Overcome of Endocrine Resistance

Aichi Cancer Center

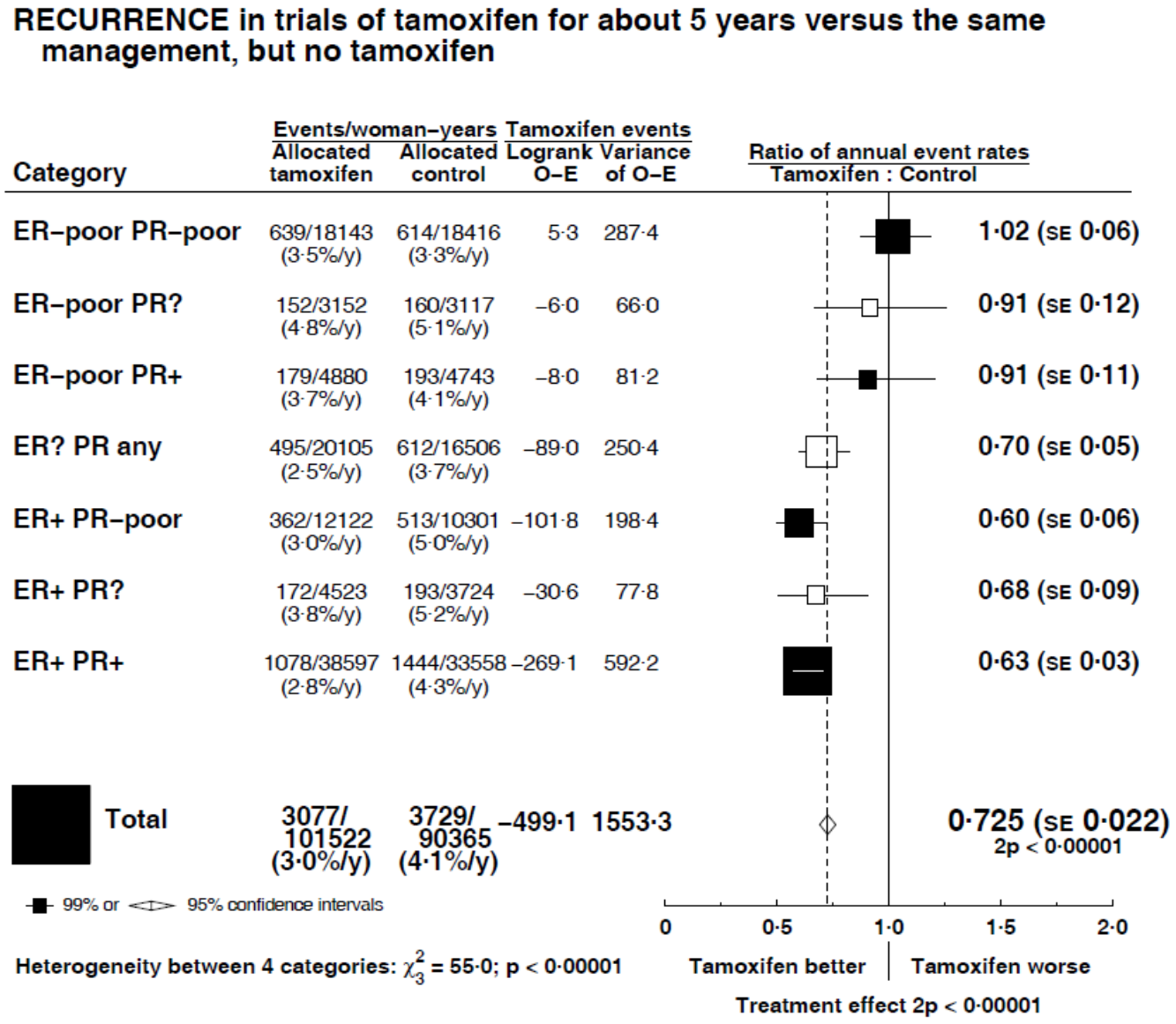
Hiroji Iwata

2019 GBCC 2019.4.25

Two topics in this presentation

- **Endocrine resistance for early breast cancer (response guide therapy)**
- **Endocrine resistance for advanced/metastatic breast cancer (new drug development)**

Resistance and responsibility for endocrine therapy



Lancet 2011; 378: 771–84

ER status is predictive marker of endocrine therapy

Is endocrine therapy responsive in all breast cancer patients with ER positive?

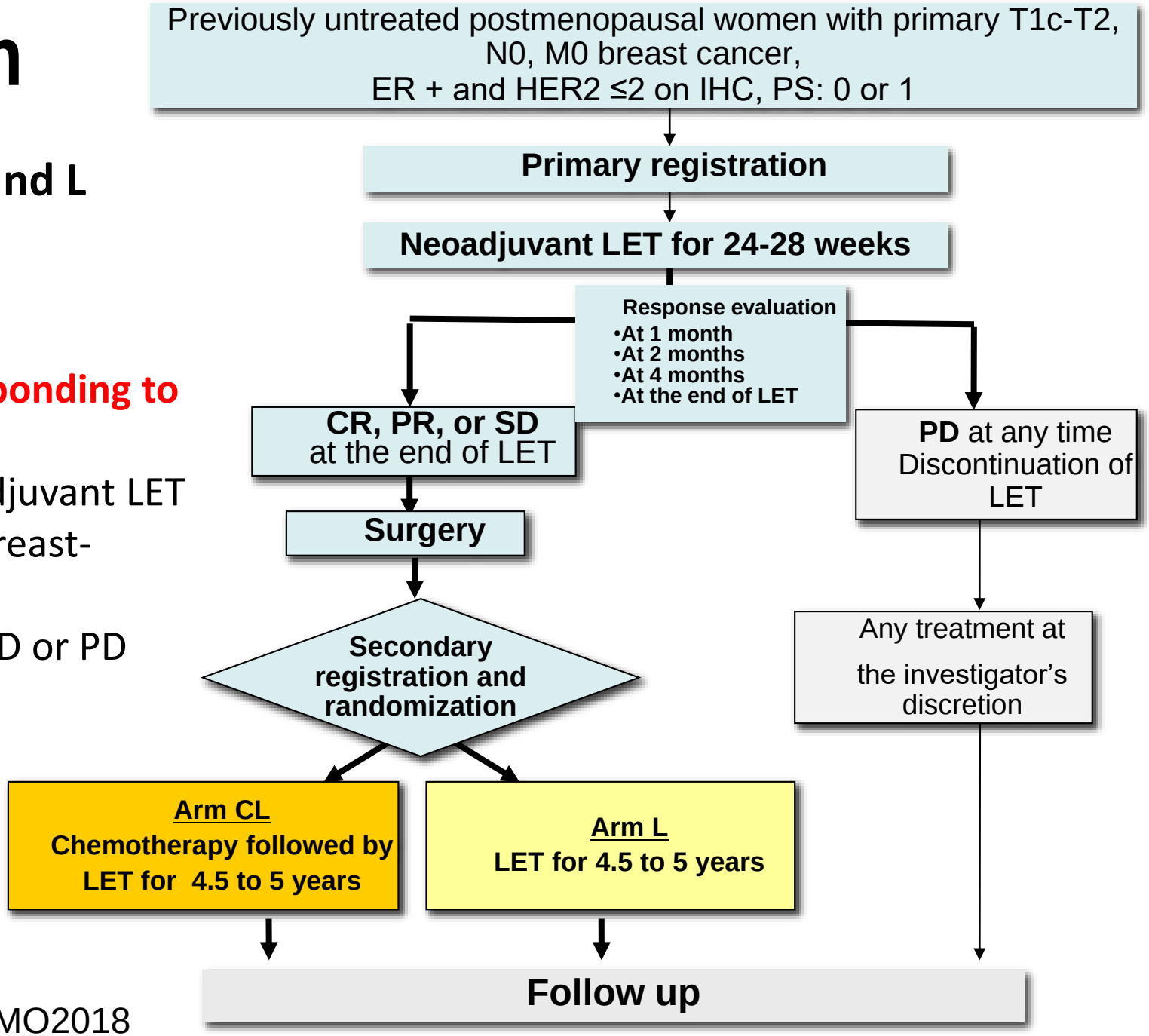
Yes or No

NEOS Study design

Primary endpoint : DFS at each CL and L

Secondary endpoints:

- OS at each arms
- **Percentage of patients clinically responding to neoadjuvant LET**
- Histological tumor response to neoadjuvant LET
- Percentage of patients undergoing breast-conserving surgery
- DFS/OS in patients showing CR, PR, SD or PD response to neoadjuvant LET
- Safety
- HRQOL
- Cost-effectiveness



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Iwata H, et al. ESMO2018

Results: Clinical response

Clinical response to NET was defined as follows:

CR: target tumor has disappeared or completely undergone tumor-related secondary changes

PR: largest diameter of the target tumor reduced by ≥30% from baseline

SD: largest diameter of the target tumor by <30% or increased by <20% from baseline

PD: largest diameter of the target tumor increased by ≥20% from baseline

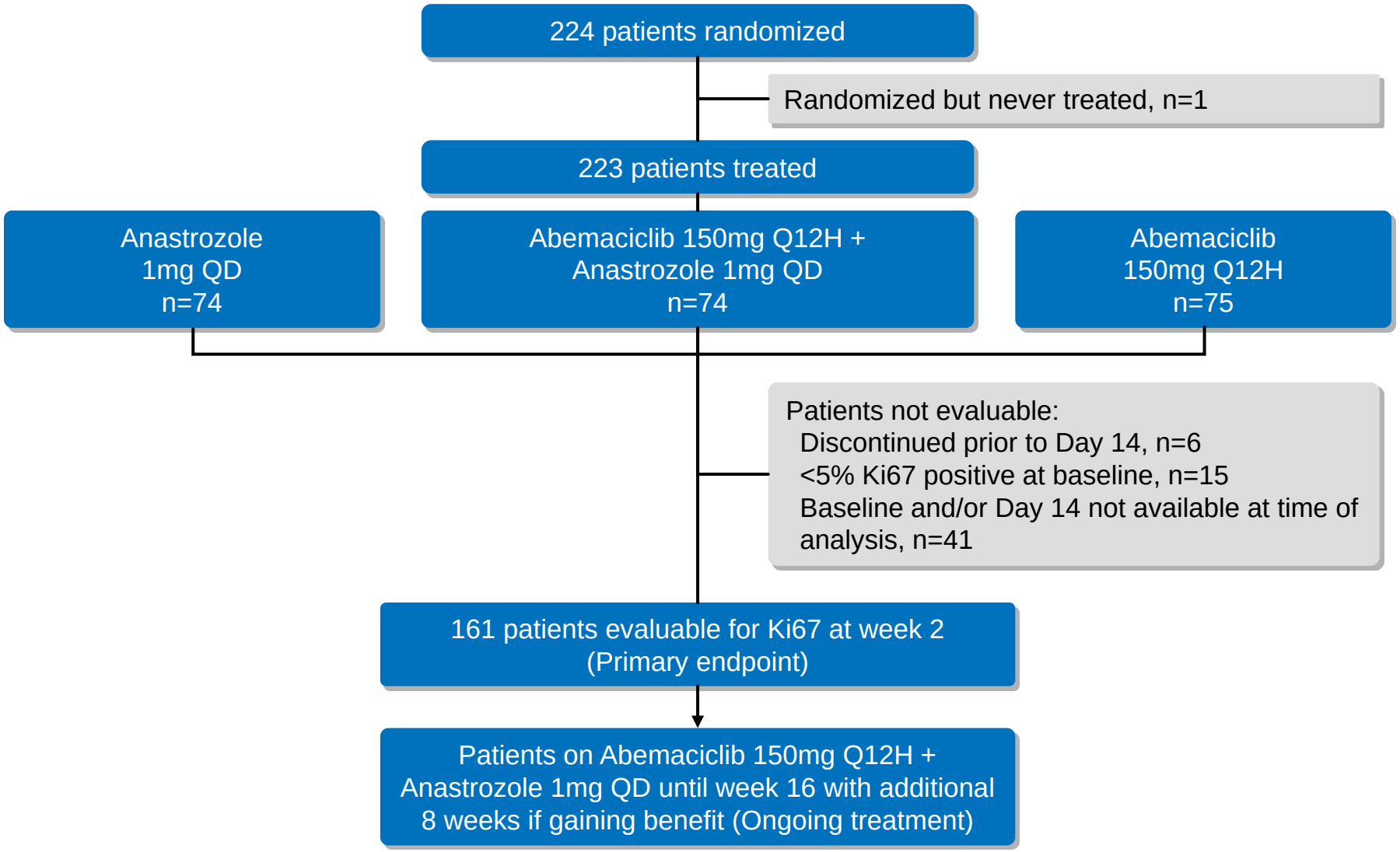
The treatment duration of NET (LET): median 179 days

The treatment duration of NET in PD cases: median 109 days (27-254 days)

	n	%
CR	16	2
PR	421	48
SD	403	45
PD	43	5
CR+PR	437	50
CR+PR+SD	840	95
Total	883	100

Iwata H, et al. ESMO2018

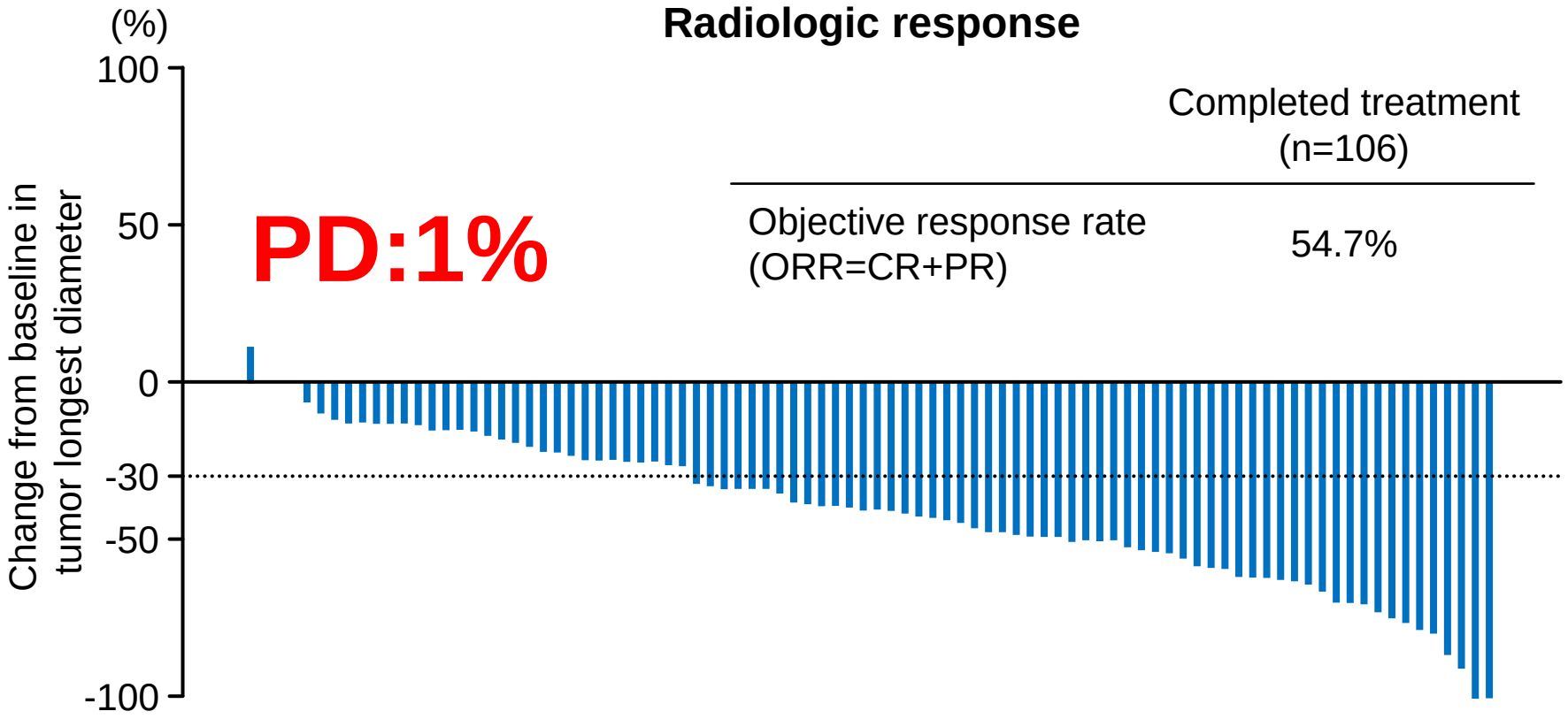
neoMONARCH consort diagram



Abbreviations: Q12H=every 12 hours; QD=once daily

Hurvitz S, et al. SABCS2016 Abst #S4-06

neoMONARCH RECIST response data over time

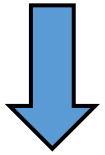


- At time of analysis:
  - Complete pathologic response in three (3.2%) of 95 patients that underwent surgery.
  - One patient discontinued therapy for progressive disease (20.7% change from baseline in tumor size at week 12).

