junji Tsurutani, Anton Egorov, Yali Liu, Jillian Cathcart, Shahid Ashfaq, Javier Cortés

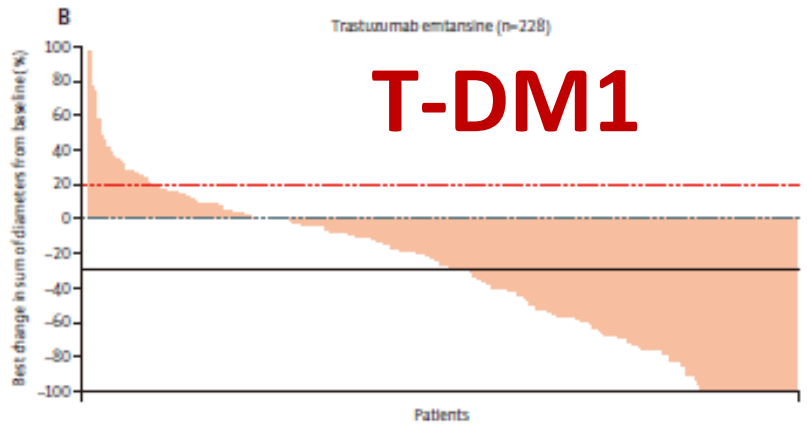
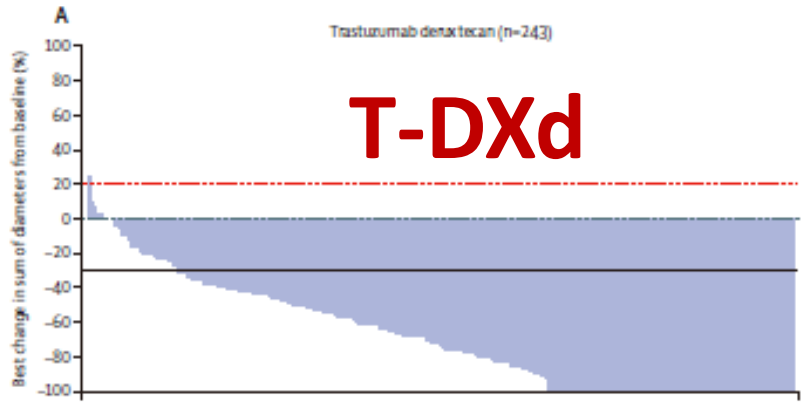
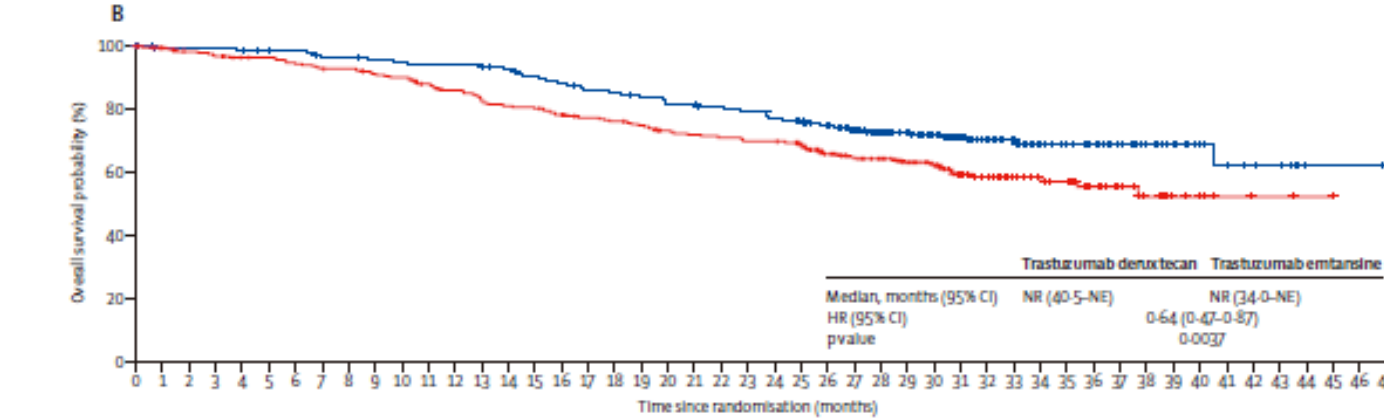
**Summary**  
**Background** An improvement in progression-free survival was shown with trastuzumab deruxtecan versus *Lancet* 2023; 401:105-17

Race		
White	71 (27%)	72 (27%)
Black or African American	10 (4%)	9 (3%)
Asian	152 (58%)	162 (62%)
Other*	28 (11%)	20 (8%)

**PFS**



**OS**



Patients

# T-DXd Destiny-Breast Trials

Study	Population	Design	Sample size
Destiny B01	HER2+, 3 <sup>rd</sup> L	Randomized, Open label	253
Destiny B02	HER2+, 3 <sup>rd</sup> L	vs Physician's choice (trastuzumab + capecitabine or lapatinib + capecitabine), Open label	600
Destiny B03	HER2+, 2 <sup>nd</sup> L	vs T-DM1	524
Destiny B04	HER2-Low (Post Chemo)	vs Physician's choice (capecitabine, eribulin, gemcitabine, paclitaxel or nab- paclitaxel), Open label	557
Destiny B05	HER2+, Residual	vs T-DM1 (Adjuvant, Post-neoadjuvant)	1600
Destiny B06	HER2-Low, HR+	vs Physician's choice (capecitabine, paclitaxel or nab-paclitaxel), Open label	866
Destiny B07	HER2+	+ durvalumab/ pertuzumab/ paclitaxel/ tucatinib/	245
Destiny B08	HER2-Low	durvalumab + paclitaxel	139
Destiny B09	HER2+, 1 <sup>st</sup> L	vs T-DXd + P vs Taxane + H + P	1134
Destiny B11	HER2+, NeoAdj	vs T-Dxd→Pacli + H + P vs AC→Pacli + H + P	644

# T-DM1: NEOPEAKS (JBCRG 20 trial)

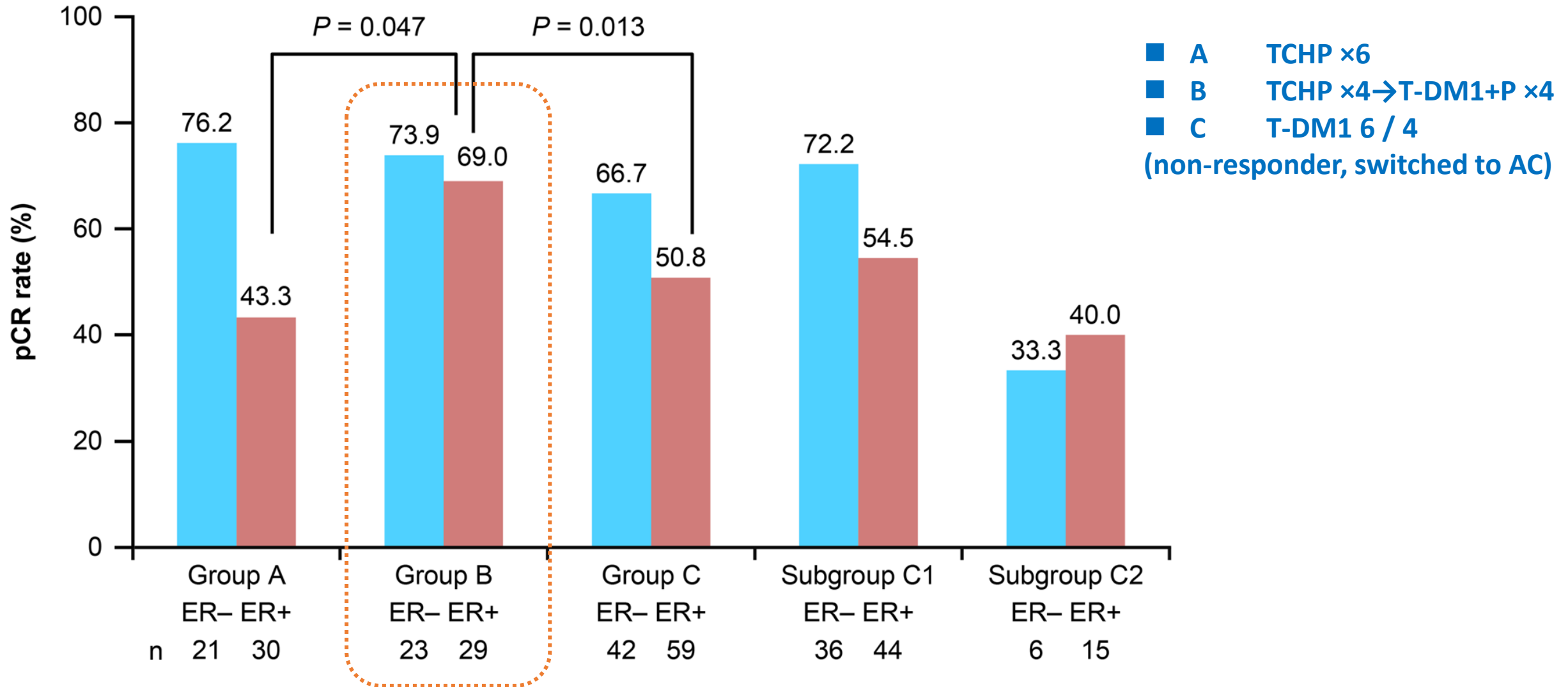
Neoadjuvant HER2: 3+/ISH+

■ A TCHP ×6

■ B TCHP ×4 → T-DM1+P ×4

■ C T-DM1 6 / 4 (non-responder, switched to AC)

# T-DM1: NEOPEAKS (JBCRG 20 trial)



# The NEW ENGLAND JOURNAL of MEDICINE

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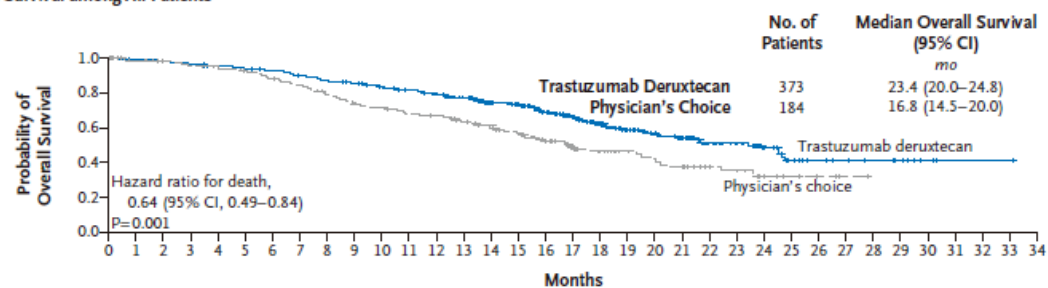
## Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators\*

**Table 3. Most Common Drug-Related Adverse Events (in ≥20% of Patients) in the Safety Analysis Set.\***

Event	Trastuzumab Deruxtecan (N=371)		Physician's Choice of Chemotherapy (N=172)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	<i>number of patients (percent)</i>			
<b>Blood and lymphatic system disorders</b>				
Neutropenia†	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anemia‡	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Thrombocytopenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Leukopenia¶	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
<b>Gastrointestinal disorders</b>				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0