Hurvitz S, et al. SABCS2016 Abst #S4-06

Primary resistance for ER+, HER2 -ve PBC

The frequency of resistance by endocrine therapy alone : 5%



The frequency of resistance by endocrine + CDK4/6i: 1%

What is predictive marker of primary resistance by endocrine therapy alone?

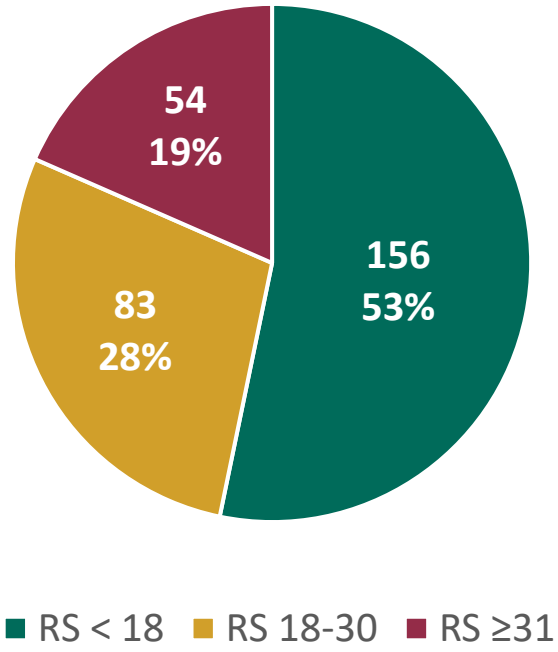
TransNEOS study

Patient Demographics and Disease Characteristics

Variable	Statistic	N=294
Age, y	Median (range)	63 (49-75)
	<50	1 (<1.0%)
	50 to 60	93 (31.6%)
	>60 to 70	168 (57.1%)
	>70	32 (10.9%)
T-stage	T1c	44 (15.0%)
	T2	250 (85.0%)
Nuclear grade	1	194 (66.0%)
	2	59 (20.1%)
	3	27 (9.2%)
	Missing	14 (4.8%)
Tumor size, mm	Median (range)	25 (20-65)
Ki-67 by IHC, %	Median (range)	16.7 (0.0, 82.5)
Ki-67 category	<10%	81 (27.6%)
	10% to 30%	115 (39.1%)
	>30%	60 (20.4%)
	Missing	38 (12.9%)

Variable	Statistic	N=294
ER by RT-PCR	Median (range)	11.7 (5.7-14.6)
ER category	Positive (≥6.5)	292 (99.3%)
	Negative (<6.5)	2 (<1.0%)
PR by RT-PCR	Median (range)	7.1 (2.6-11.4)
PR category	Positive (≥5.5)	210 (71.4%)
	Negative (<5.5)	84 (28.6%)
HER2 category	Negative (<10.7)	234 (79.6%)
	Positive (≥11.5)	9 (3.1%)
	Equivocal (10.7 to <11.5)	51 (17.3%)
Recurrence Score result	Median (range)	17 (0-68)

Distribution of Patients by RS Group (n=294)

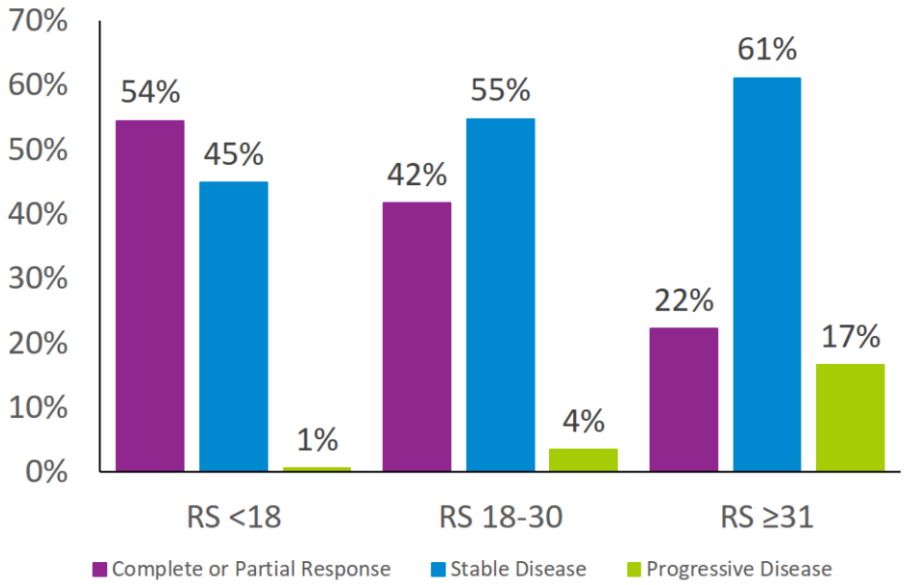


- Of 333 tumor samples submitted, 294 were eligible with evaluable RS results and clinical response data.
- For the patients included in the TransNEOS study (N=294), 53% had RS <18, 29% had RS 18-30, and 18% had RS ≥31.

Iwata H, et al. BCRT 173(1);123-133: 2019

Primary Analysis: Recurrence Score Group Is Associated With Rate of Clinical Response to NAHT

Percent Clinical Response to NAHT by Recurrence Score Group (N=294)



Clinical response, n	RS <18	RS 18-30	RS ≥31	Total
CR + PR	85	35	12	132
SD	70	46	33	149
PD	1	3	9	13
Total	156	84	54	294

Primary Pre-Specified Endpoint was met:

- Recurrence Score group (RS<18 vs RS≥31) was significantly associated with rate of clinical response (CR+PR) (chi-square test, p<0.001).
- With the RS 18-30 group included, RS group remained significantly associated with clinical response (Cochran-Armitage trend test, p<0.001).

Iwata H, et al. BCRT 173(1);123-133: 2019

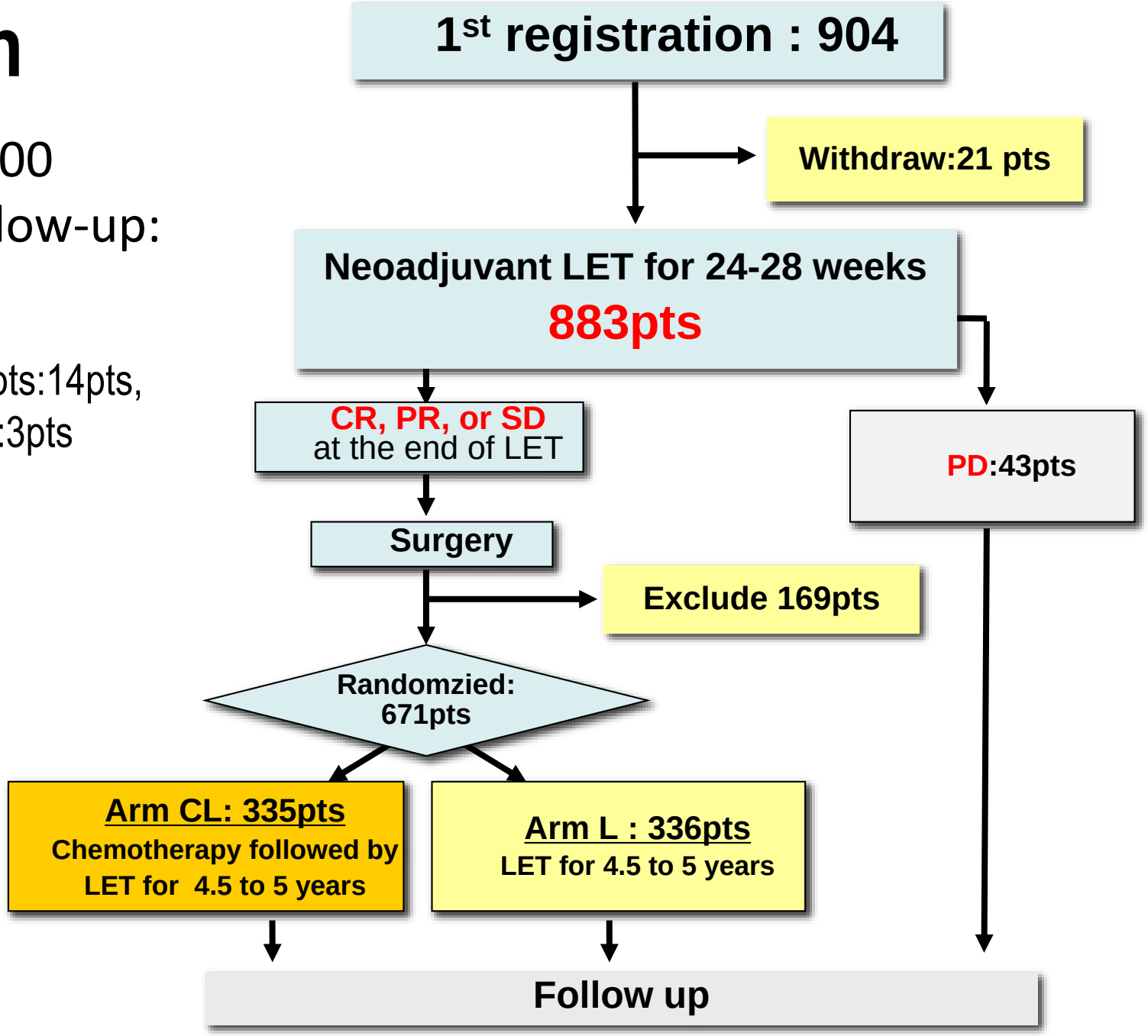
NEOS Study design

May 2008 and June 2013 from 100 institutions in Japan (median follow-up: 5.9 years)

The reason of withdraw (21pts) : refused by pts:14pts, not eligible:2pts, transference:2pts, unknown:3pts

Secondary endpoints:

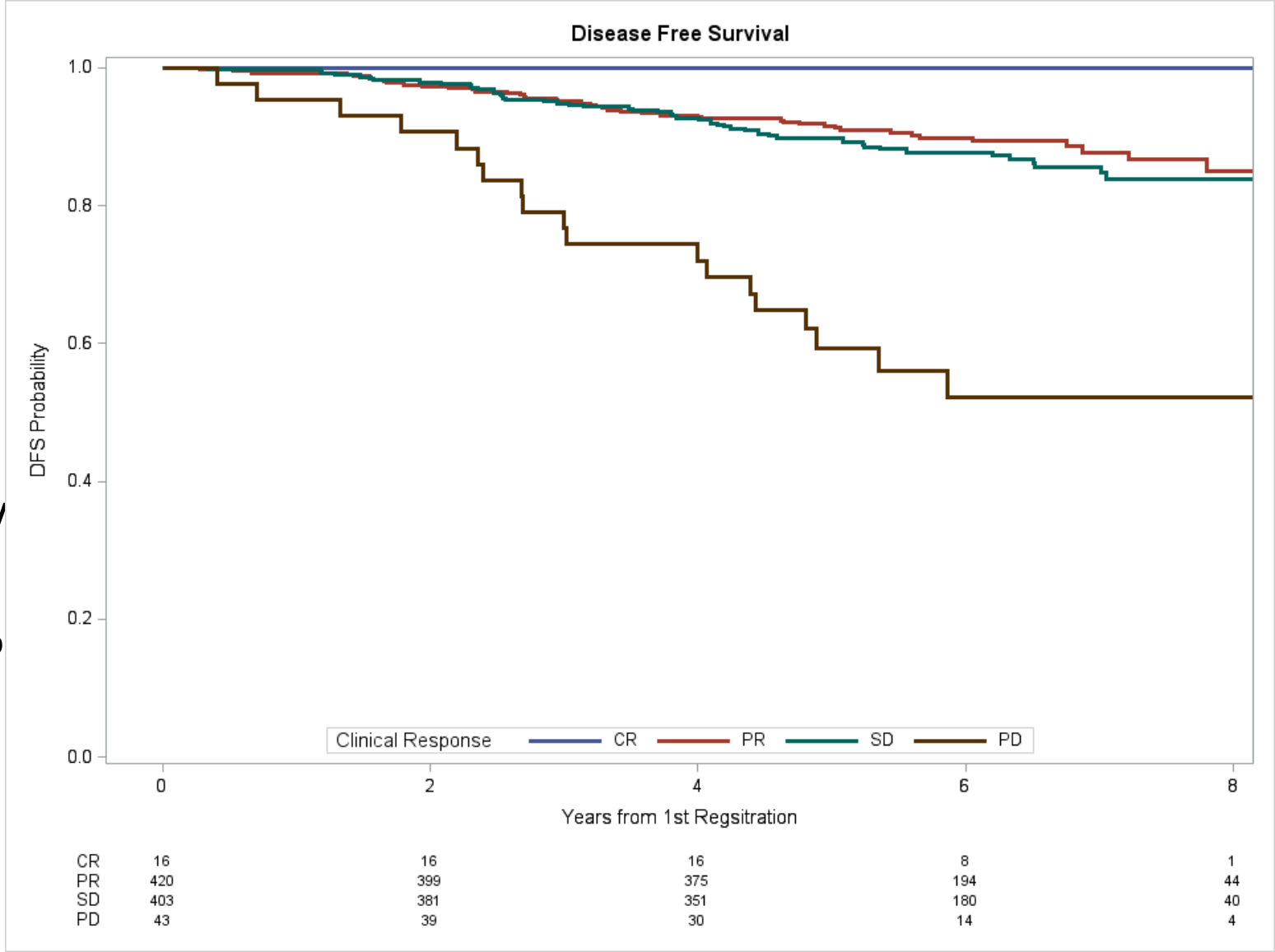
- Percentage of patients clinically responding to neoadjuvant LET
- DFS/OS in patients showing CR, PR, SD or PD response to neoadjuvant LET



DFS IN EACH GROUPS ACCORDING TO CLINICAL RESPONSE

DFS is defined as the time from the date of primary enrollment until the date of the first event (recurrence in the ipsilateral preserved breast, the ipsilateral chest wall, the regional lymph node, or distant organ metastasis, or secondary cancer without cutaneous basal cell carcinoma/spindle cell carcinoma, and uterine carcinoma *in situ* or all-cause deaths)

DFS in PD pts to NET were statistically significantly worse than CR, PR, SD pts (p<0.0001, hazard ratio 4.73 (95% CI:2.89-7.75).



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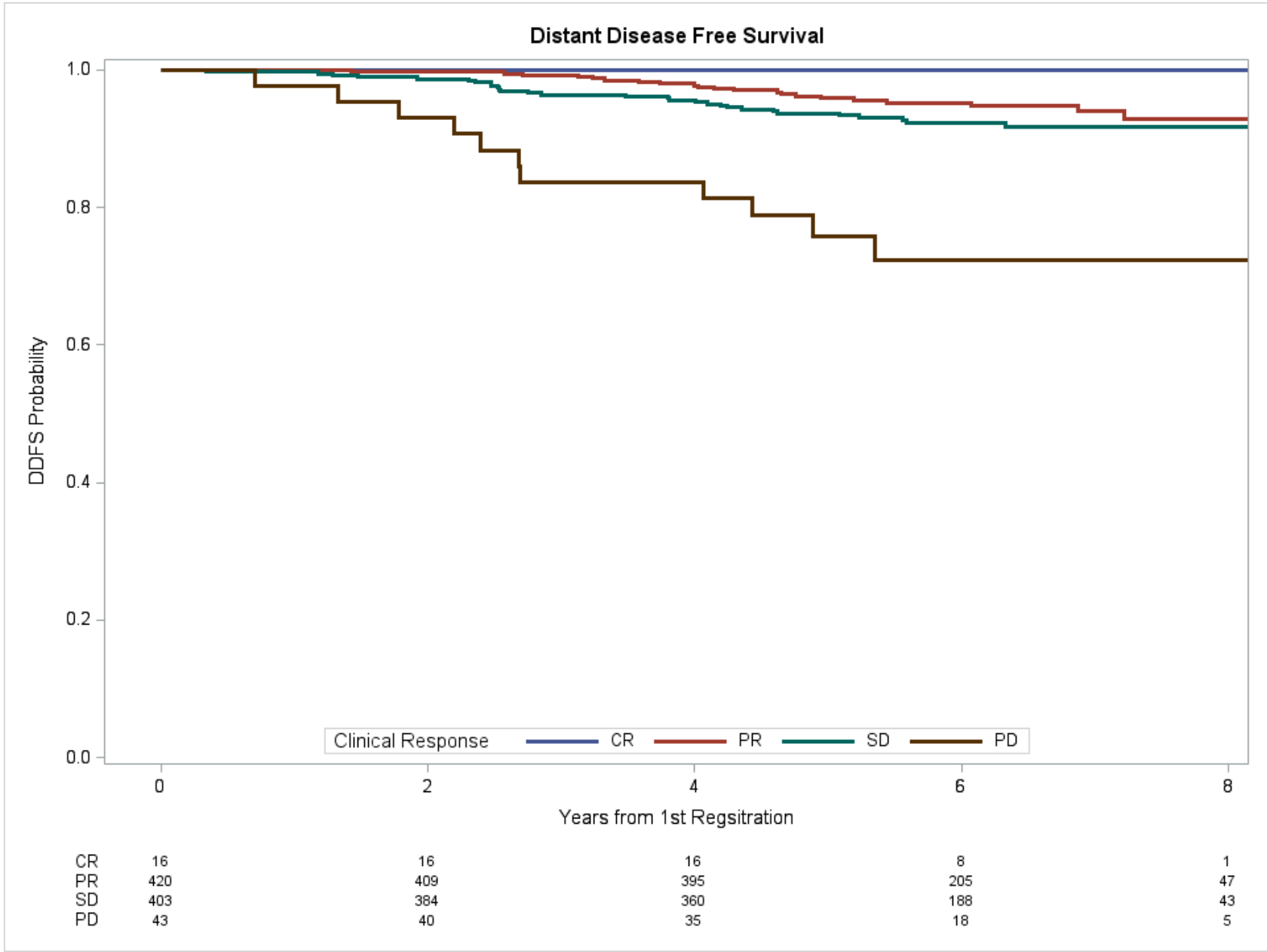
DDFS IN EACH GROUPS ACCORDING TO CLINICAL RESPONSE

DDFS is defined as the time from the date of primary enrollment until the date of the first event in distant organ (including bone, liver, lung, et al)

DDFS in PD pts to neoadjuvant ET were statistically significantly worse than CR, PR, SD pts ($p<0.001$, hazard ratio 4.83 (95% CI:2.52-9.29).



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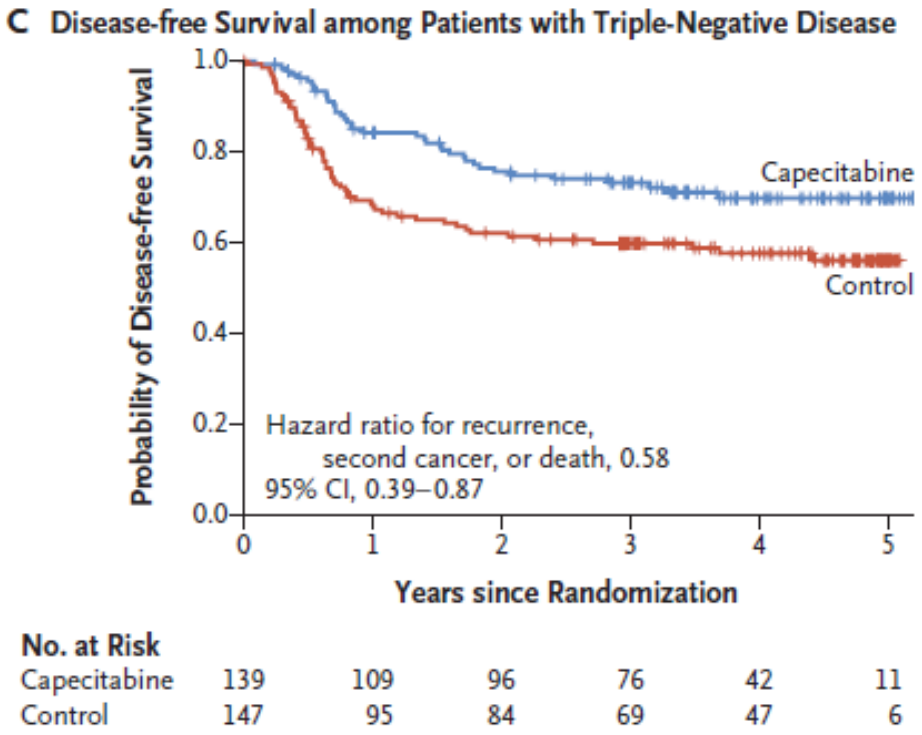
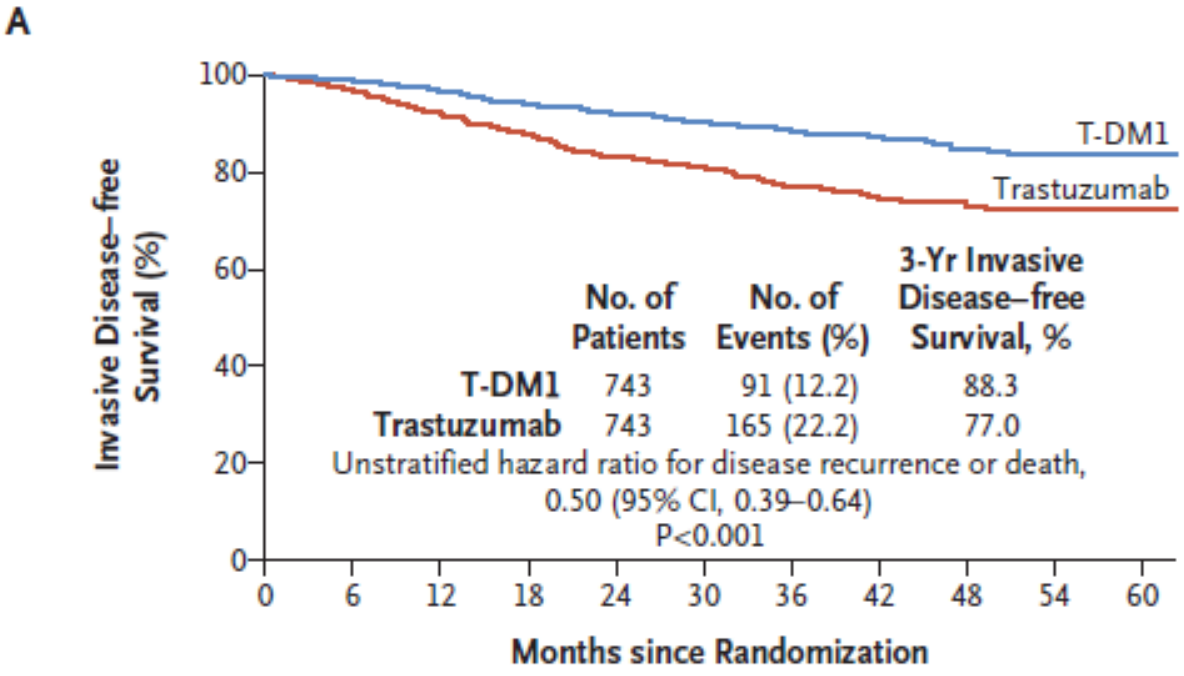
Respose guilded therapy by neoadjuvant chemotherapy

CREAT-X (TN)



Masuda N, etal. N Engl J Med 2017;376:2147-59

KATHERINE (HER2)



Minckwitz VG, et al. N Engl J Med 2018.

Respose guilded therapy by neoadjuvant chemotherapy

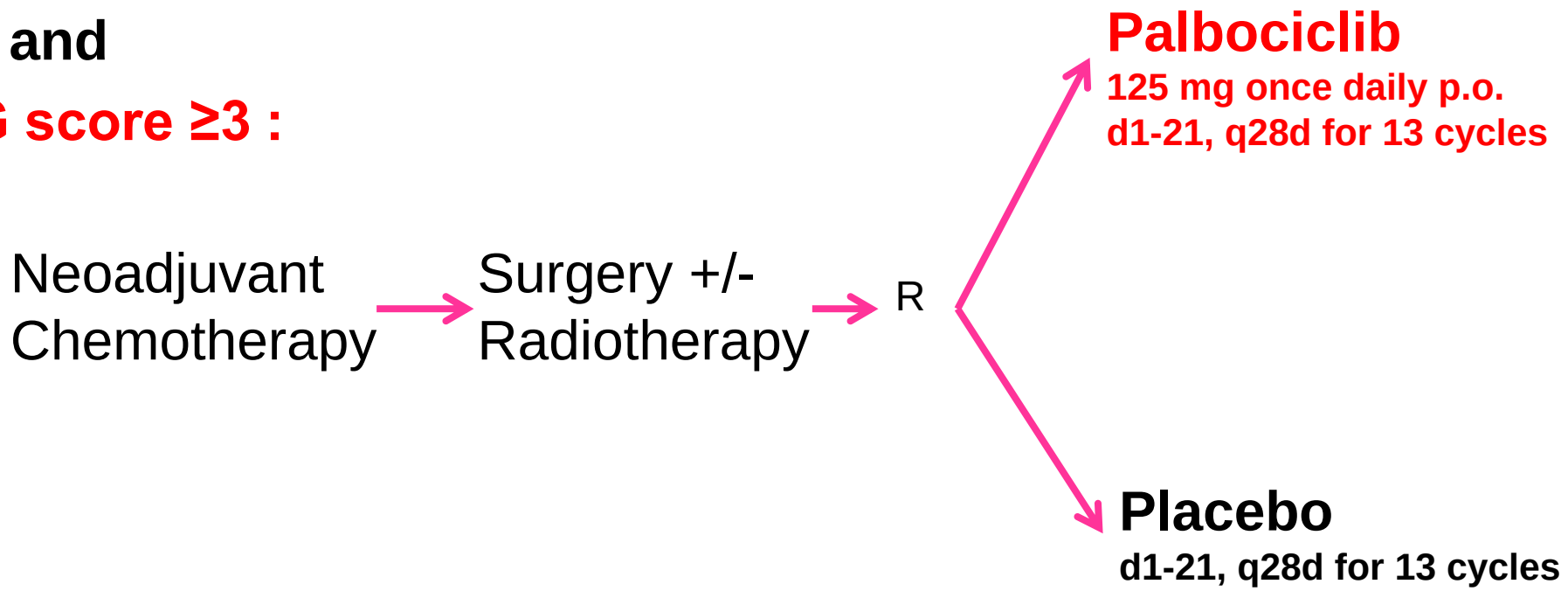
Penelope study

N=1250 pts. with

HR+/HER2- breast cancer

no pCR and

CPS-EG score ≥3 :



All patients will receive concommitantly endocrine therapy according to local standards

GBG GERMAN BREAST GROUP

NEOS Study design

Primary endpoint : DFS at each CL and L

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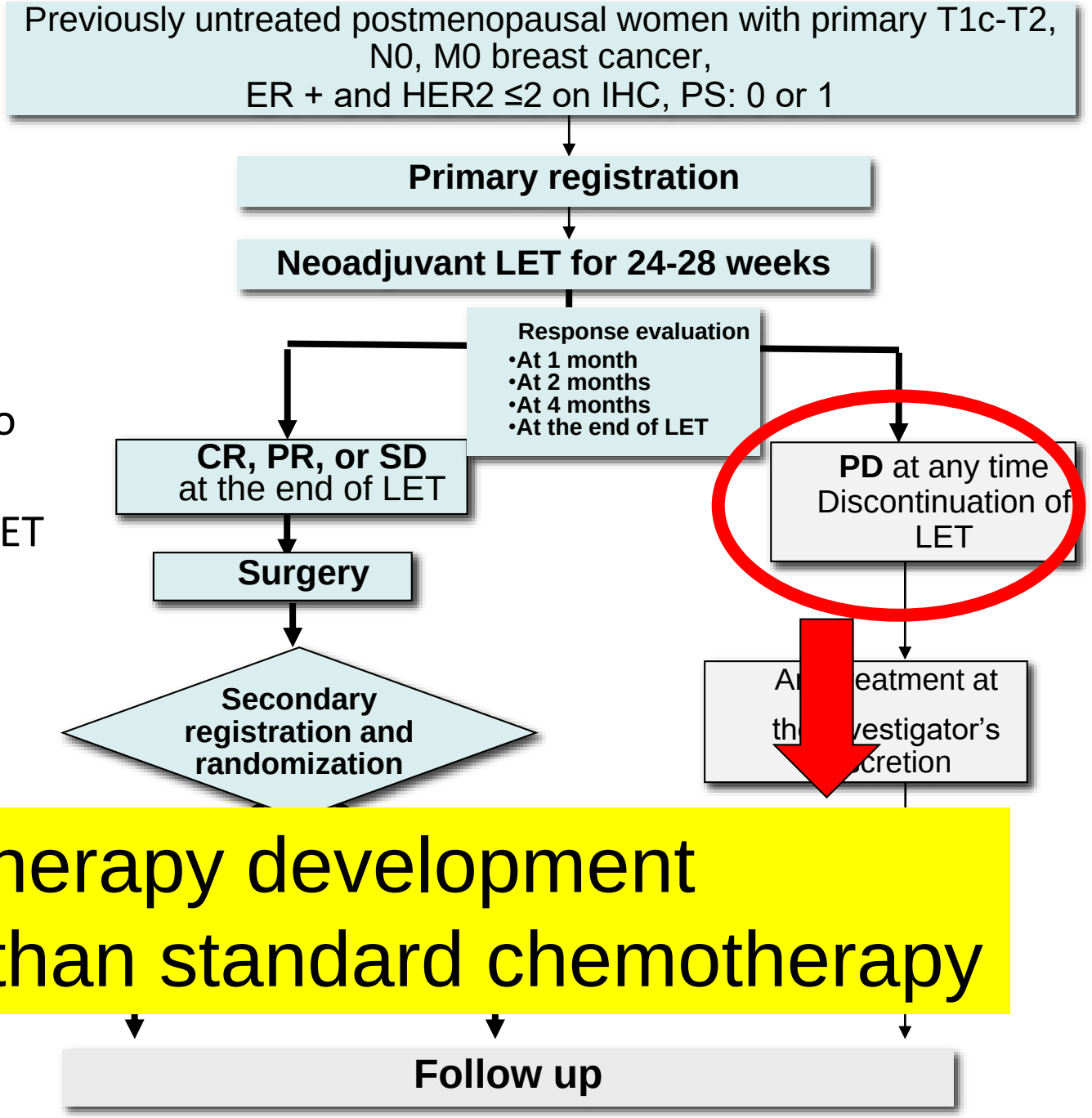