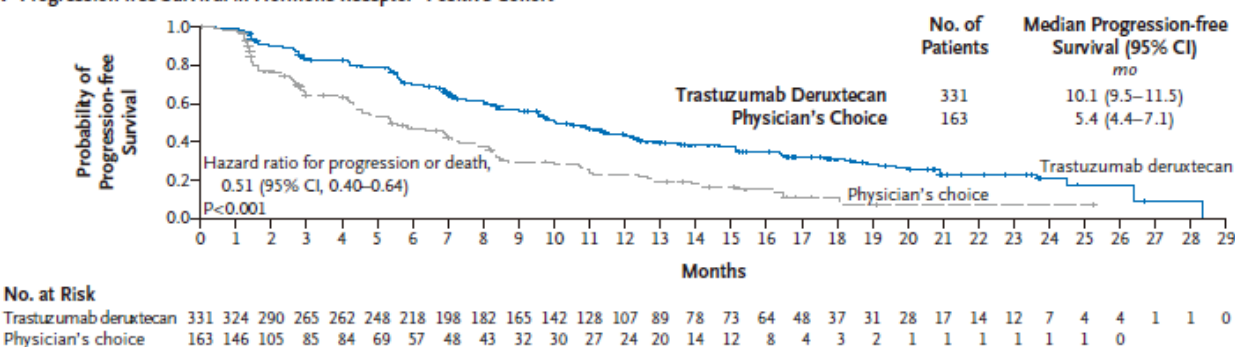
**D Overall Survival among All Patients**



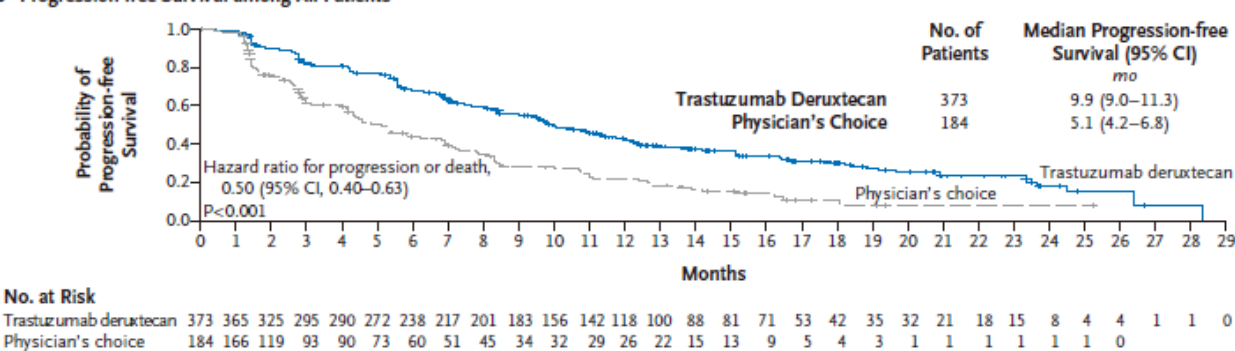
Race — no. (%)†

White	156 (47.1)	78 (47.9)	176 (47.2)	91 (49.5)
Black	7 (2.1)	2 (1.2)	7 (1.9)	3 (1.6)
Asian	131 (39.6)	66 (40.5)	151 (40.5)	72 (39.1)
Other	37 (11.2)	16 (9.8)	39 (10.5)	17 (9.2)
Missing data	0	1 (0.6)	0	1 (0.5)

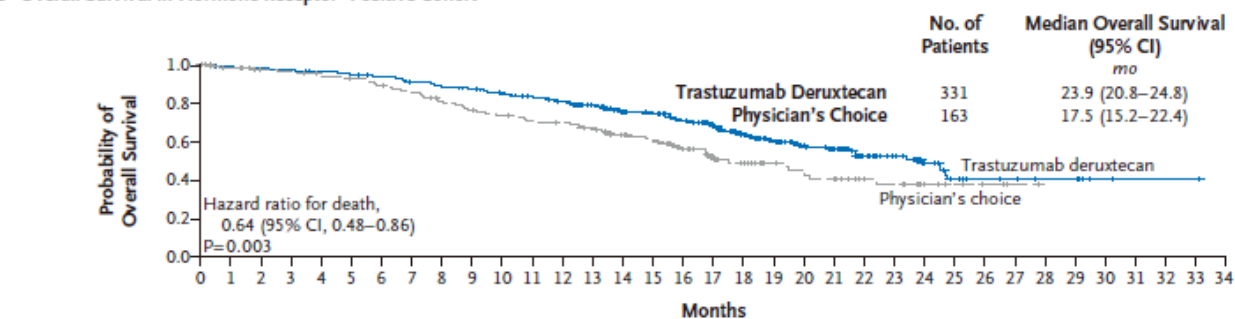
**A Progression-free Survival in Hormone Receptor–Positive Cohort**



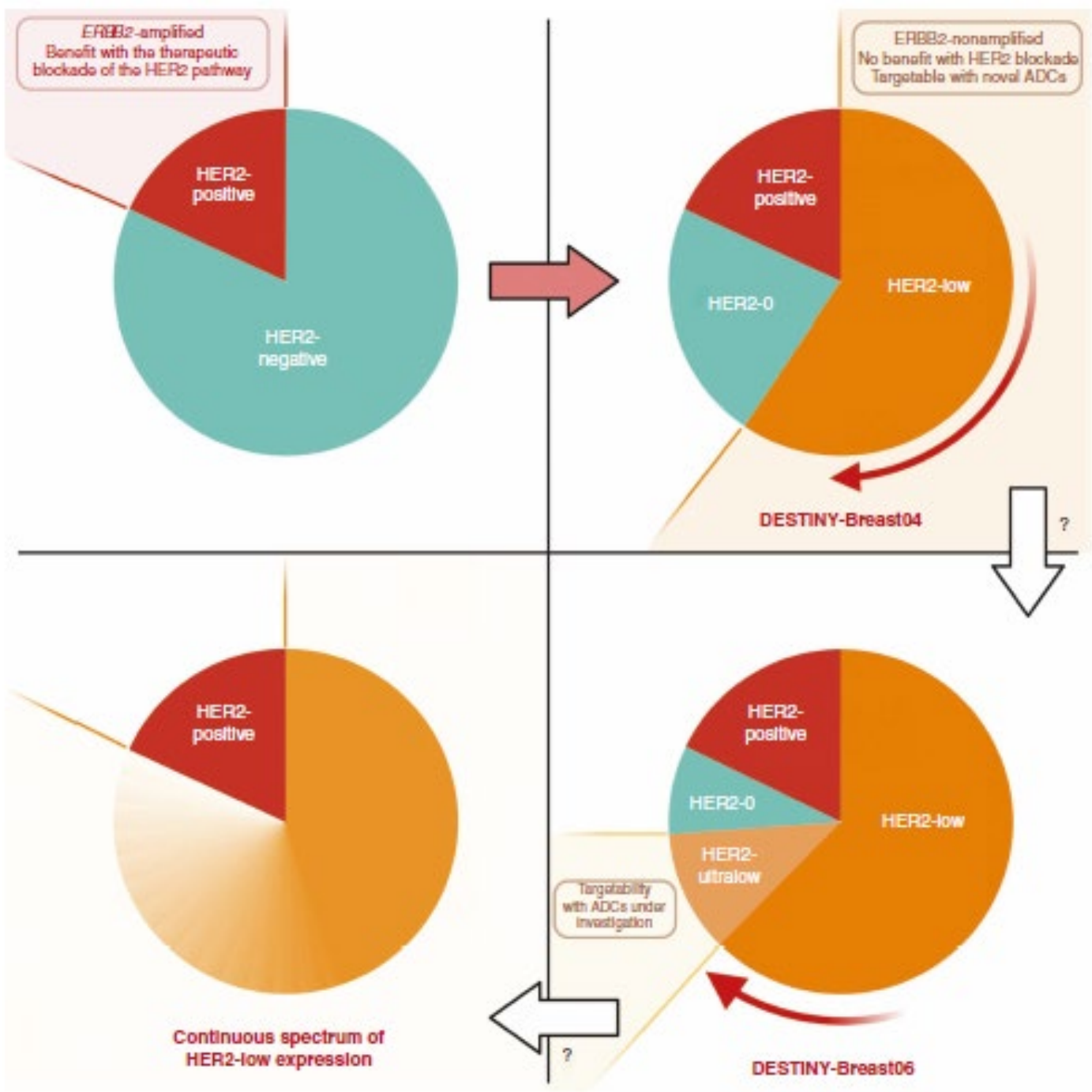
**B Progression-free Survival among All Patients**



**C Overall Survival in Hormone Receptor–Positive Cohort**







**IN FOCUS**

**Navigating the HER2-Low Paradigm in Breast Oncology: New Standards, Future Horizons**

Paolo Tarantino<sup>1,2,3,4</sup>, Giuseppe Curigliano<sup>3,4</sup>, and Sara M. Tolane<sup>1,2</sup>

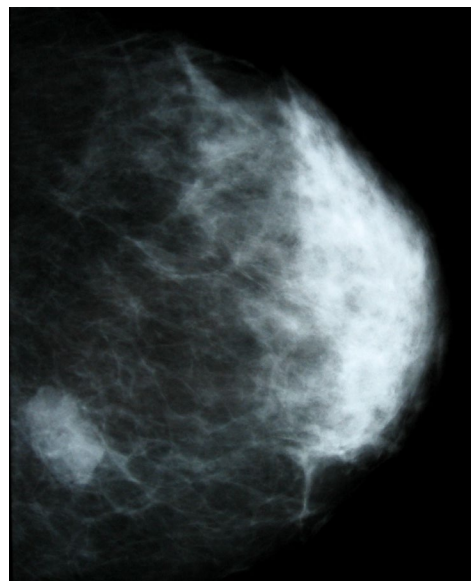
The results of the DESTINY-Breast04 trial have confirmed the benefit of treating HER2-low (IHC 1+ or 2+/ISH-negative) breast cancer with T-DXd.