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Iwata H, et al. ESMO2018

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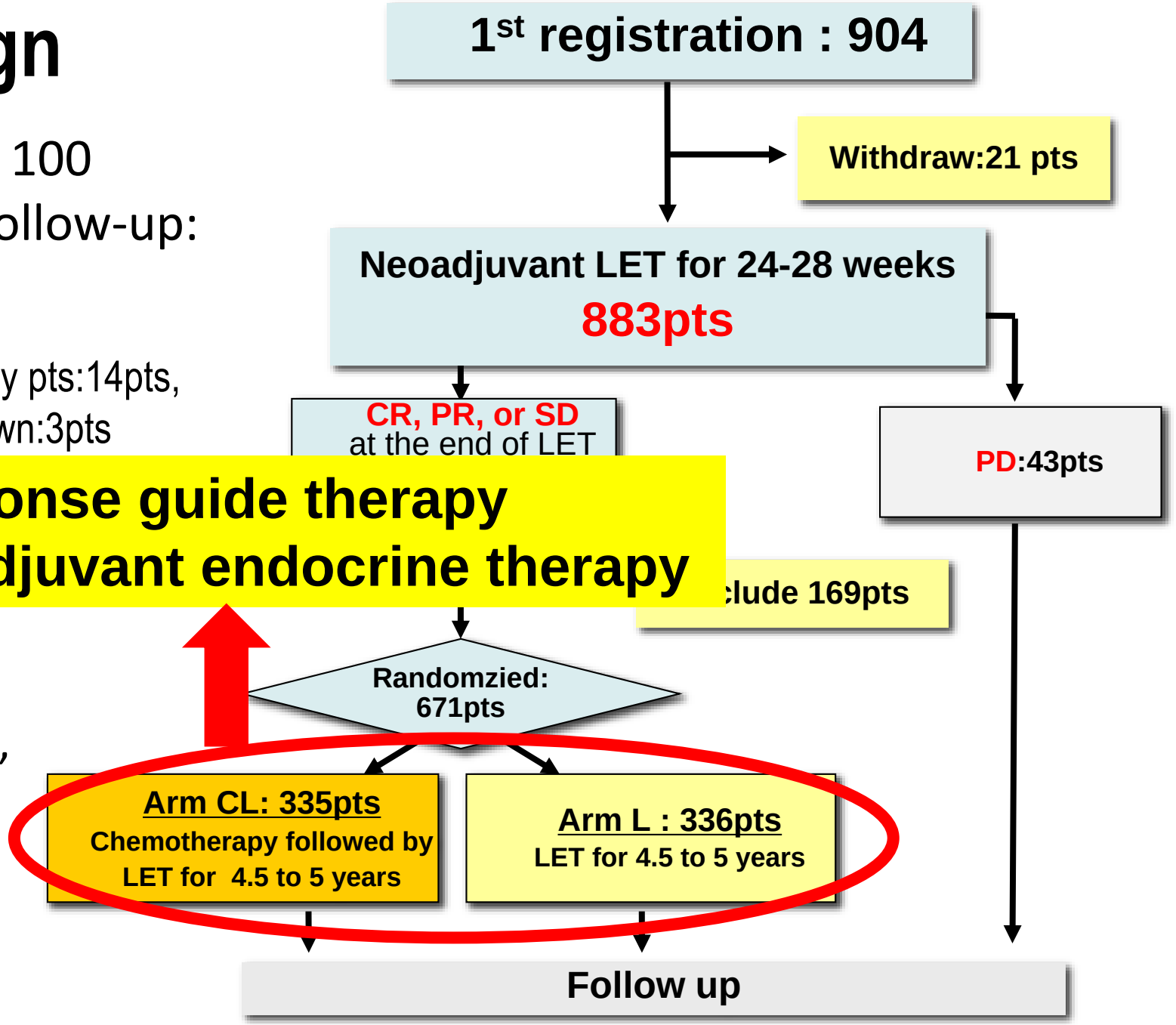
Secondary endp

- Percentage o clinically responding to neoadjuvant LET
- DFS/OS in patients showing CR, PR, SD or PD response to neoadjuvant LET

Response guide therapy using neoadjuvant endocrine therapy



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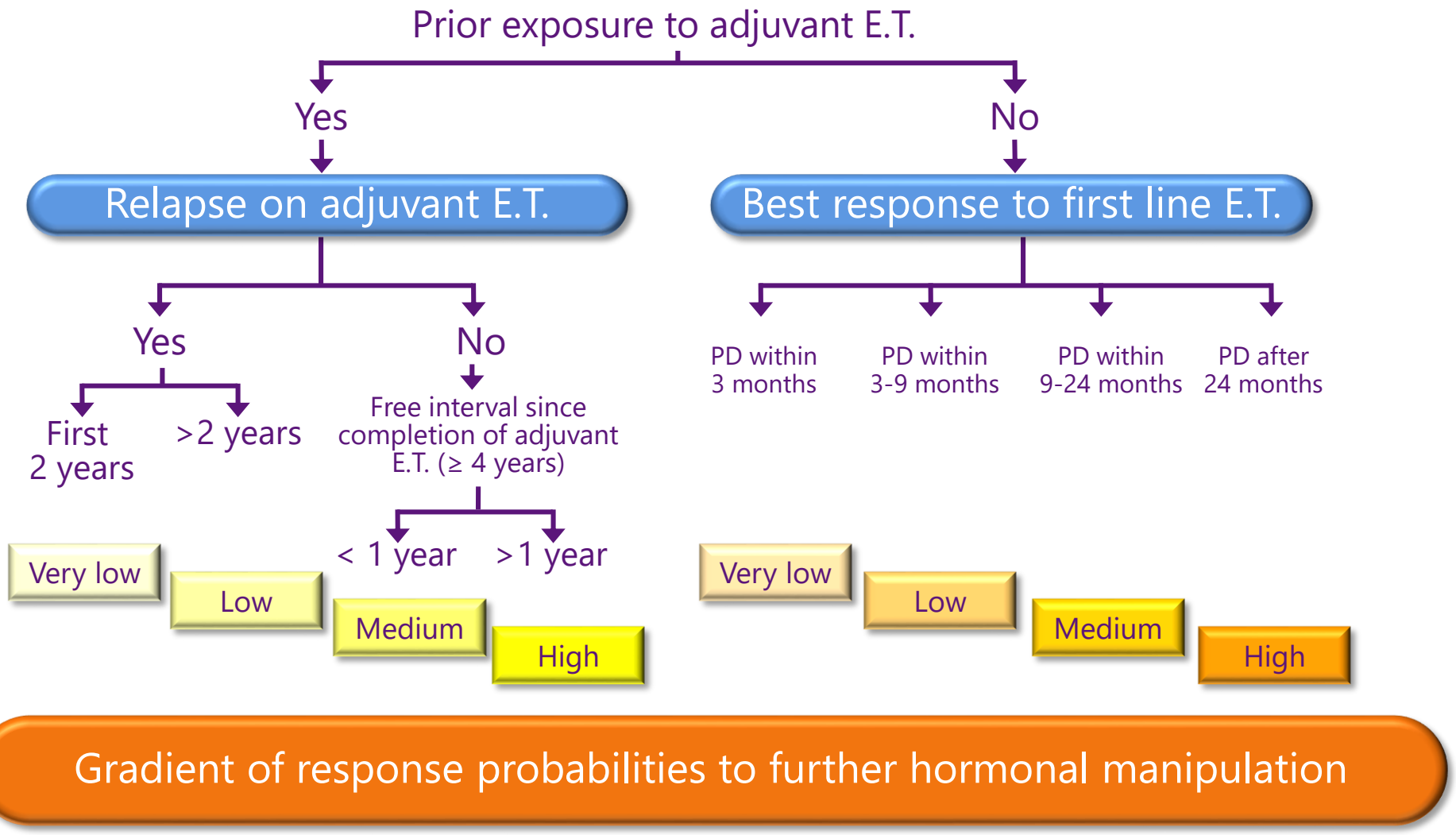
The responsibility of endocrine therapy for MBC



Piccart MJ. 2013 ABC-2 Consensus Session

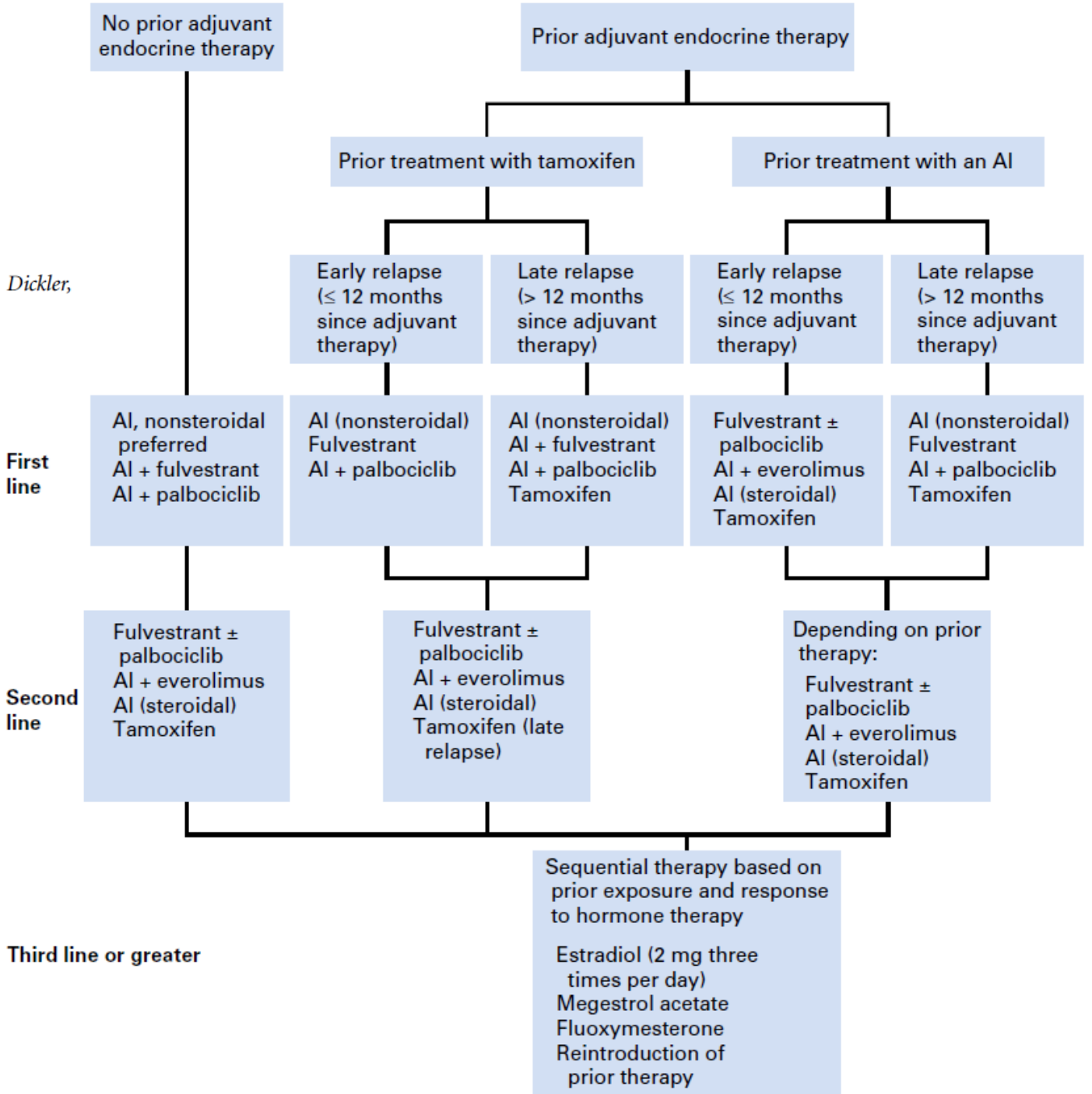
VOLUME 34 · NUMBER 25 · SEPTEMBER 1, 2016

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline

Hope S. Rugo, R. Bryan Rumble, Erin Macrae, Debra L. Barton, Hannah Klein Connolly, Maura N. Dickler, Lesley Fallowfield, Barbara Fowble, James N. Ingle, Mohammad Jahanzeb, Stephen R.D. Johnston, Larissa A. Korde, James L. Khatcheressian, Rita S. Mehta, Hyman B. Muss, and Harold J. Burstein

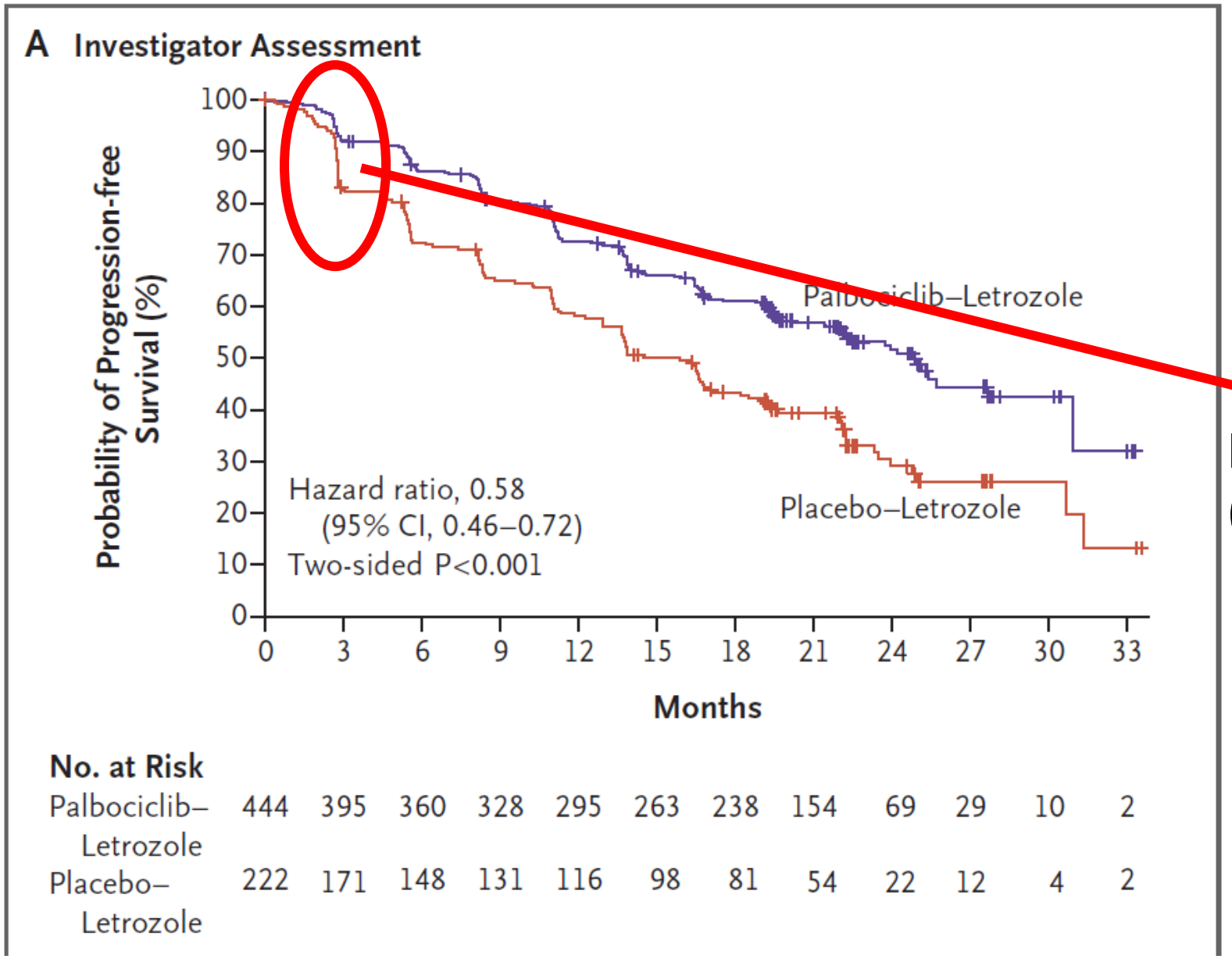
Fig 1. Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of pal-



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 17, 2016 VOL. 375 NO. 20

Palbociclib and Letrozole in Advanced Breast Cancer

Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D., Karen Gelmon, M.D., Nadia Harbeck, M.D., Ph.D., Oleg N. Lipatov, M.D., Janice M. Walshe, M.D., Stacy Moulder, M.D., Eric Gauthier, Pharm.D., Ph.D., Dongrui R. Lu, M.Sc., Sophia Randolph, M.D., Ph.D., Véronique Diéras, M.D., and Dennis J. Slamon, M.D., Ph.D.



Primary resistant cases to LET (about 20%)

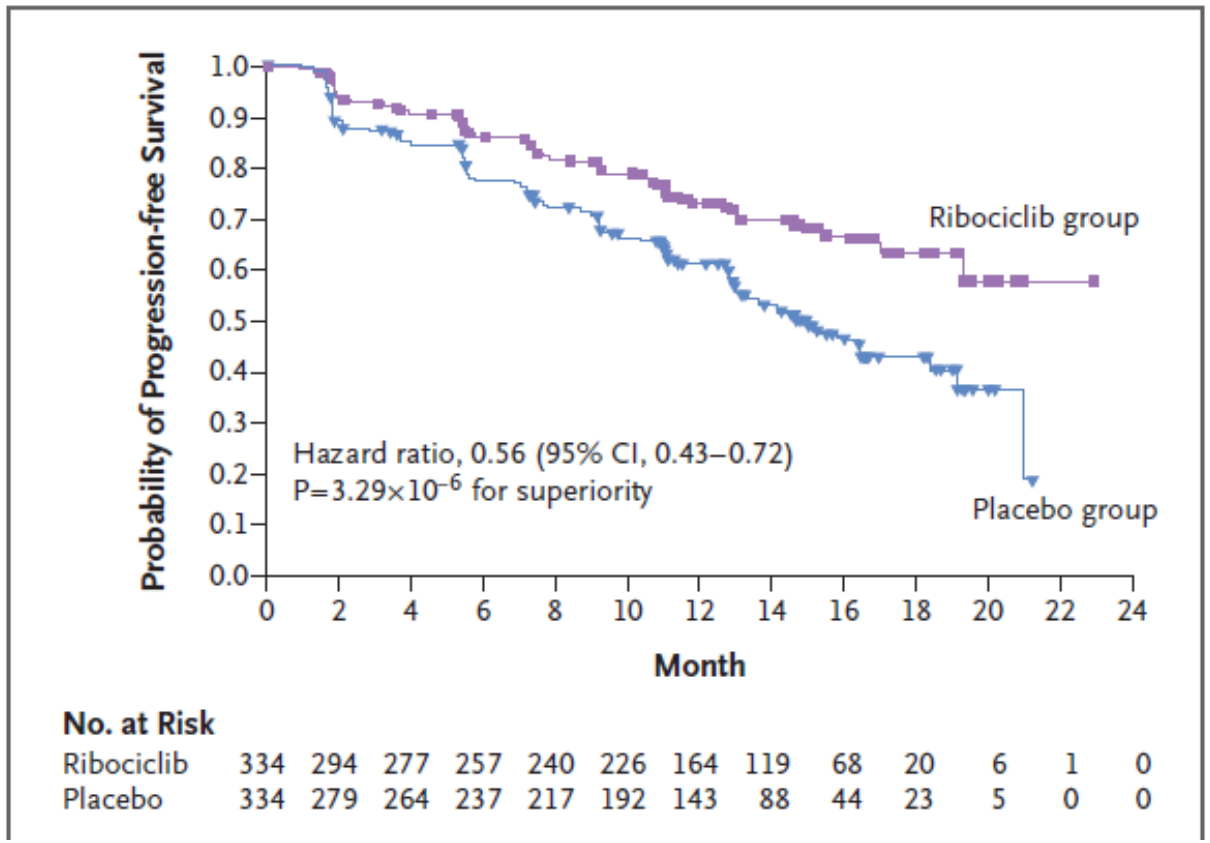
Improve PFS by Palbociclib

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

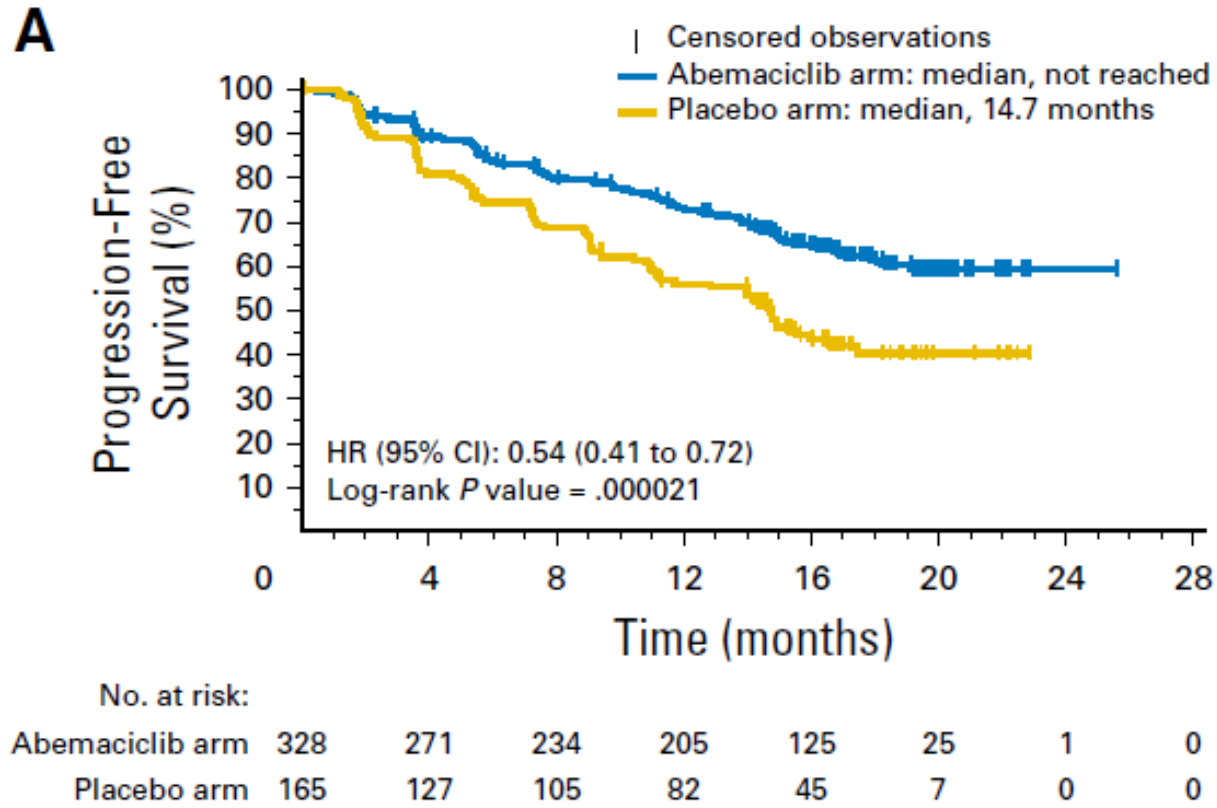
G.N. Hortobagyi, S.M. Stemmer, H.A. Burris, Y.-S. Yap, G.S. Sonke, S. Paluch-Shimon, M. Campone, K.L. Blackwell, F. André, E.P. Winer, W. Janni, S. Verma, P. Conte, C.L. Arteaga, D.A. Cameron, K. Petrakova, L.L. Hart, C. Villanueva, A. Chan, E. Jakobsen, A. Nusch, O. Burdaeva, E.-M. Grischke, E. Alba, E. Wist, N. Marschner, A.M. Favret, D. Yardley, T. Bachelot, L.-M. Tseng, S. Blau, F. Xuan, F. Souami, M. Miller, C. Germa, S. Hirawat, and J. O'Shaughnessy



N Engl J Med 2016;375:1738-48.

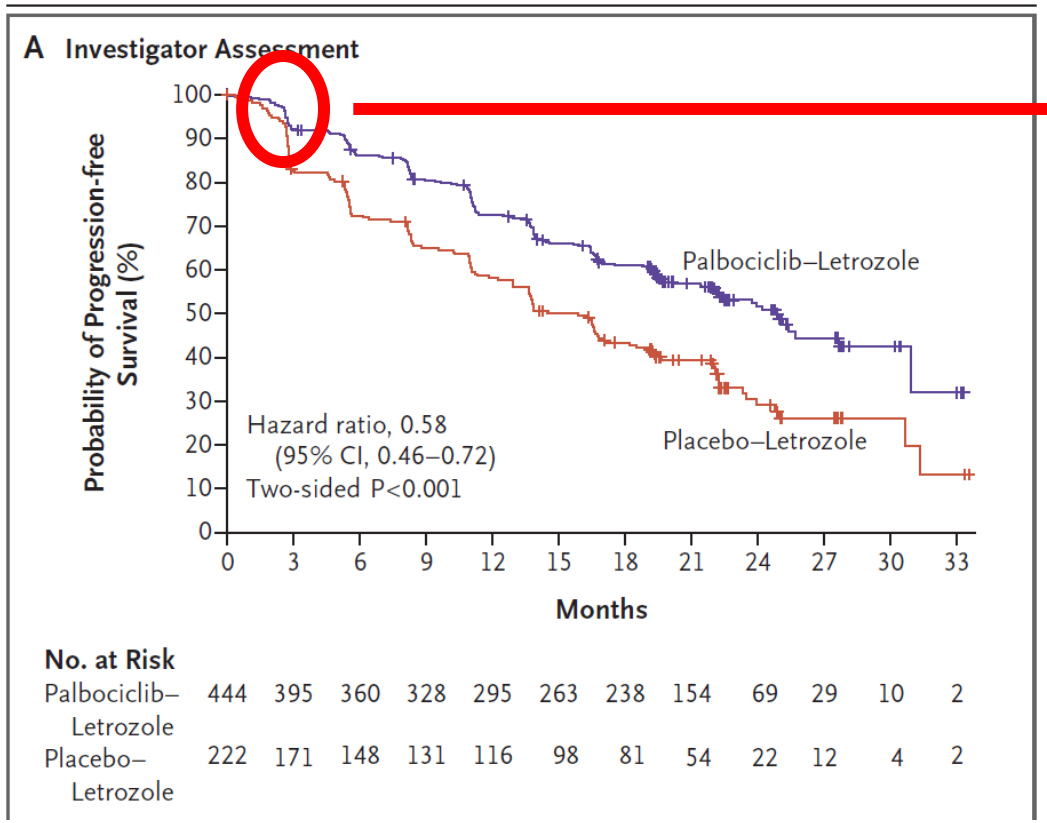
MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer

Matthew P. Goetz, Masakazu Toi, Mario Campone, Joohyuk Sohn, Shani Paluch-Shimon, Jens Huober, In Hae Park, Olivier Trédan, Shin-Cheh Chen, Luis Manso, Orit C. Freedman, Georgina Garnica Jaliffe, Tammy Forrester, Martin Frenzel, Susana Barriga, Ian C. Smith, Nawel Bourayou, and Angelo Di Leo



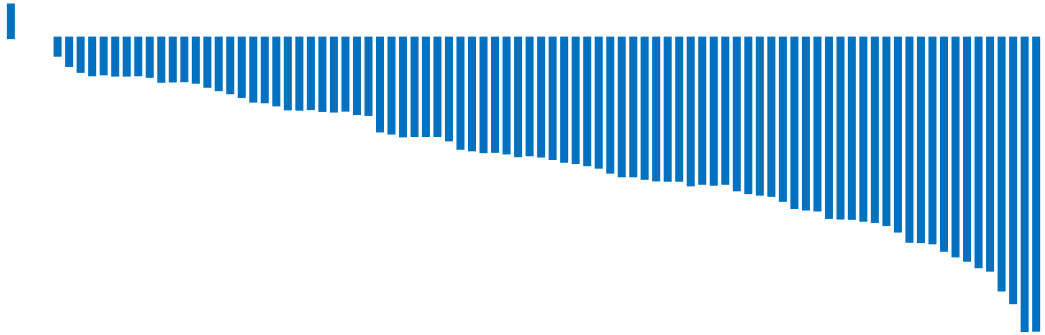
J Clin Oncol 35:3638-3646. © 2017

Primary endocrine resistance



Resistance to AI+Palbociclib (about 10%)

Primary resistance cases to endocrine + CDK4/6 inhibitor is *only 1%* in neoMONARCH

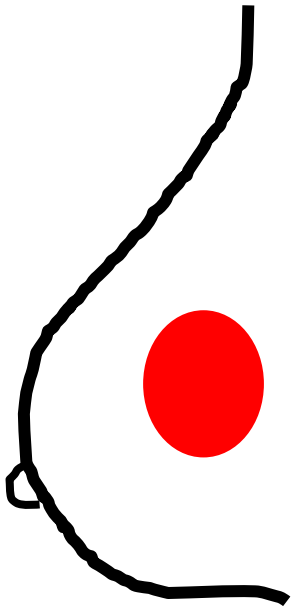


Resistance cases

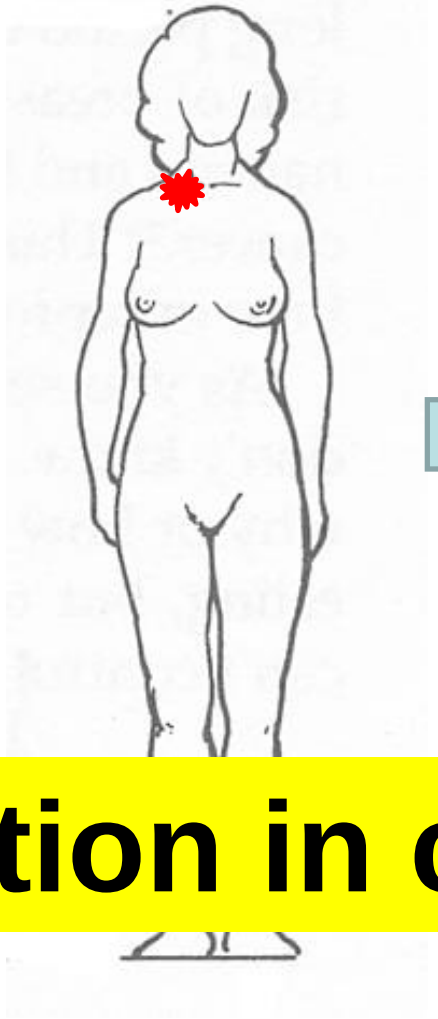
	Endocrine alone (AI)	AI + CDK4/6 inhibitor
PBC	5%	1%
MBC	20%	10%

What happen?