DESTINY-Breast06 trial will include a cohort of patients with **ultralow HER2** score (HER2 IHC >0 <1+ expression) Cancer Discov 2022

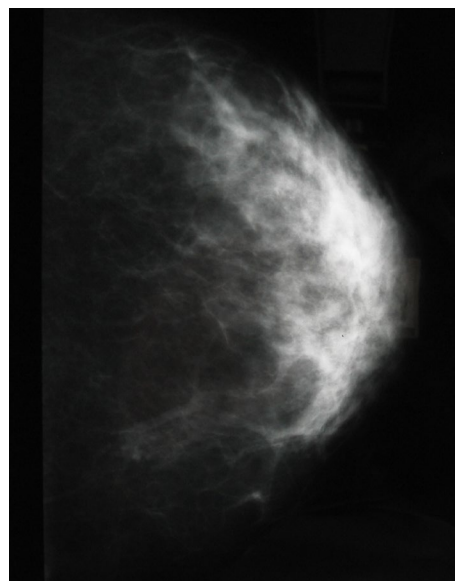
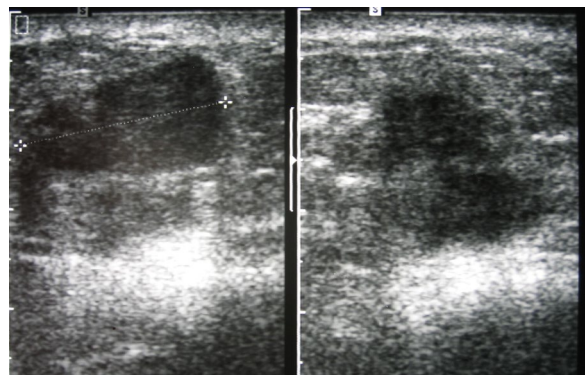
# Agenda

- Epidemiology in Japan
- Radiofrequency ablation therapy
- ADC
- Oral fluoropyrimidines
- A carcinogenesis model

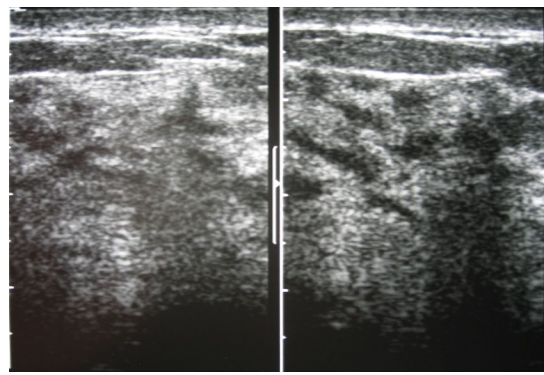
# CEF:CR



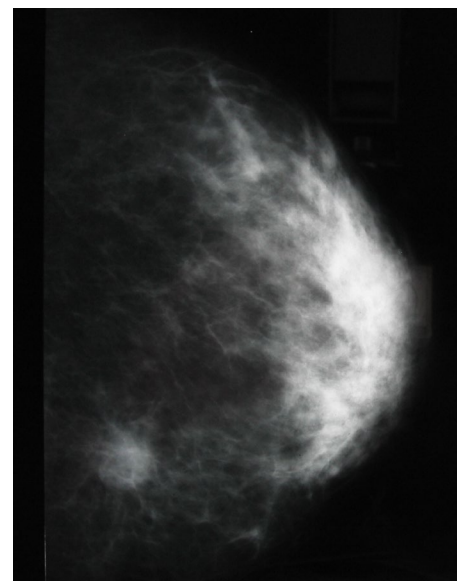
Pre-treat



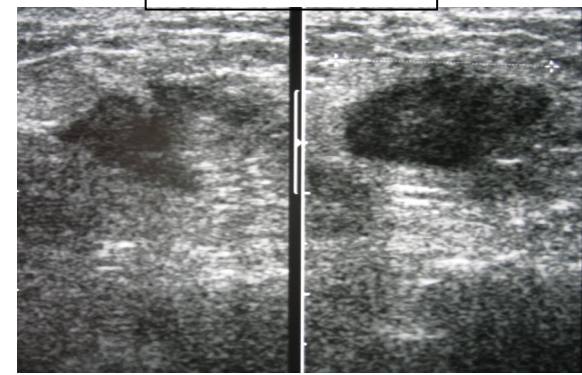
FEC (post)

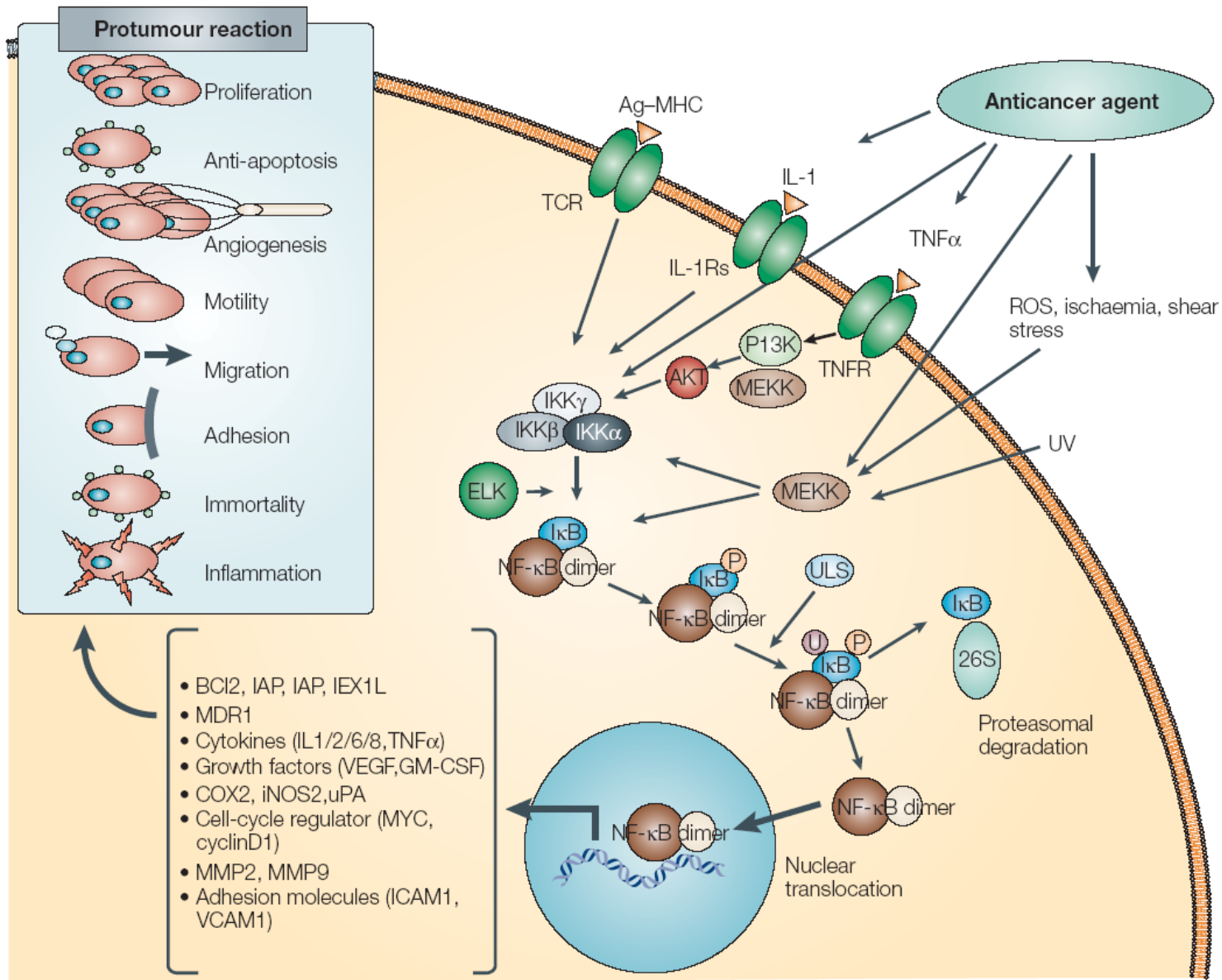


# DOC:PD



DOC (post)





Nuclear factor k-B induction by anticancer drugs  
*Nature Reviews Cancer* 5, 297, 2005 Nakanishi C & Toi M.