Primary

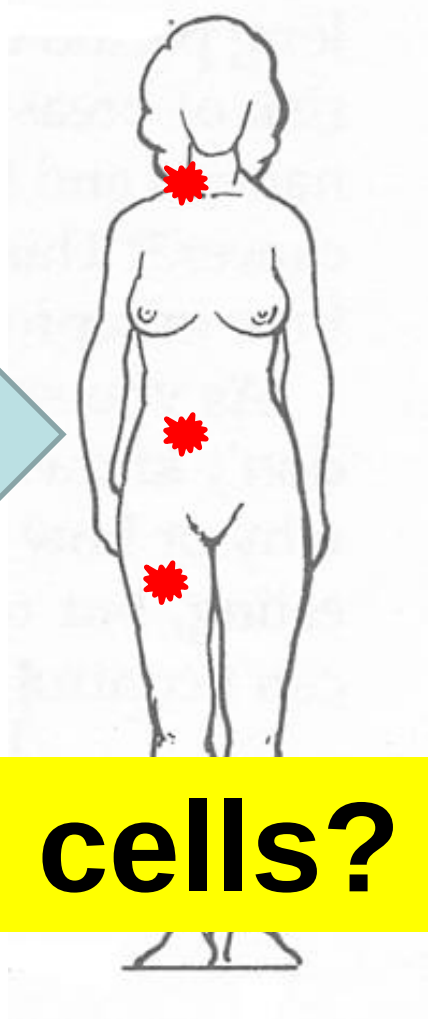


Single metastatic



Progress

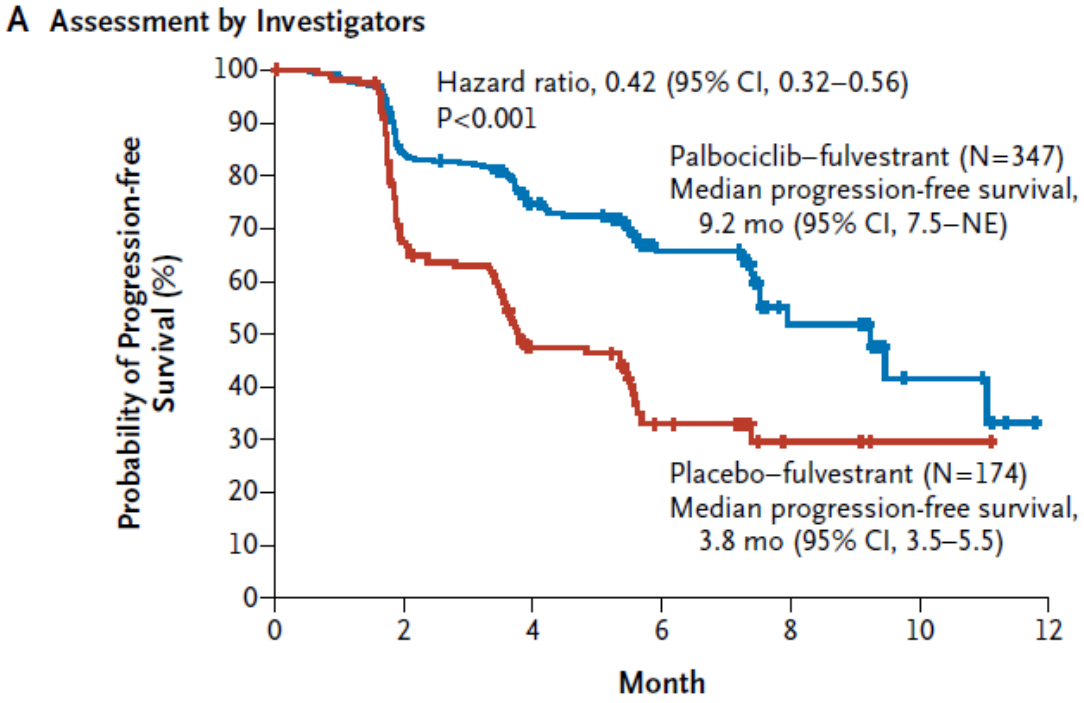
Multiple metastasis



Molecular alteration in cancer cells?

Acquired resistance (Paloma 3 study)

Target population : non steroidal AI (nsAI) resistance patients



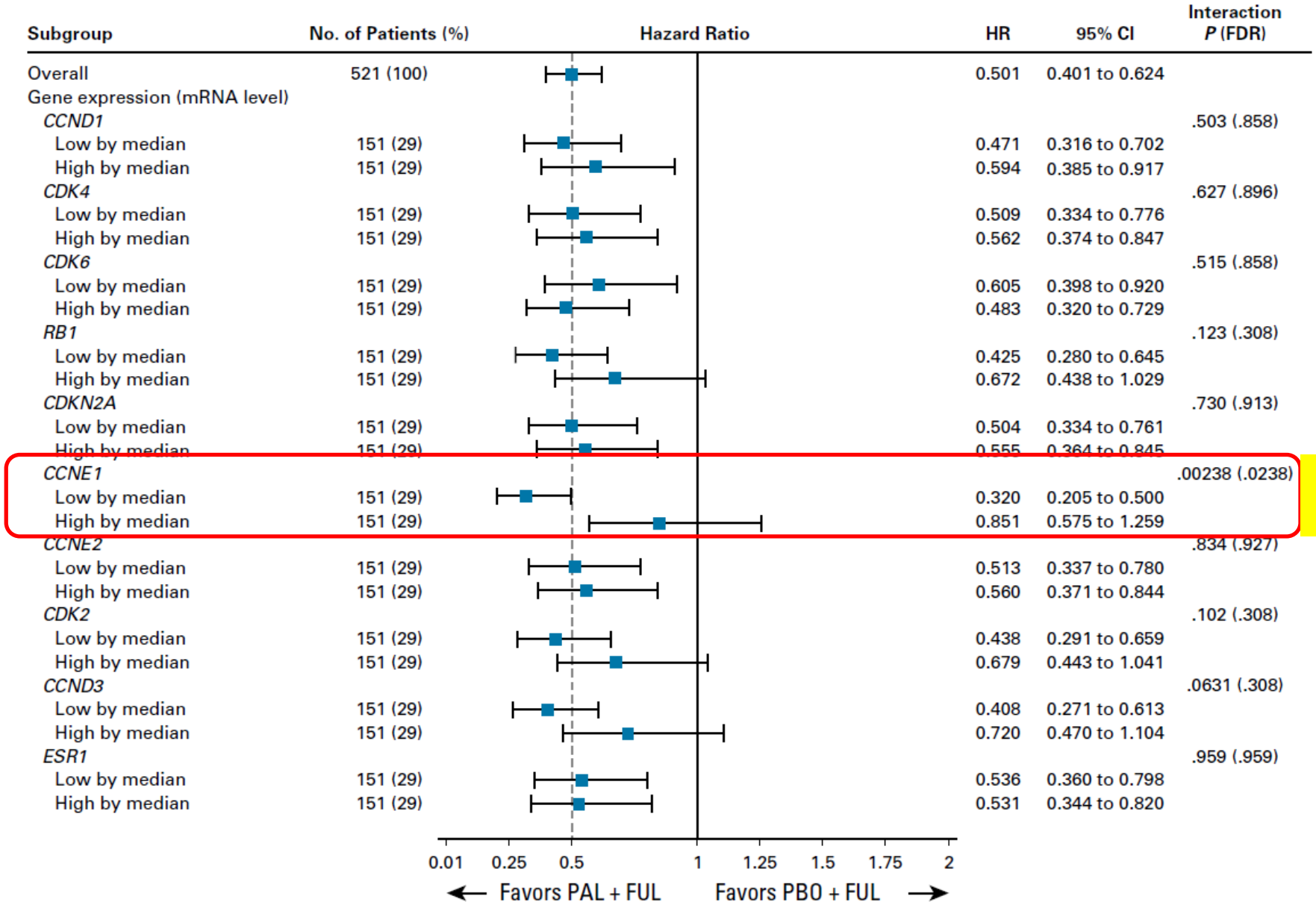
No. at Risk						
Palbociclib–fulvestrant	347	279	132	59	16	6
Placebo–fulvestrant	174	109	42	16	6	1

Resistance to FUL (about 40%)

Improve the PFS by Palbociclib (about 20%)

What is predictive marker of Palbociclib for nsAI resistance patients ?

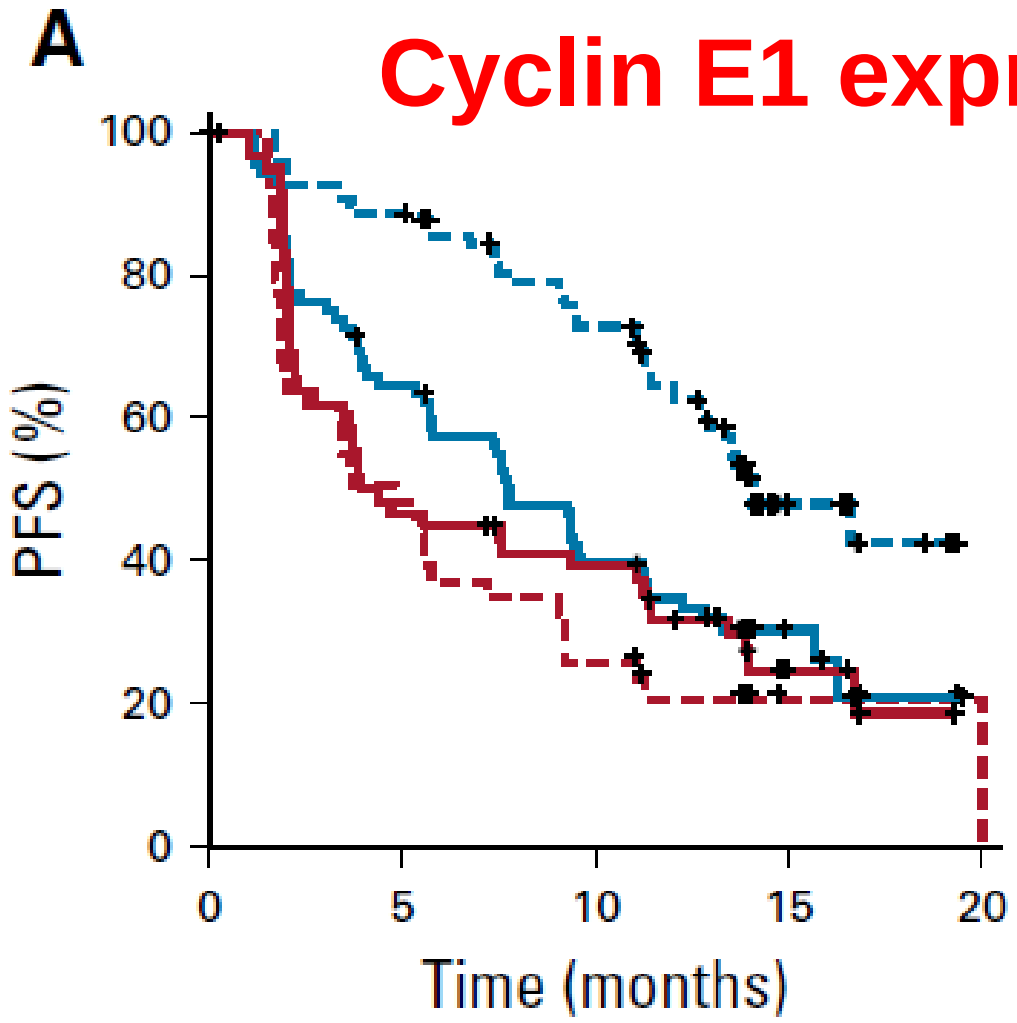
Association of cell cycle pathway gene expression and efficacy of PAL in combination with FUL



***CCNE1* Low vs High**

Turner N, et al. JCO 37; 2019

Cyclin E1 expression Low vs High



Low: PAL + FUL (n = 103; mPFS, 14.1 months)
Low: PBO + FUL (n = 48; mPFS, 4.8 months)
High: PAL + FUL (n = 91; mPFS, 7.6 months)
High: PBO + FUL (n = 60; mPFS, 4.0 months)

Low: HR, 0.32 (95% CI, 0.20 to 0.50)
High: HR, 0.85 (95% CI, 0.58 to 1.26)
Interaction $P = .00238$

Cyclin E1 Expression and Palbociclib Efficacy in Previously Treated Hormone Receptor–Positive Metastatic Breast Cancer

Nicholas C. Turner, MD, PhD[1]; Yuan Liu, PhD[2]; Zhou Zhu, PhD[2]; Sherene Loi, MD, PhD[3]; Marco Colleoni, MD[4]; Sibylle Loibl, MD, PhD[5]; Angela DeMichele, MD, MSCE[6]; Nadia Harbeck, MD, PhD[7]; Fabrice André, MD, PhD[8]; Mohamed Amine Bayar, MSc[8]; Stefan Michiels, PhD[8]; Zhe Zhang, MS[2]; Carla Giorgetti, PhD[9]; Monica Arnedos, MD[8]; Cynthia Huang Bartlett, MD[10]; and Massimo Cristofanilli, MD[11]

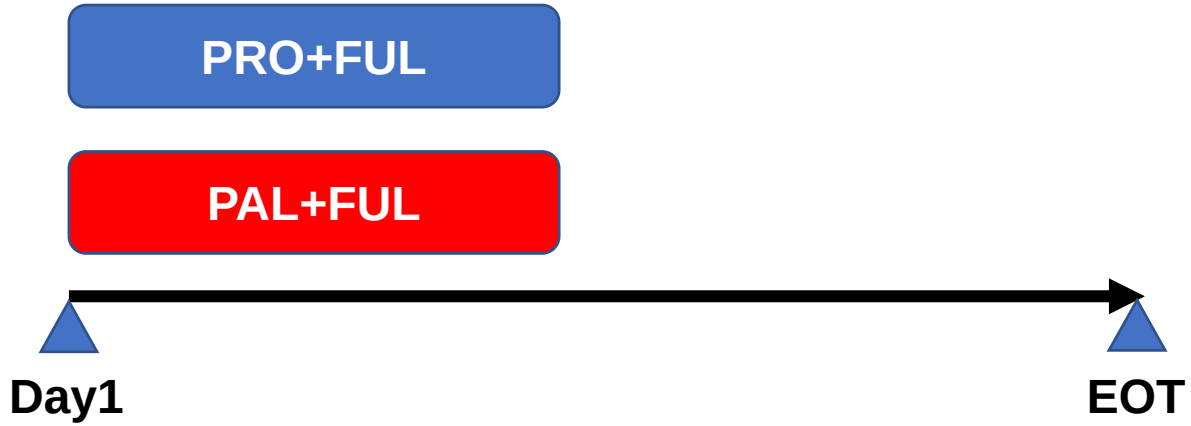
High CCNE1 mRNA expression was associated with relative resistance to palbociclib

J Clin Oncol 37. © 2019 by American Society of Clinical Oncology

Acquired resistance of FUL + Palbociclib

Acquired resistance to palbociclib + FUL

Paloma3



Total paired day1 and EOT plasma sample N=194

87 genes associated with **mammalian cell cycle**, **ER signaling**, or **breast cancer biology** were hybridized to the library. All coding regions were covered with the exception of 7 genes (***BRAF, EGFR, KRAS, NOTCH1, NOTCH2, NOTCH3,*** and ***PIK3CA***) where only hotspot mutations were included.