**Chemotherapy**

**Anti-tumor  
(Apoptosis)**

**Pro-tumor  
(Survival)**

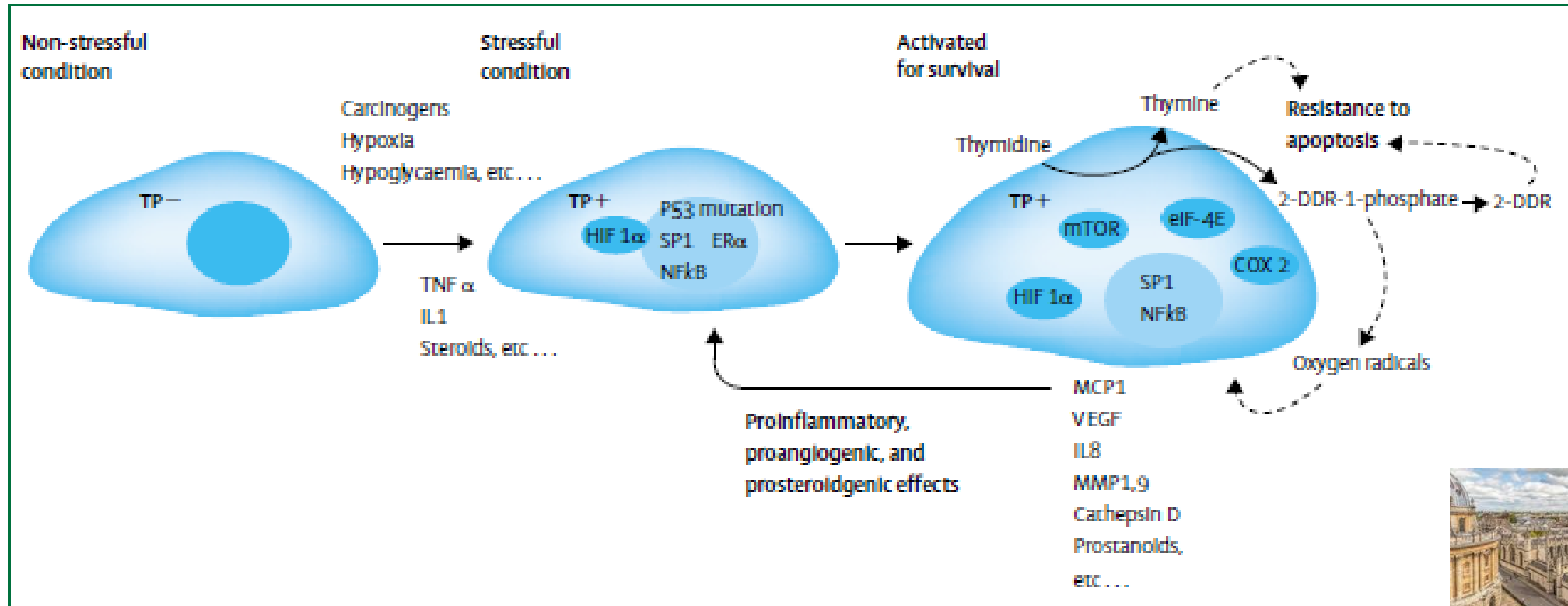
**Primary  
Resistance**

**Activation of pathways;**

**Transcription factors, chemokines, enzymes**

**NF-kB, COX-2, Thymidine phosphorylase (TP) ...**

# Thymidine Phosphorylase (TP)



Toi M et al. Lancet Oncol 2005



**Chemotherapy**

**A Working Hypothesis**

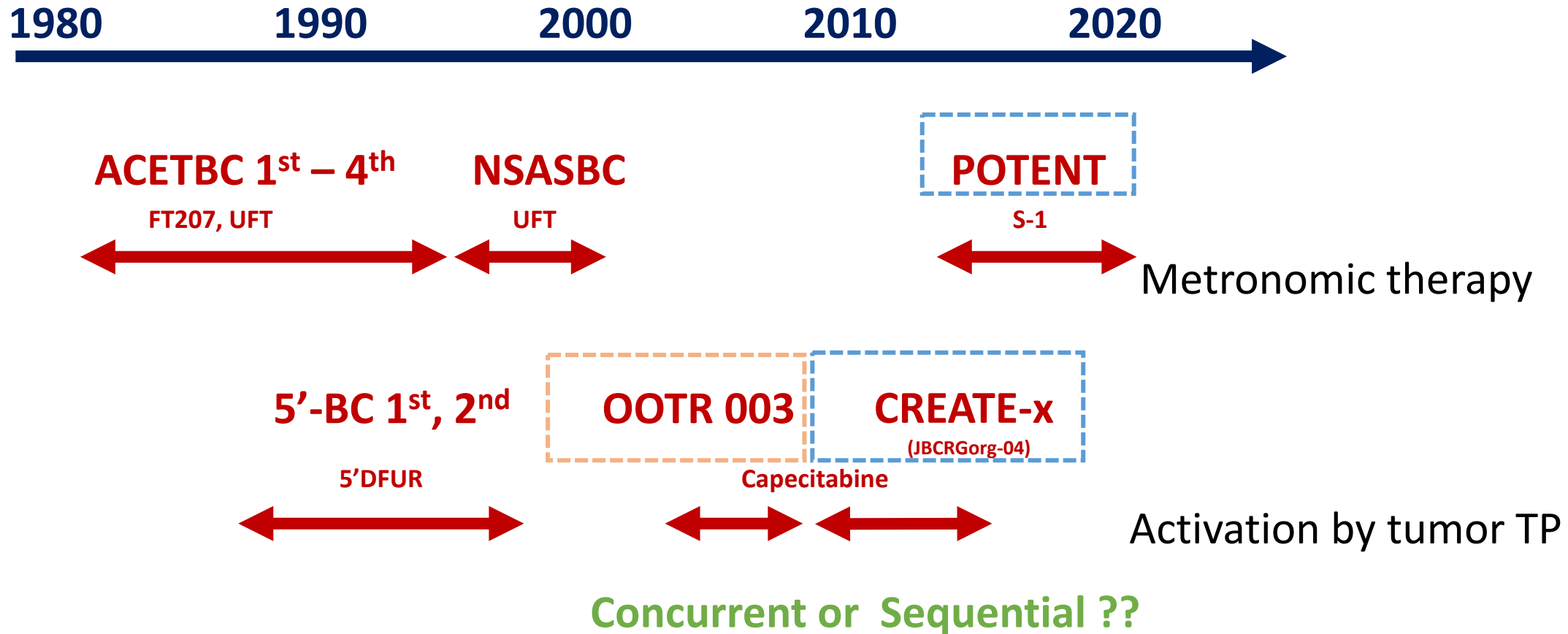
**Anti-tumor**

**Pro-tumor**

**TP: Salvage cycle of nucleoside metabolism  
Chemotherapy induces TP  
TP is a converting enzyme of Capecitabine**

**Concurrent or Sequential ??**

# Oral Fluoropyrimidines Adjuvant trials in Japan



ACETBC: Adjuvant Chemo-Endocrine Therapy for Breast Cancer, NSAS: National Surgical Adjuvant Study, OOTR: Organisation for Oncology and Translational Research, JBCRG org: Japan Breast Cancer Research Group organisation



# CREATE-X trial (JBCRG<sub>org</sub>-04)

Multidrug  
Cytotoxic  
Chemotherapy  
(containing A)

Surgery

Non-pCR  
Residual  
Invasive

R

Standard therapy  
HR+: ET alone  
TNBC: No further

Standard therapy  
+ Capecitabine

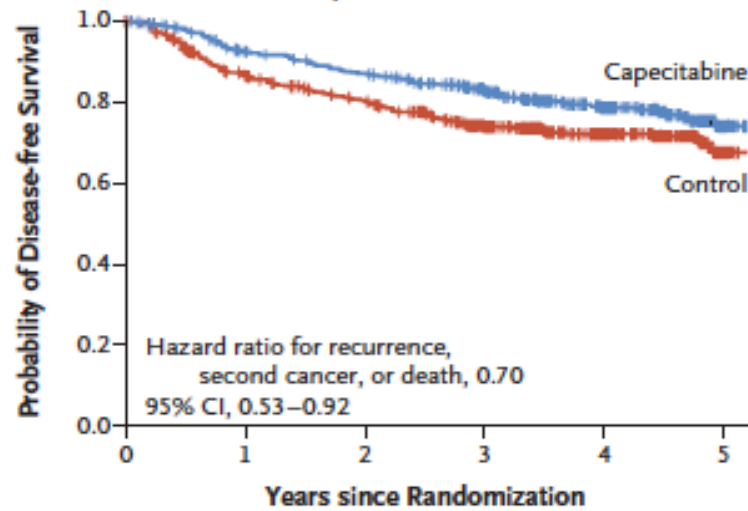


Started in 2007

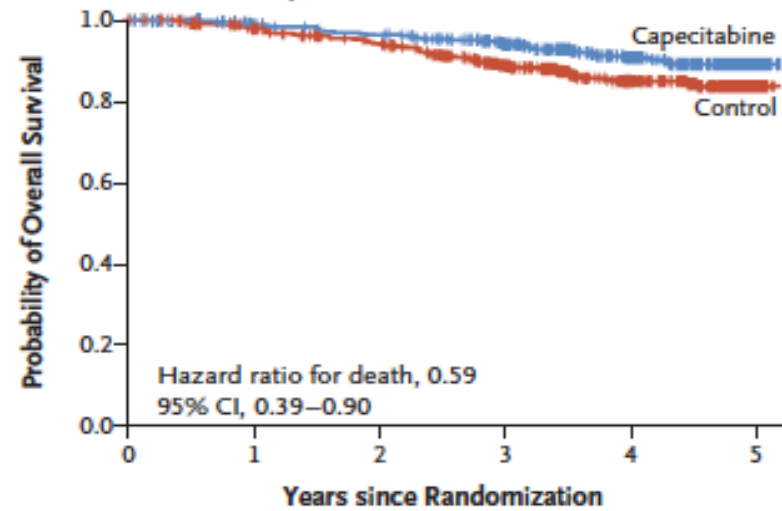
N=900

Japan and Korea

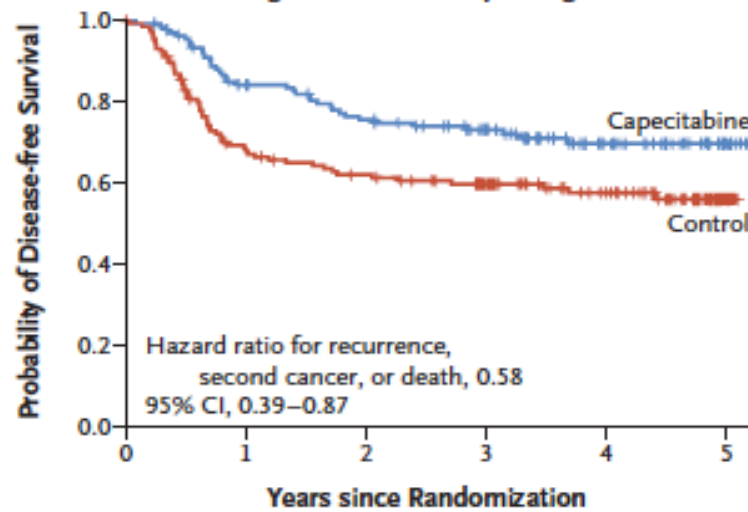


**A Disease-free Survival in Full Analysis Set****No. at Risk**

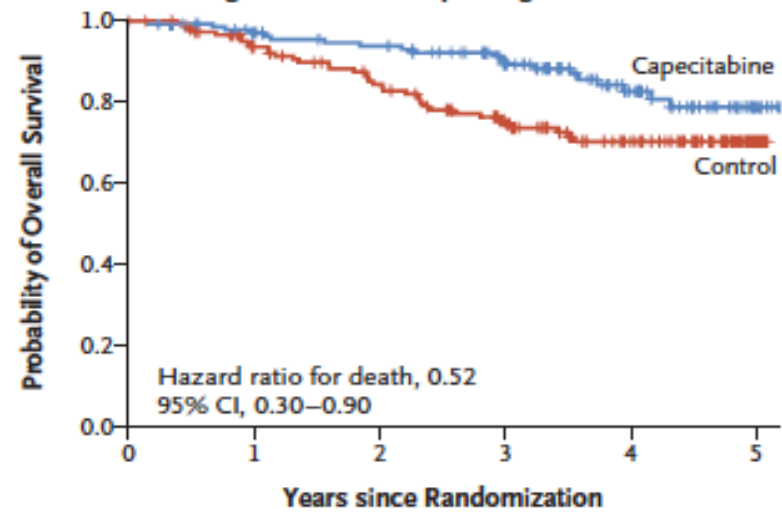
Capecitabine	443	385	359	286	175	34
Control	444	366	328	255	158	19

**B Overall Survival in Full Analysis Set****No. at Risk**

Capecitabine	443	408	391	321	197	43
Control	444	406	375	297	180	27

**C Disease-free Survival among Patients with Triple-Negative Disease****No. at Risk**

Capecitabine	139	109	96	76	42	11
Control	147	95	84	69	47	6

**D Overall Survival among Patients with Triple-Negative Disease****No. at Risk**

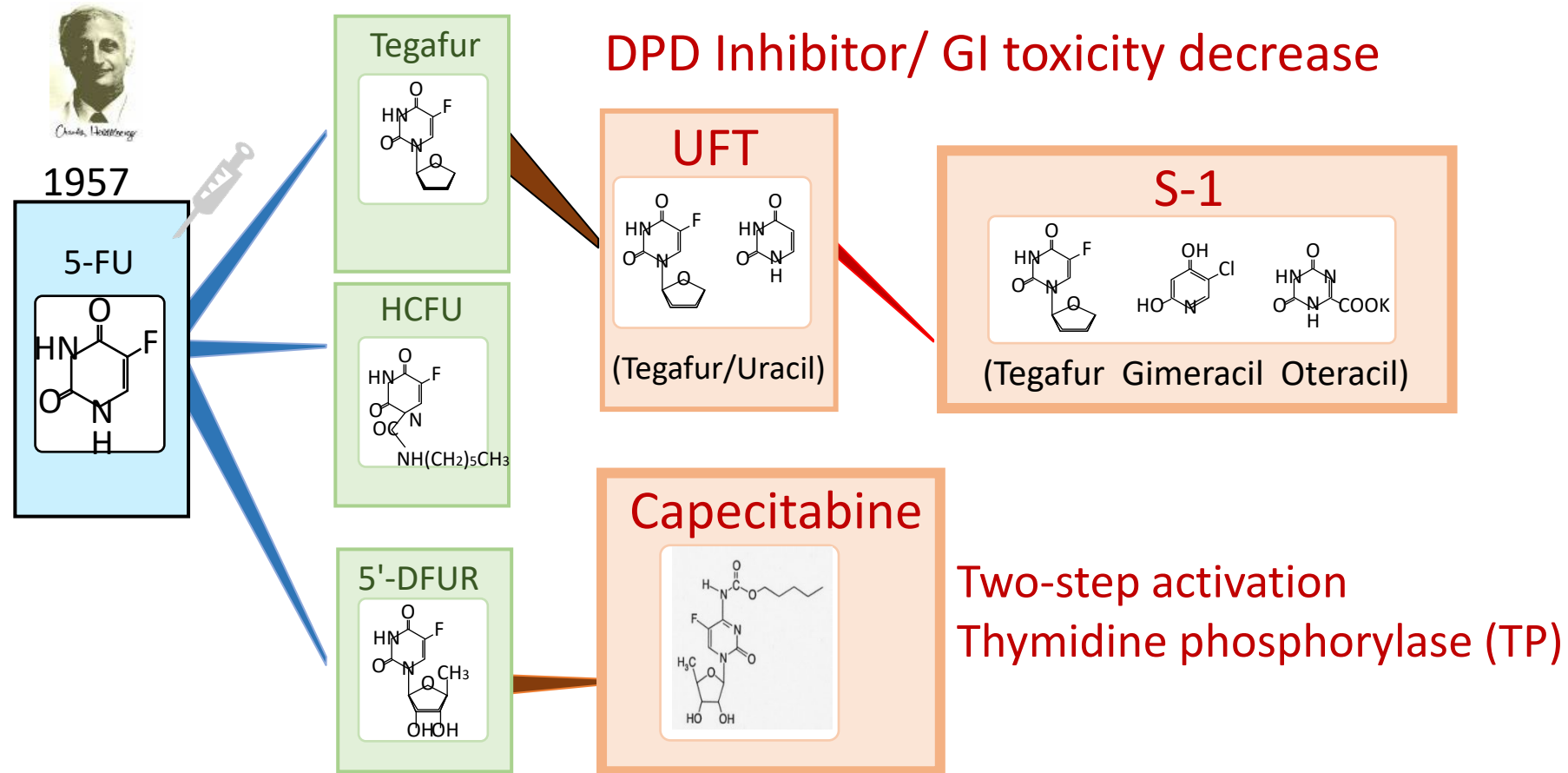
Capecitabine	139	124	116	91	50	11
Control	147	125	108	82	52	9