AKT1	CDC25A	E2F2	FBXW7	HDAC5	MYCL	PA2G4	PPP2CB	SMAD4
AKT2	CDH1	E2F3	FOXA1	HRAS	MYCN	PELP1	PPP2R1A	TBL1XR
BCAR1	CDH2	E2F4	GATA3	IGF1	NOTCH1	PGR	PTEN	TFDP1
BRAF	CDK4	E2F5	GPER1	KRAS	NOTCH2	PHB2	PPP2R1B	TFF1
BRCA1	CDK6	E2F6	GPS2	MAP2K4	NOTCH3	PIK3CA	RB1	TP53
CCND1	CDKN1A	EGFR	GSK3B	MAP3K1	NROB1	PIK3R1	RBL1	TPRX1
CCND2	CDKN1B	ERBB2	HDAC1	MED1	NROB2	PPP1CA	RBL2	WNT7A
CCND3	CDKN2A	ESR1	HDAC2	MTA1	NRAS	PPP1CB	RUNX	
CCNE1	CDKN2B	ESR2	HDAC3	MYB	NRG1	PPP1CC	SKP1	
CCNE2	E2F1	FABPS	HDAC4	MYC	NRIP1	PPP2CA	SMAD3	

In addition, **matched samples** were analyzed using droplet digital polymerase chain reaction (**ddPCR**, Bio-Rad® QX200) **for *PIK3CA* and *ESR1* variants detected at baseline**

Change From Baseline in ctDNA Mutation Frequency

	PAL + FUL (n=127)			PBO + FUL (n=67)		
Gene	Day 1, n (%)†	EOT, n (%)†	*P* value*	Day 1, n (%)†	EOT, n (%)†	*P* value
PIK3CA	47 (37)	51 (40)	0.42	19 (28)	22 (33)	0.45
ESR1	36 (28)	45 (35)	0.15	19 (28)	24 (36)	0.18
TP53	30 (24)	33 (26)	0.45	23 (34)	25 (37)	0.68
RB1	2 (2)	9 (7)	0.02	2 (3)	2 (3)	1
PTEN	5 (4)	7 (6)	0.48	3 (4)	3 (4)	1
AKT1	7 (6)	7 (6)	NA	2 (3)	2 (3)	NA

- **Gene level mutation analysis of EOT plasma revealed no significant difference between palbociclib plus fulvestrant vs placebo plus fulvestrant, with the exception of *RB1*.**
  - **The most commonly observed mutations were in *PIK3CA*, *ESR1*, and *TP53***

CONCLUSIONS

- The low prevalence of mutations in cell cycle control genes at EOT suggests that mutations in cell cycle genes may not be a common mechanism of resistance to CDK4/6 inhibitors in HR+/HER2– advanced breast cancer previously treated with endocrine therapy.
- No difference in genomic landscape was observed between palbociclib plus fulvestrant and fulvestrant plus placebo at the time of progression, which suggests that the main mechanism of disease progression is endocrine resistance.

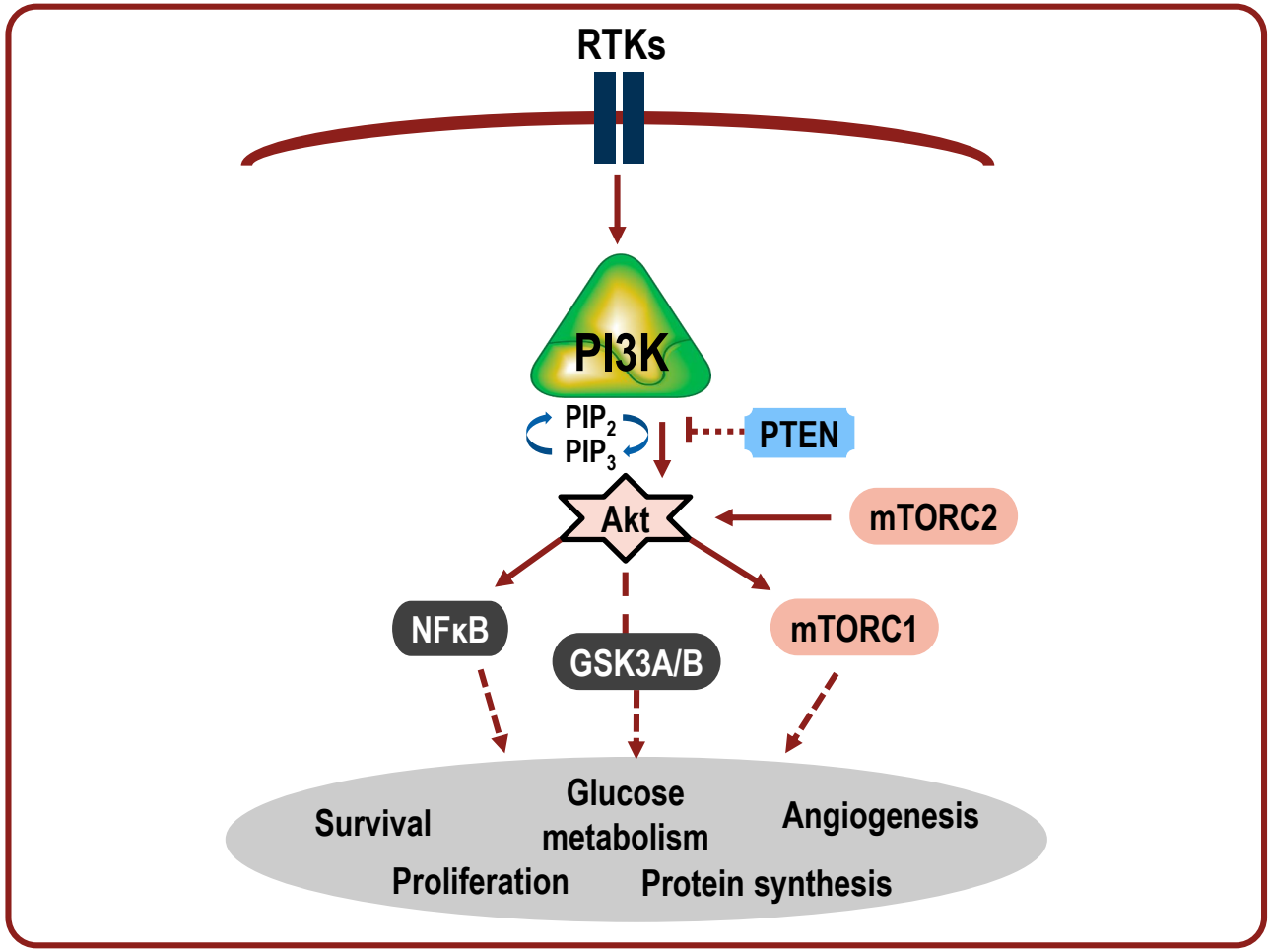
Endocrine resistance mechanism

PIK3CA mutation

ESR1 mutation

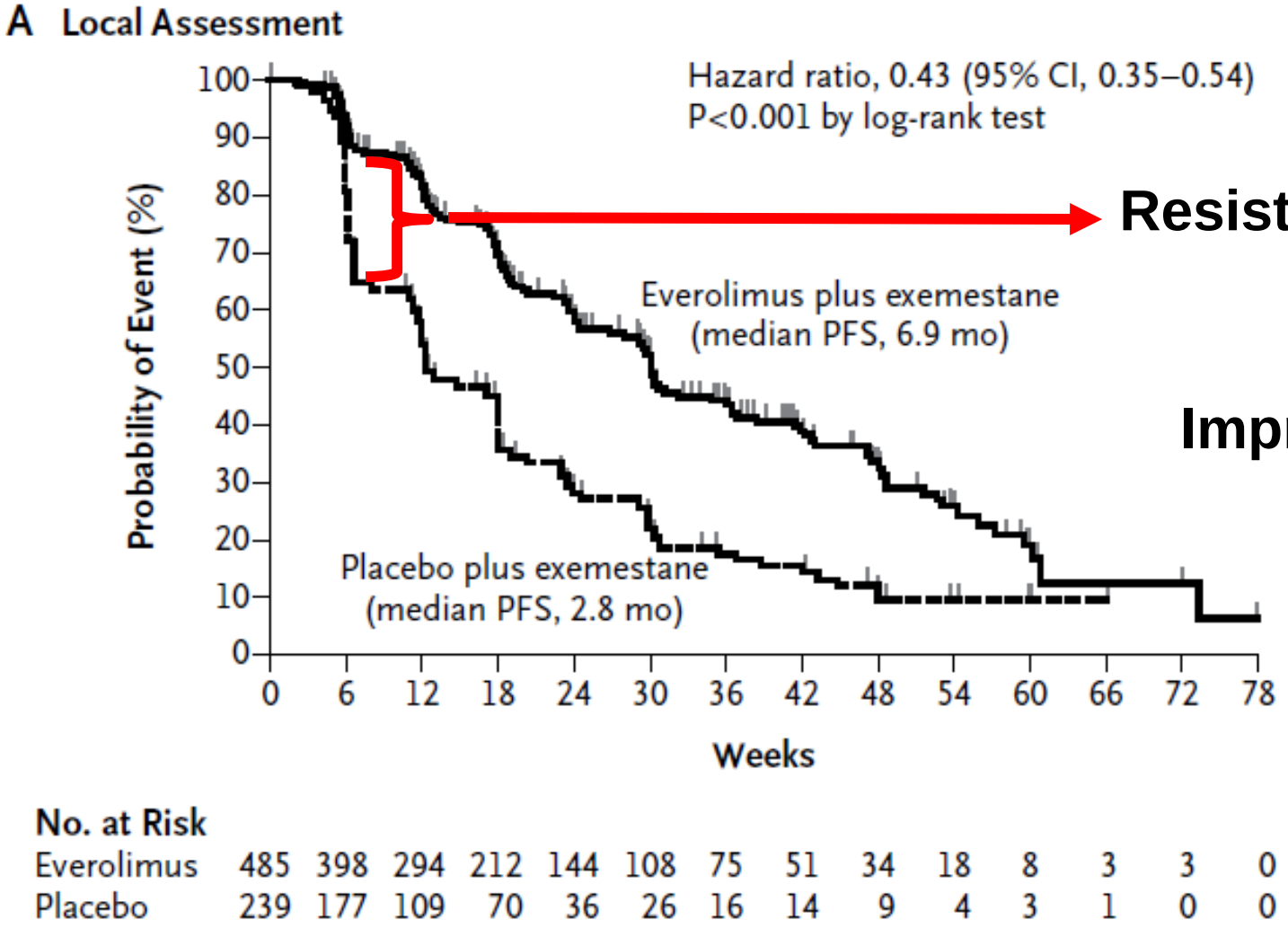
The PI3K pathway

- PI3K is involved in the production of PIP_3, which activates Akt[1]
- **PI3K pathway hyperactivation is implicated in malignant transformation, cancer progression and endocrine therapy resistance[1–4]**
- Around 40% of patients with HR+, HER2– breast cancer present an activating tumor mutation of *PIK3CA*[5,6] that leads to PI3K activation



1. Miller TW, et al. *J Clin Oncol* 2011;29:4452–4461; 2. Saal LH et al. *Proc Natl Acad Sci U S A* 2007;104:7564–7569; 3. Hosford SR, Miller TW. *Pharmgenomics Pers Med*. 2014;7:203–215; 4. Shaw RJ & Cantley LC. *Nature*. 2006;441:424–430; 5. The Cancer Genome Atlas Network. Nature 2012;490:61–70; 6. Mollon L, *et al. AACR* 2018 (poster 2107).

Acquired resistance cases to nsAI



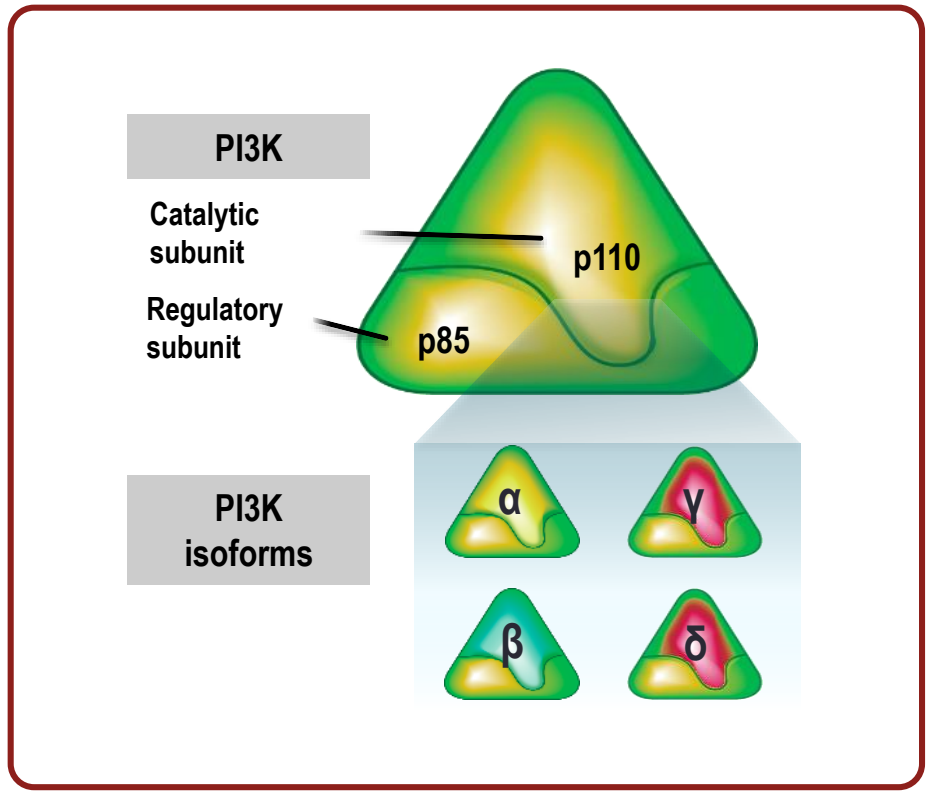
Resistance to Exemestane (about 40%)

Improve the PFS by mTOR inhibitor

HR:0.43

PIK3CA mutations and Alpelisib

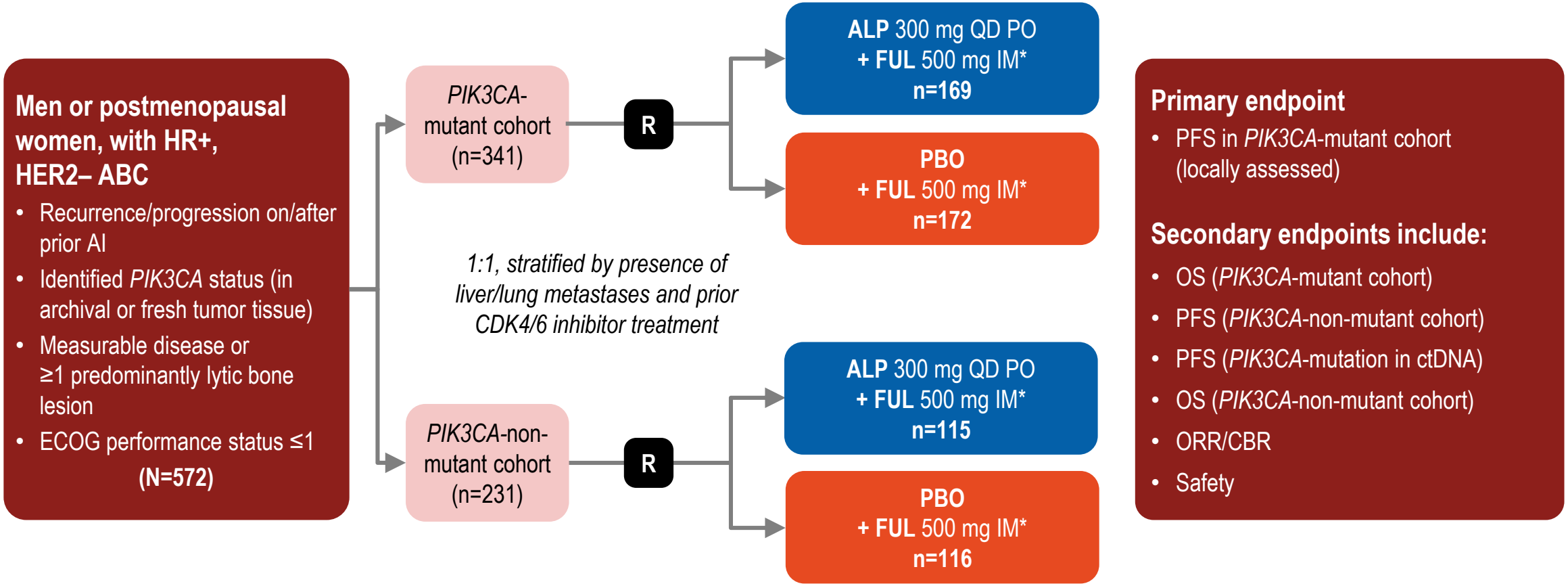
- PI3K includes catalytic and regulatory subunits; *PIK3CA* encodes the α-isoform of catalytic subunit[1,2]
  - Activation of this subunit can lead to pathway hyperactivation
- Pan-PI3K inhibitors target multiple isoforms of PI3K, leading to excess toxicities and marginal efficacy[3–5]
- **Alpelisib (BYL719) is a specific inhibitor of the PI3K α-isoform[6]**
- Alpelisib has demonstrated antitumor activity in preclinical models harboring *PIK3CA* alterations[6]



There is a strong rationale for targeting the α-isoform of PI3K in patients with a *PIK3CA* mutation

1. Engelman JA. Nat Rev Cancer 2009;9:550–562; 2. Janku F. Cancer Treat Rev 2017;59:93–101; 3. Baselga J, et al. J Clin Oncol 2018;36 (Suppl): LBA 1006; 4. Di Leo A, et al. Lancet Oncol 2018 19(1):87–100; 5. Baselga J, et al. Lancet Oncol 2017;18(7):904–916; 6. Fritsch C et al. Mol Cancer Ther 2014;13:1117–1129.