# Fluoropyrimidines Class Effect

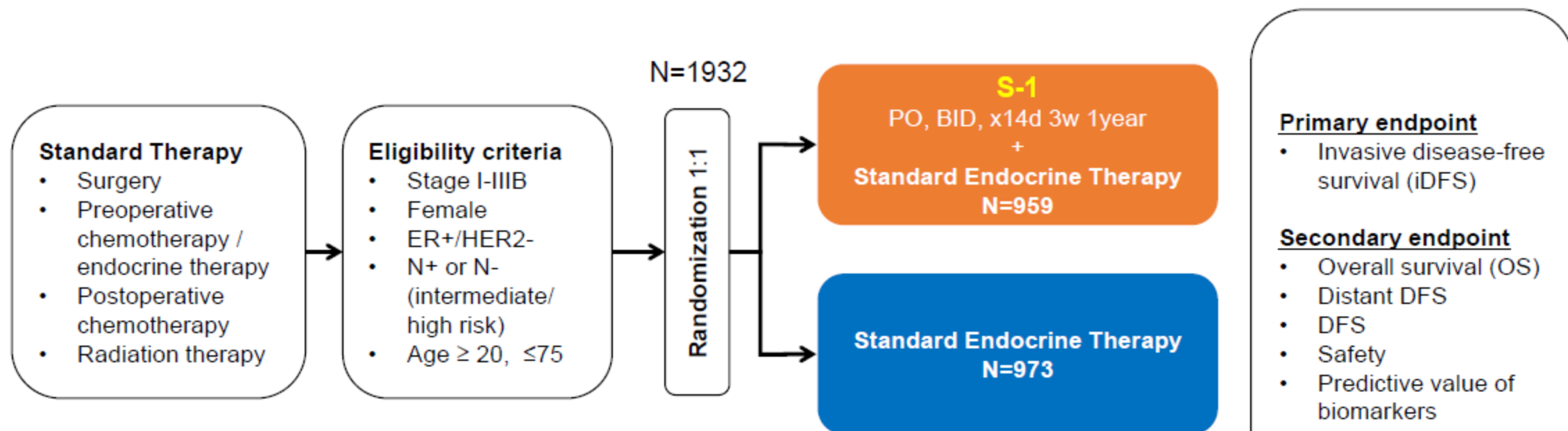
**Active Compound**

**Pro-Drug (Oral)**

**Biochemical Modulation**



# POTENT Trial Design



**Stratification factors:**

- Age (-54/55-)
- Nodal status (N+/N-)
- Chemotherapy (Yes/No)
- Preoperative endocrine therapy ( $\geq 4$  months/ No)
- ER status (1-9%/10%-)
- Institution

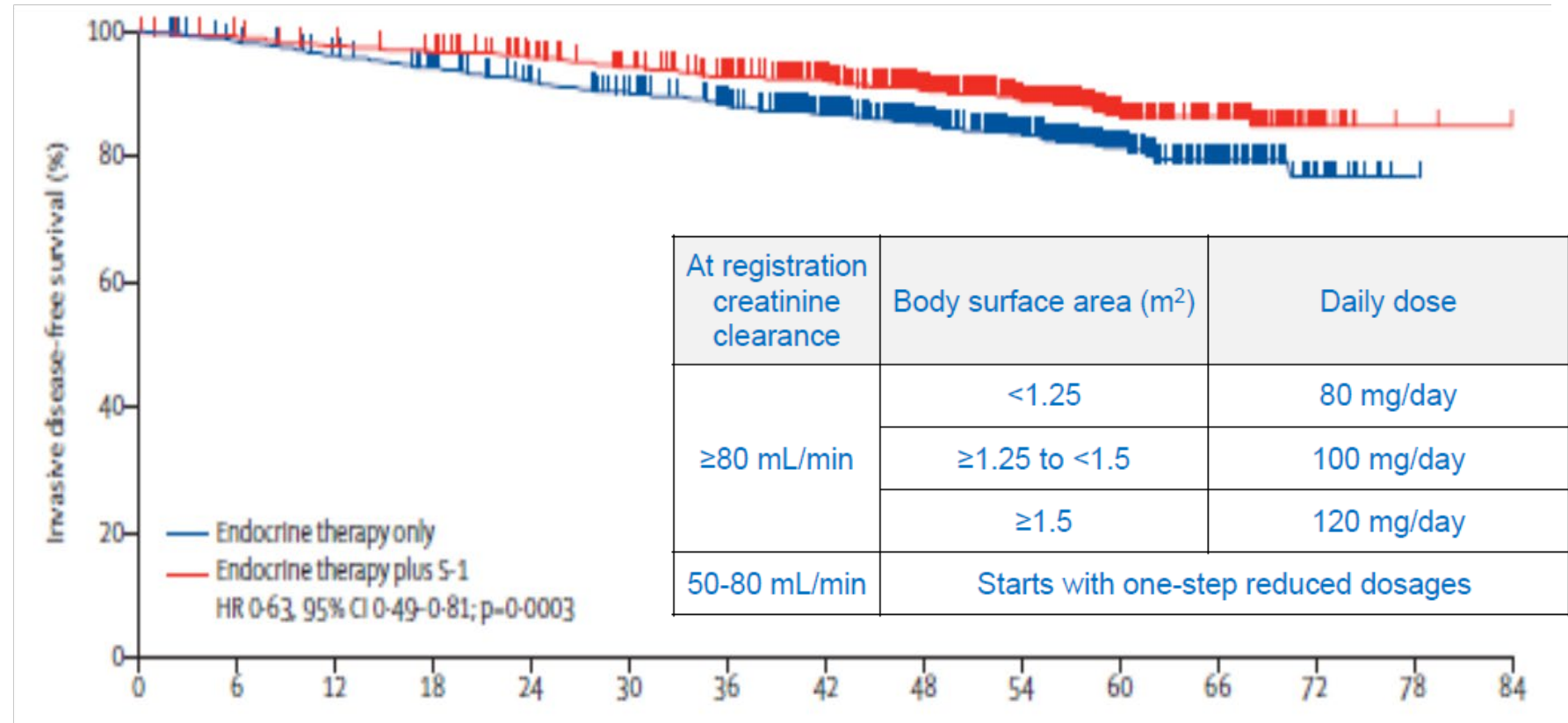
jRCTs051180057/ CRB5180002

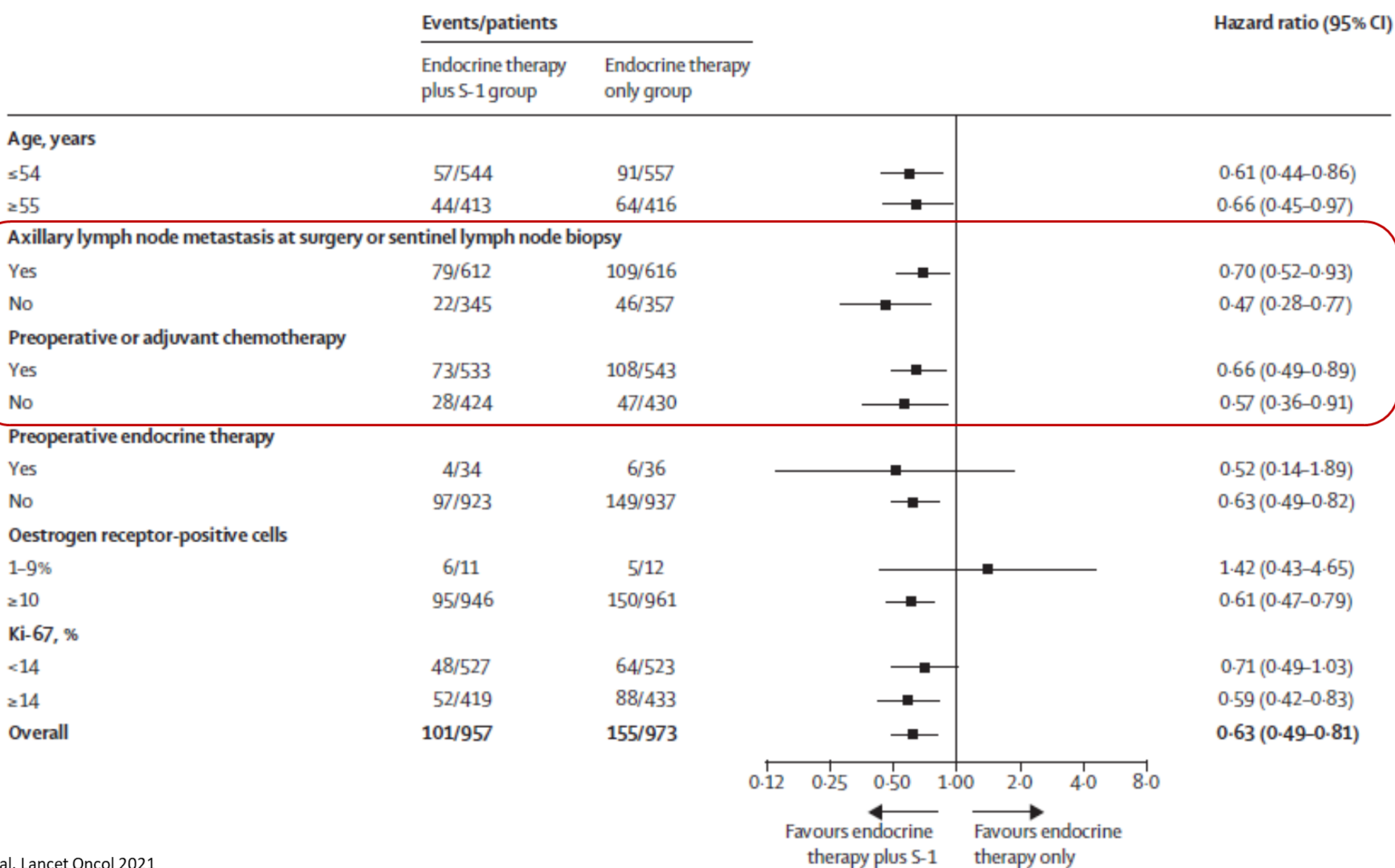
Patients were recruited between February 2012 and February 2016

- ER+, HER2-, Intermediate-High Risk, 1930 cases
- S1 1-year

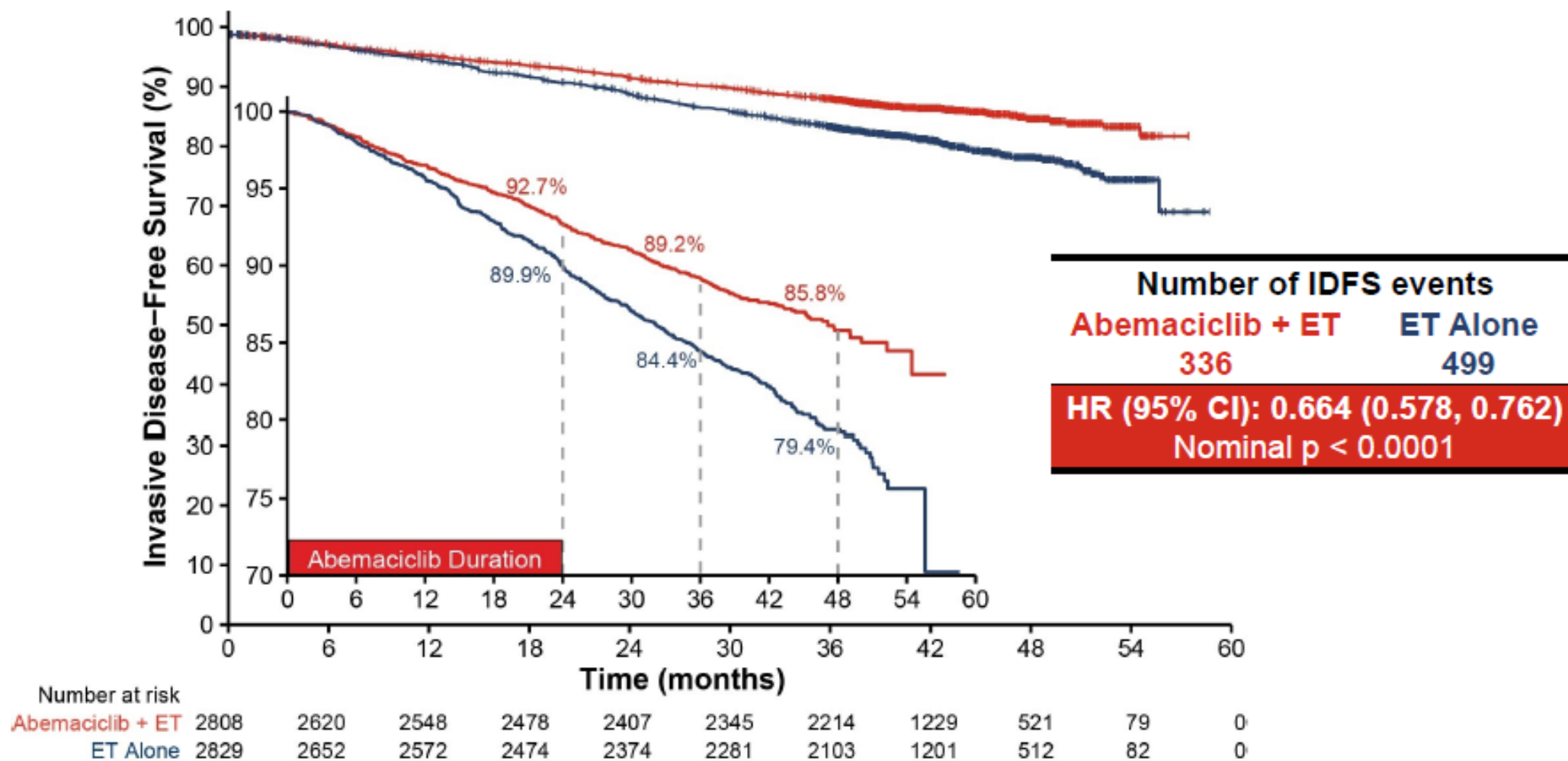
# POTENT

iDFS





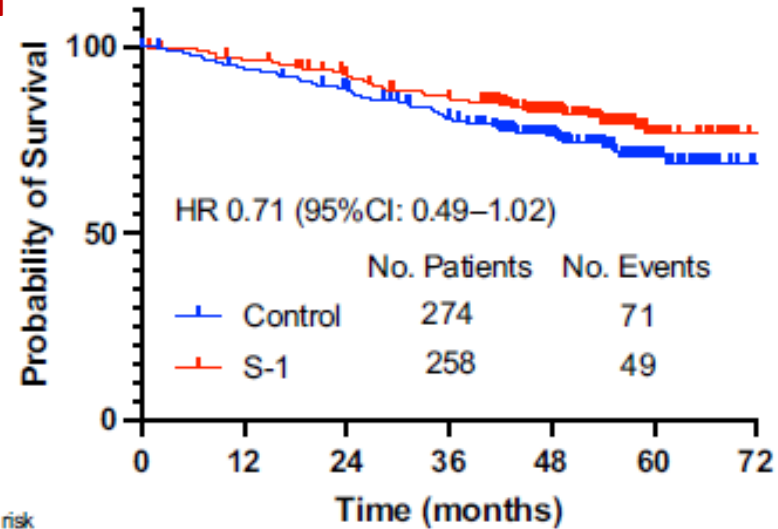
# IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib



**33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2- and 3-year IDFS rates (2.8% and 4.8% respectively)**

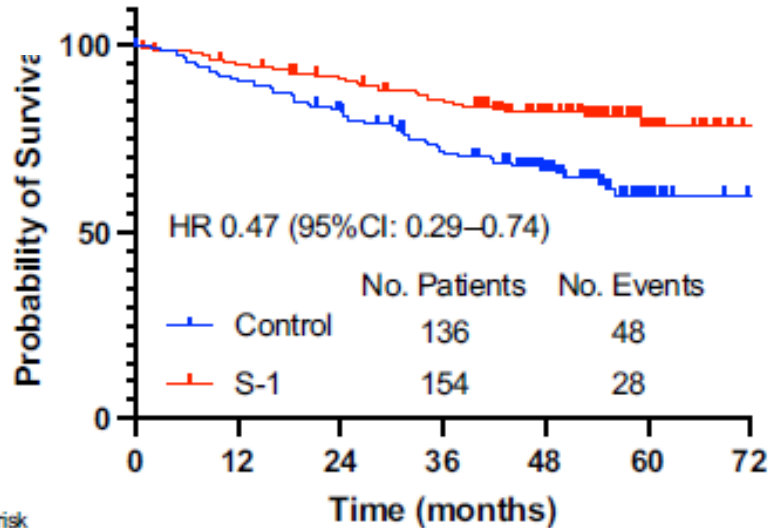
Patients who met monarchE criteria

# Effects of S-1 in patients fulfilling monarchE criteria



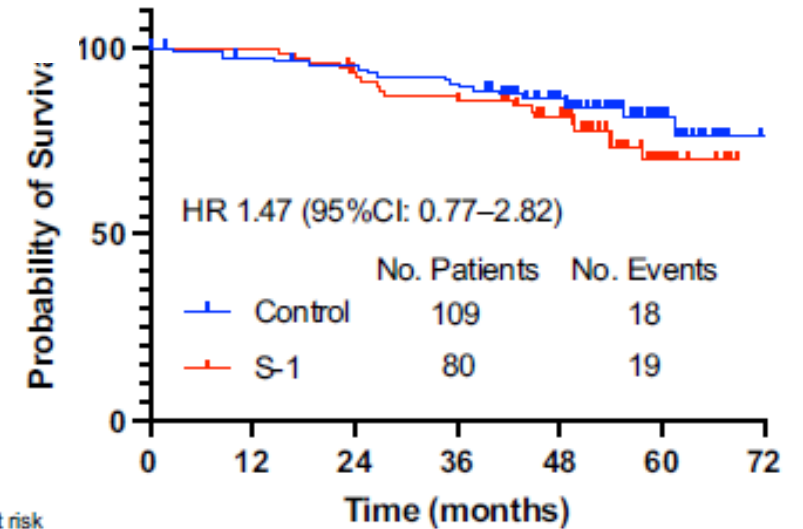
No. at risk	Time (months)						
	0	12	24	36	48	60	72
Control	274	254	237	210	150	44	9
S-1	258	246	228	211	161	41	3

Cohort 1 criteria with 1-3 positive nodes



No. at risk	Time (months)						
	0	12	24	36	48	60	72
Control	136	123	110	91	68	17	5
S-1	154	144	135	124	95	23	3

Cohort 1 criteria with 4- positive nodes



No. at risk	Time (months)						
	0	12	24	36	48	60	72
Control	109	104	101	96	67	20	4
S-1	80	80	73	68	54	17	1



# Kyoto University Risk Score Calculation Tool

**Tumor stage**

T1       T2       T3-T4

**Nodal metastasis**

positive       negative

**ER-positivity**

1-9%        $\geq 10\%$

**Histological grade**

Grade1       Grade2       Grade3

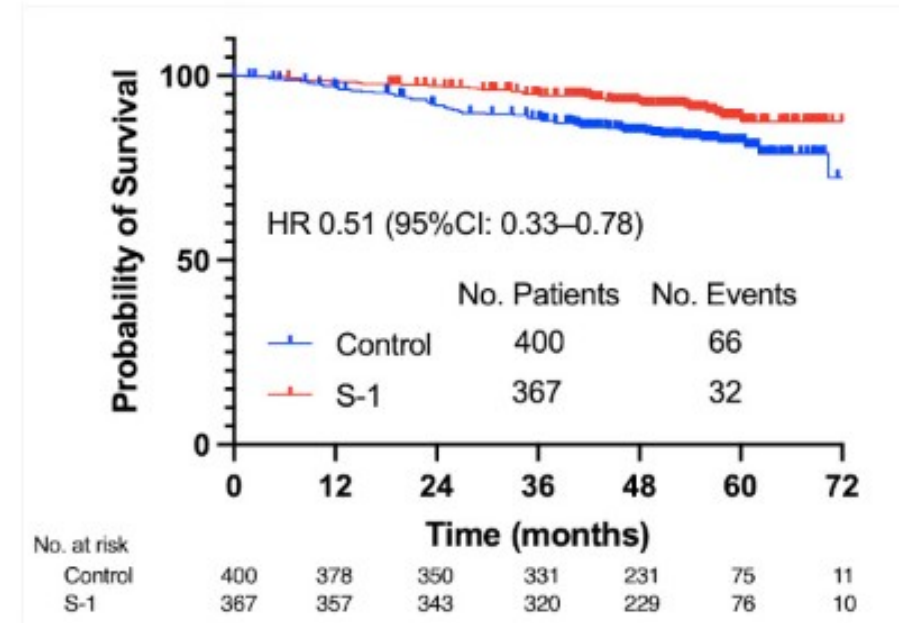
**Ki-67 LI**

<14%        $\geq 14\%$ , <30%        $\geq 30\%$



## Group2 (Classified)



5-y iDFS rate:  
82.0% vs 88.7% (Control vs S-1)

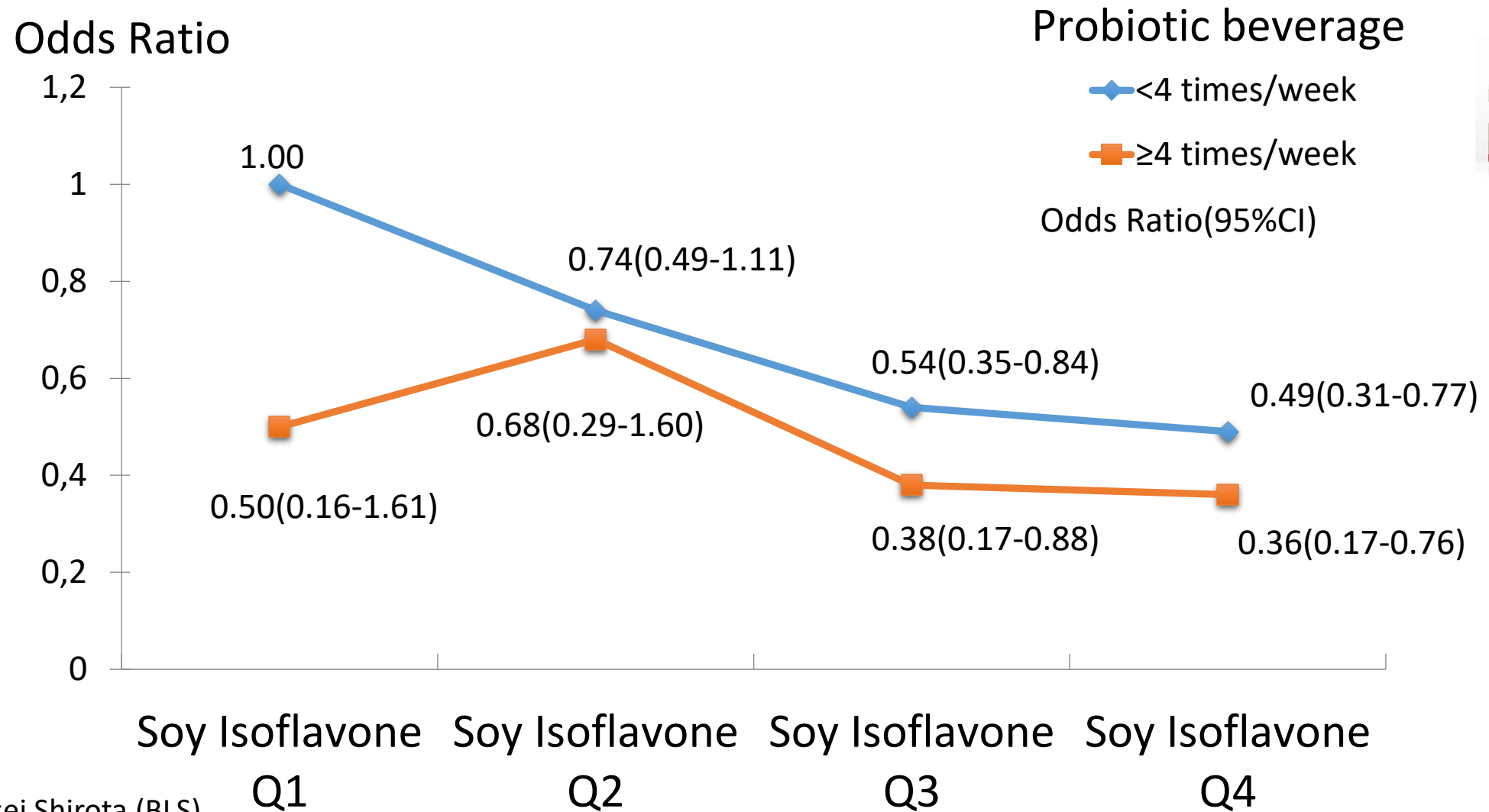
• 1: Toi M, et al. Lancet Oncol 2021.      2: Takada M, et al. Breast Cancer Res Treat 2023.

**In Asia**  
**Good for Health**  
**Maybe Cancer Preventive**



# Probiotic Yakult® (BLS) and Soy Isoflavone

## Long-term intake may prevent breast cancer



## Article

# Evolutionary histories of breast cancer and related clones

<https://doi.org/10.1038/s41586-023-06333-9>

Received: 4 July 2022

Accepted: 15 June 2023

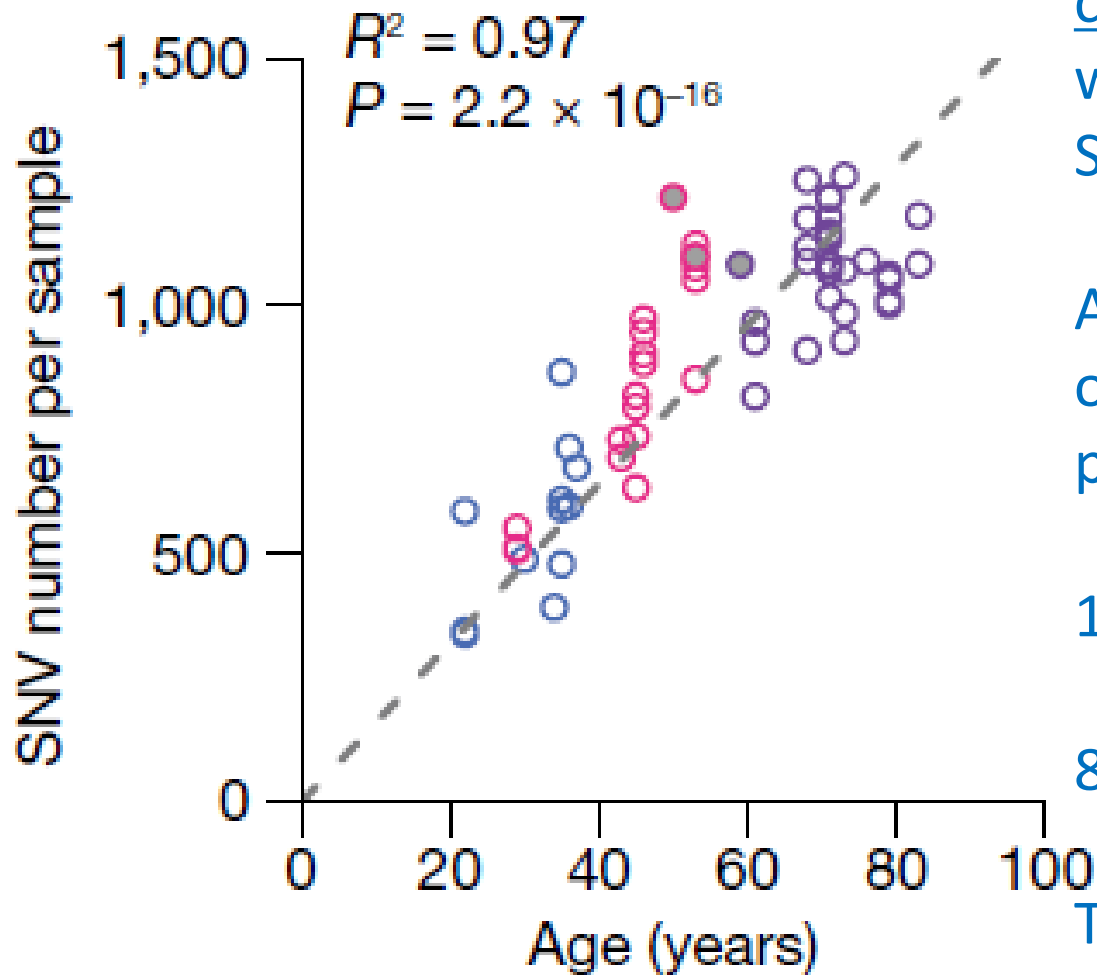
Published online: 26 July 2023

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Tomomi Nishimura<sup>1,2,3,26</sup>, Nobuyuki Kakiuchi<sup>1,4,5,26</sup>, Kenichi Yoshida<sup>1,6</sup>, Takaki Sakurai<sup>7,8</sup>, Tatsuki R. Kataoka<sup>7,9</sup>, Eiji Kondoh<sup>10,11</sup>, Yoshitsugu Chigusa<sup>10</sup>, Masahiko Kawai<sup>12</sup>, Morio Sawada<sup>13</sup>, Takuya Inoue<sup>13</sup>, Yasuhide Takeuchi<sup>1,7</sup>, Hirona Maeda<sup>1,7</sup>, Satoko Baba<sup>14,15,16</sup>, Yusuke Shiozawa<sup>1</sup>, Ryunosuke Saiki<sup>1</sup>, Masahiro M. Nakagawa<sup>1,2</sup>, Yasuhito Nannya<sup>1,17</sup>, Yotaro Ochi<sup>1</sup>, Tomonori Hirano<sup>1,5,18</sup>, Tomoe Nakagawa<sup>1,18</sup>, Yukiko Inagaki-Kawata<sup>1,3</sup>, Kosuke Aoki<sup>1</sup>, Masahiro Hirata<sup>7</sup>, Kosaku Nanki<sup>19</sup>, Mami Matano<sup>19</sup>, Megumu Saito<sup>19,20</sup>, Eiji Suzuki<sup>3,21</sup>, Masahiro Takada<sup>3</sup>, Masahiro Kawashima<sup>3</sup>, Kosuke Kawaguchi<sup>3</sup>, Kenichi Chiba<sup>22</sup>, Yuichi Shiraishi<sup>22</sup>, Junko Takita<sup>12</sup>, Satoru Miyano<sup>23,24</sup>, Masaki Mandai<sup>10</sup>, Toshiro Sato<sup>19</sup>, Kengo Takeuchi<sup>14,15,16</sup>, Hironori Haga<sup>7</sup>, Masakazu Toi<sup>3,27</sup> & Seishi Ogawa<sup>1,18,25,27</sup> ✉



Single nucleotide variants (SNVs) found in 64 single-cell-derived organoids from 6 healthy breastfeeding women, 6 premenopausal, 9 postmenopausal BC pts. SBS1 (9.9%), SBS5 (80.7%), SBS40 (9.4%)

According to the linear regression model, the number of SNVs depended on age, years after menopause, parity and the presence of a driver mutation.

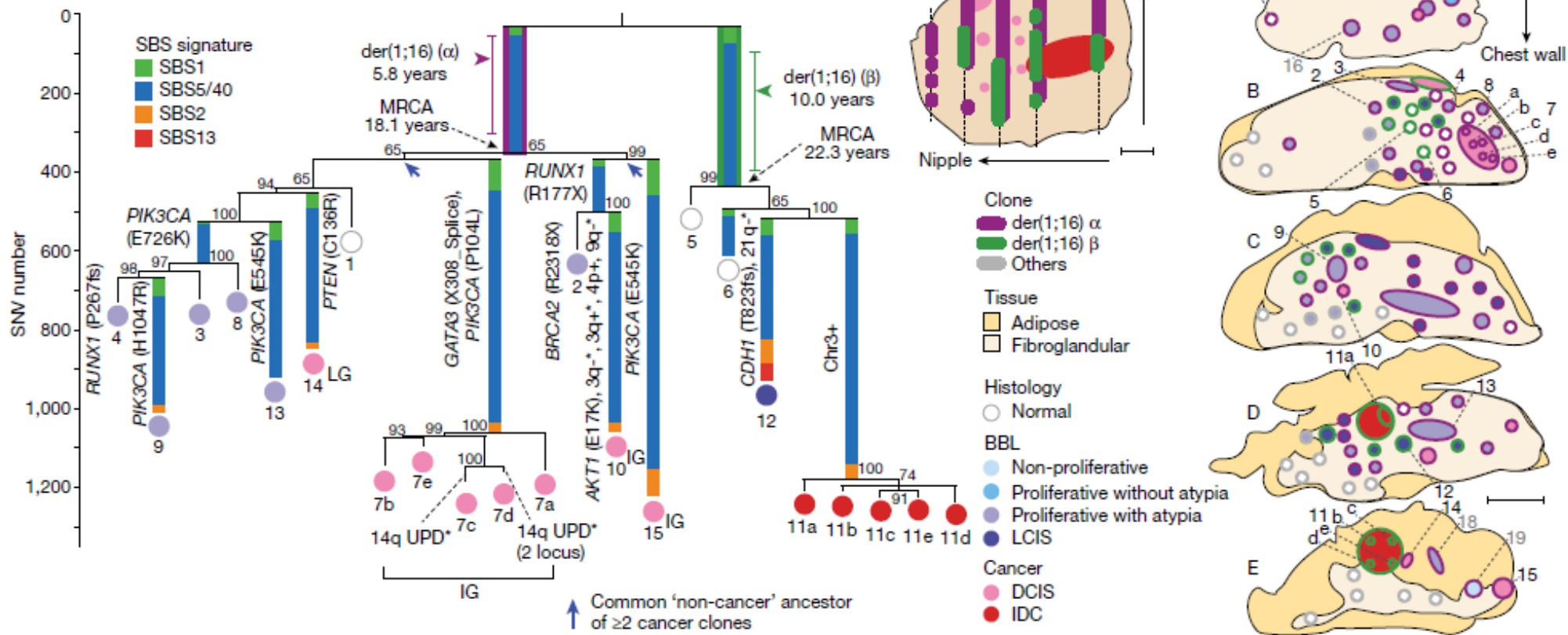
19.5 muts per genome per year before menopause

8.1 muts per genome per year after menopause

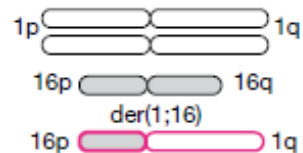
The mut number was reduced by 54.8 per delivery

PIK3CA mut increased the number of SNVs by 210.4 (4/71)

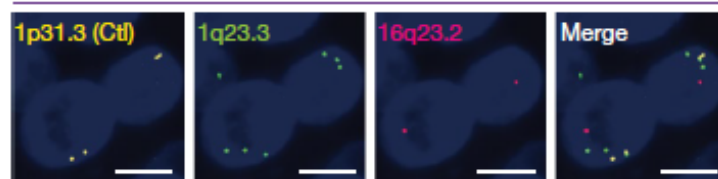
**a** Case KU779 (48 y.o., premenopausal)  
IDC (pT2N0M0, Luminal A-like)



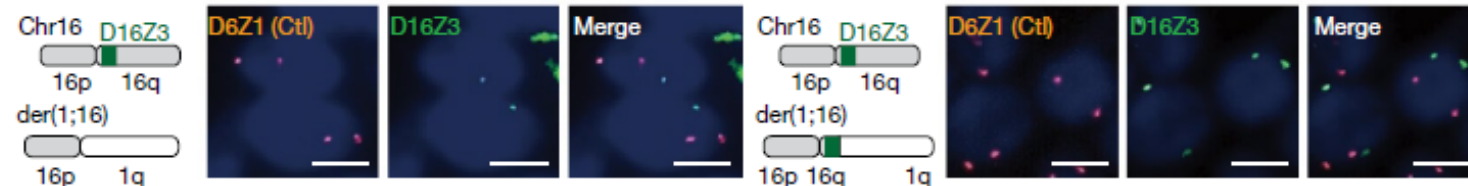
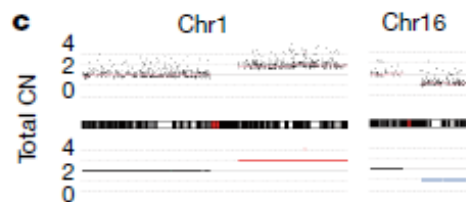
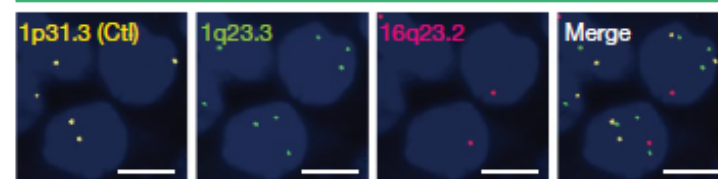
**b** der(1;16) positive (= 1q+/16q-)

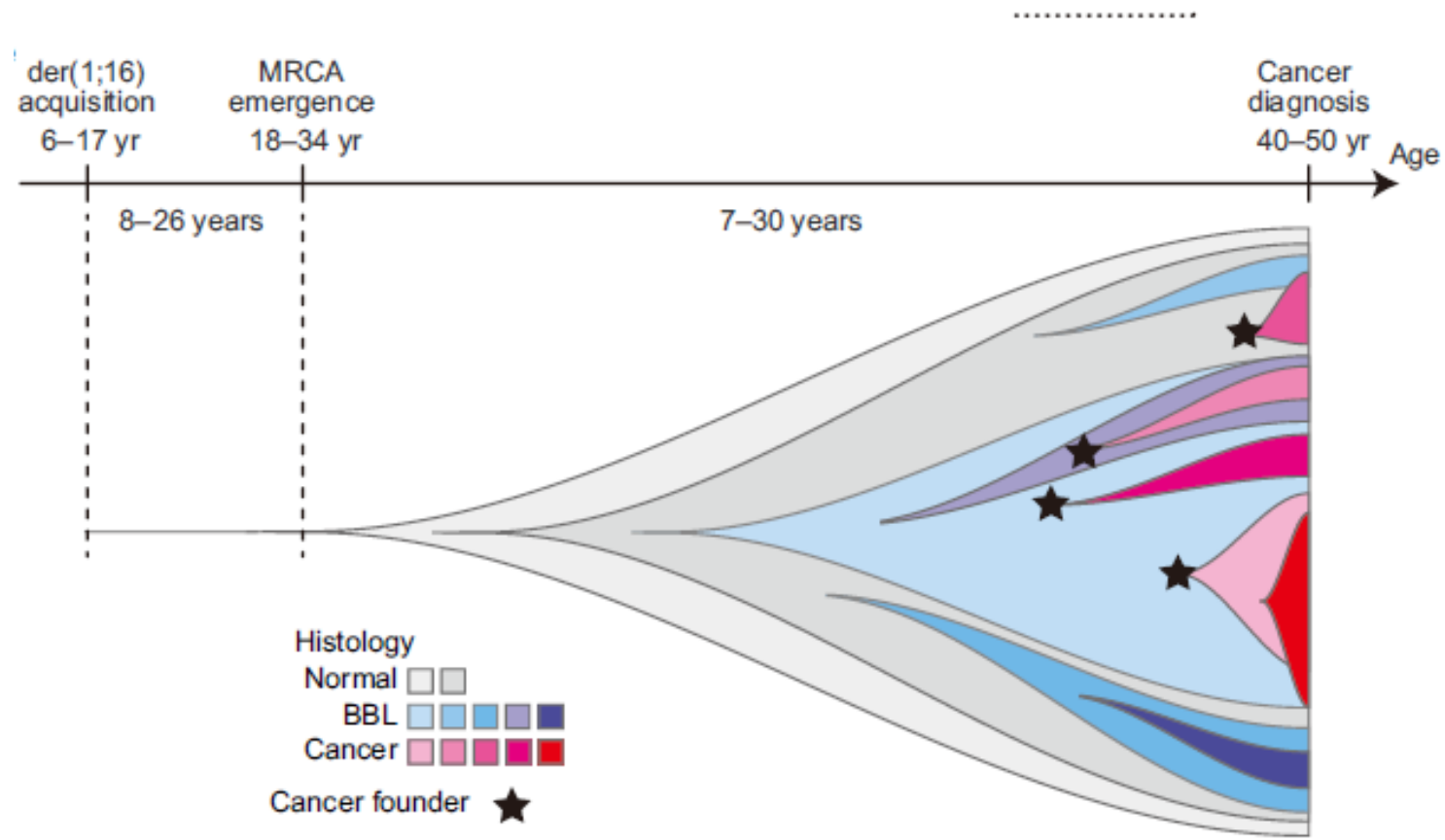
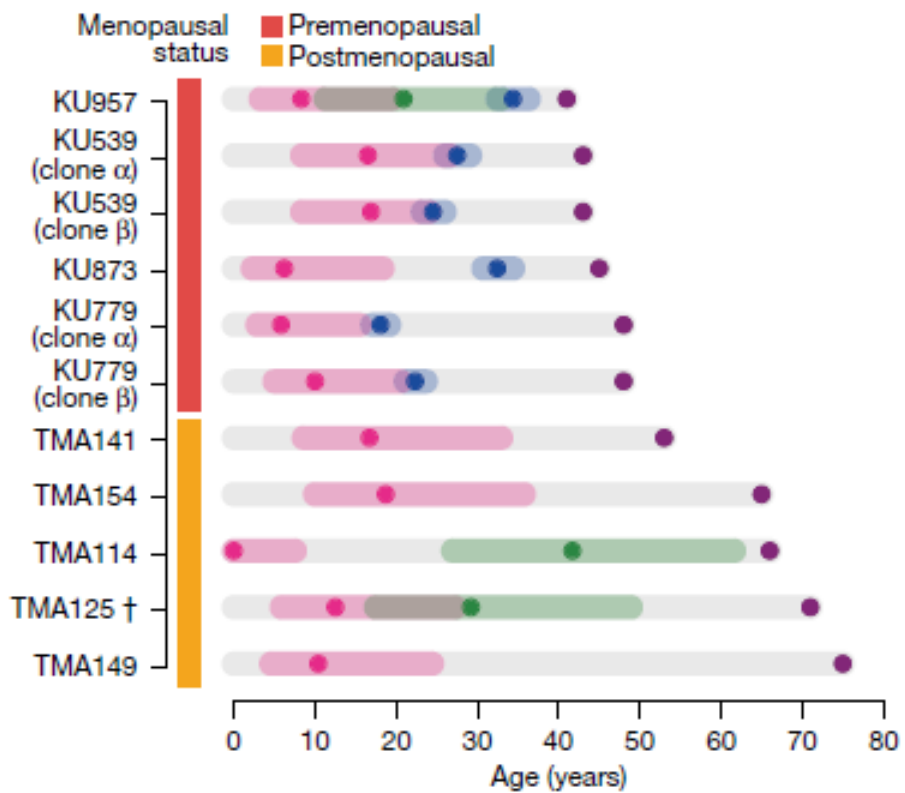


**d** der(1;16) clone α



der(1;16) clone β





Benign breast lesion: BBL

# Companion Dx and Biological Assays

**Molecule: Protein, ISH, DNA sequence**

**ER**

**HER2**

**Ki-67**

**PD-1, PD-L1**

**gBRCA1/2**

**PIK3CA...**

**Expression profiling..**

**Intrinsic Subtype**

**Genomic assays**

**Estrogen module**

**Cell proliferation**

**Inflammatory**

**Gene repair**

**NGS..**

**TMB**

**HRD**

**Immune signature**

**Liquid biopsy**

**Organoids**

**Metabolic pathway**



**Vielen Dank!**

# Agenda

- Epidemiology in Japan
- Radiofrequency ablation therapy
- ADC
- Oral fluoropyrimidines
- A carcinogenesis model