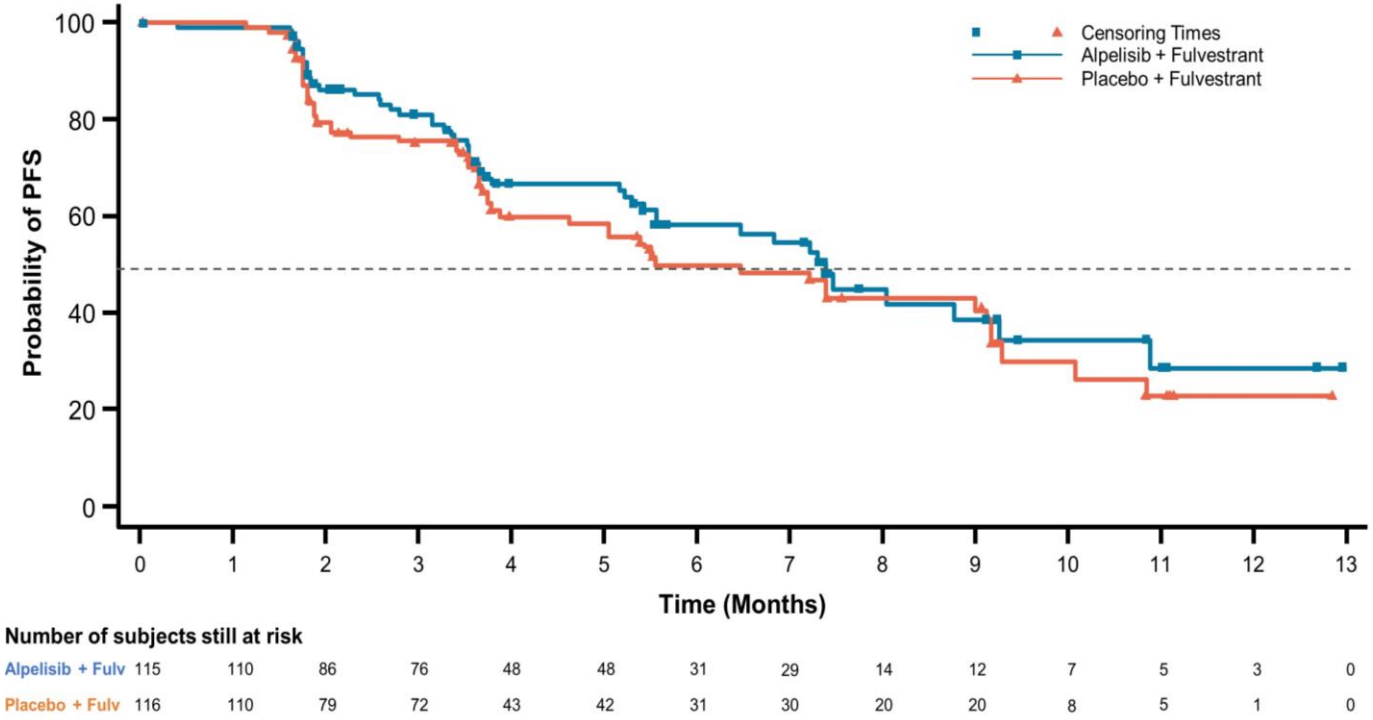
SOLAR-1: A Phase III randomized, controlled trial (NCT02437318)



*Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28 day cycles;

Proof of Concept: PFS in the *PIK3CA*-non-mutant cohort

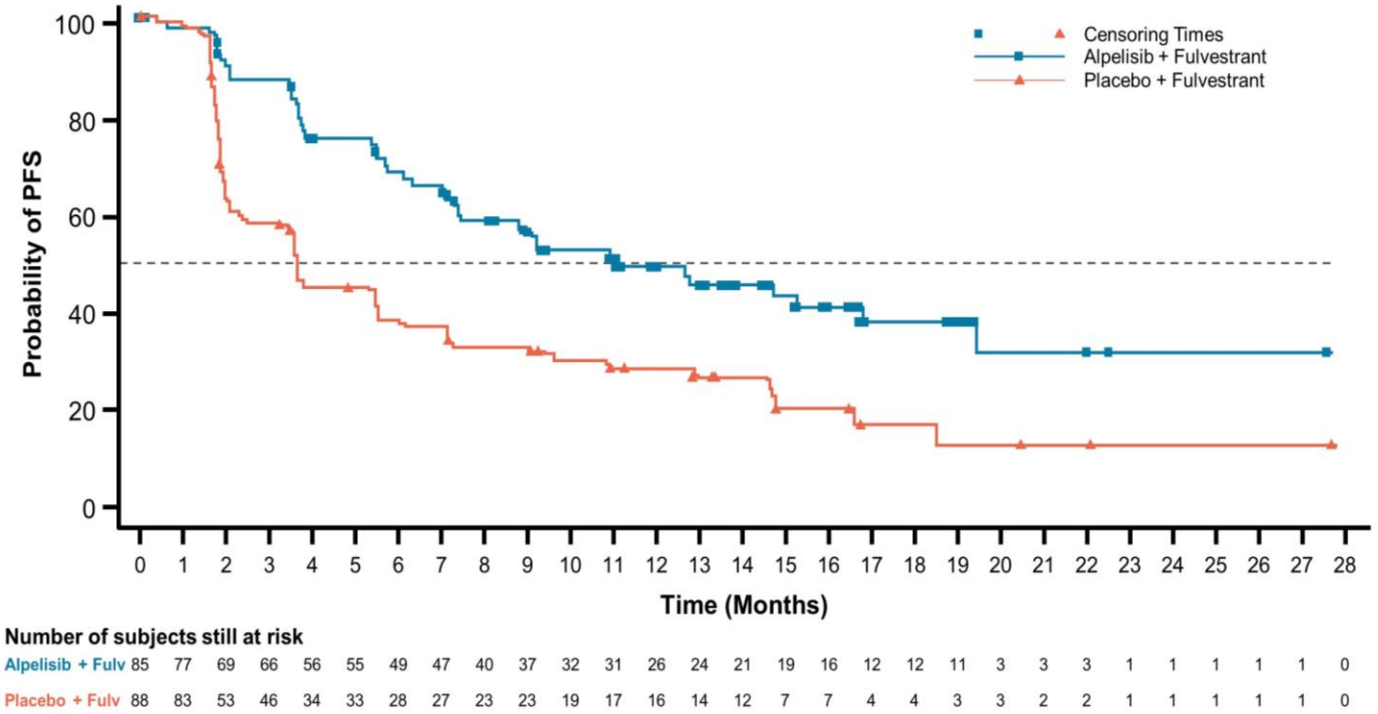
Proof of concept criteria were not met in the PIK3CA-non-mutant cohort



Data cut-off: Dec 23, 2016	Alpelisib + fulvestrant (N=115)	Placebo + fulvestrant (N=116)
Number of PFS events, n (%)	49 (42.6)	57 (49.1)
Progression	47 (40.9)	57 (49.1)
Death	2 (1.7)	0
Censored	66 (57.4)	59 (50.9)
Median PFS (95% CI)	7.4 (5.4–9.3)	5.6 (3.9–9.1)
HR (95% CI)	0.85 (0.58–1.25)	
Posterior probability HR<1, %	79.4	

- Proof of concept criteria: estimated hazard ratio ≤0.60 and posterior probability ≥90% that the hazard ratio was <1
- Patients with *PIK3CA*-non-mutant disease were followed up for safety alongside the *PIK3CA*-mutant cohort

BIRC audit: Centrally assessed PFS in the *PIK3CA*-mutant cohort



Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=85)	Placebo + fulvestrant (N=88)
Number of PFS events, n (%)	43 (50.6)	63 (71.6)
Median PFS (95% CI)	11.1 (7.3–16.8)	3.7 (2.1–5.6)
HR (95% CI)	0.48 (0.32–0.71)	

- Blinded independent review committee audit of 50% of randomized patients in the *PIK3CA*-mutant cohort (n=173)
- A full BIRC review of all patient data in the *PIK3CA*-mutant cohort was not required, based on prespecified thresholds

Endocrine resistance mechanism

PIK3CA mutation

Resistance to FUL

Improve by PIK3CA inhibitor (Alpelisib)

ESR1 mutation

Endocrine resistance mechanism

PIK3CA mutation

ESR1 mutation

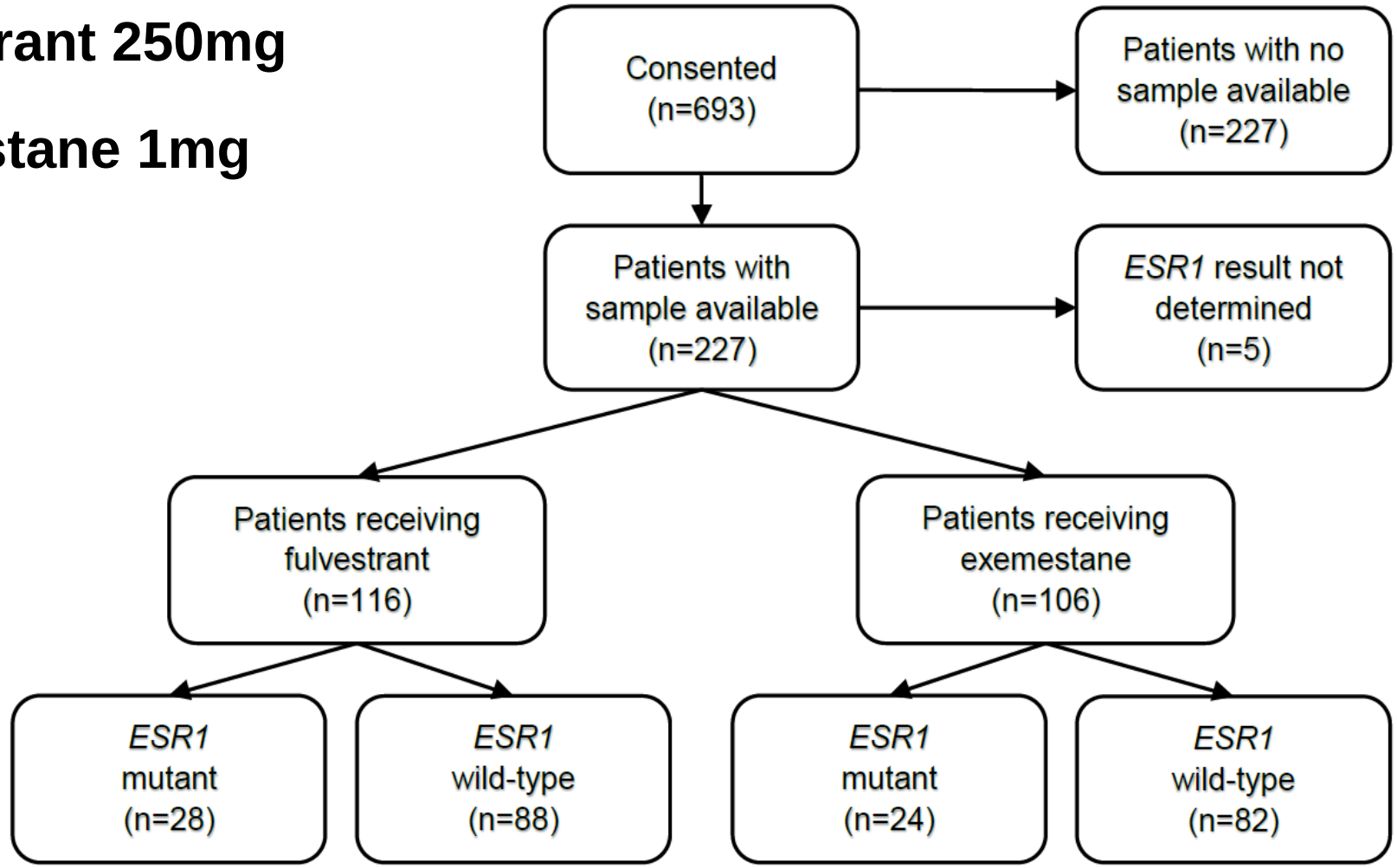
EFECT study CONSORT diagram

Prior AI

R

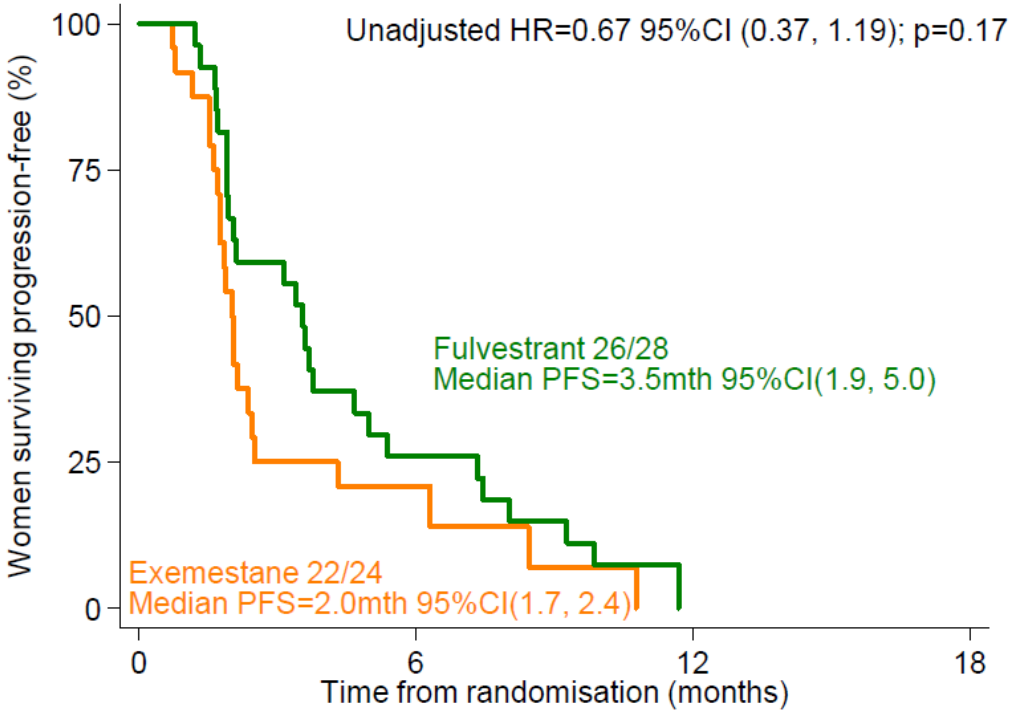
Fulvestrant 250mg

Exemestane 1mg



Detection of ESR1 mutations at baseline is associated with shorter PFS in EFECT

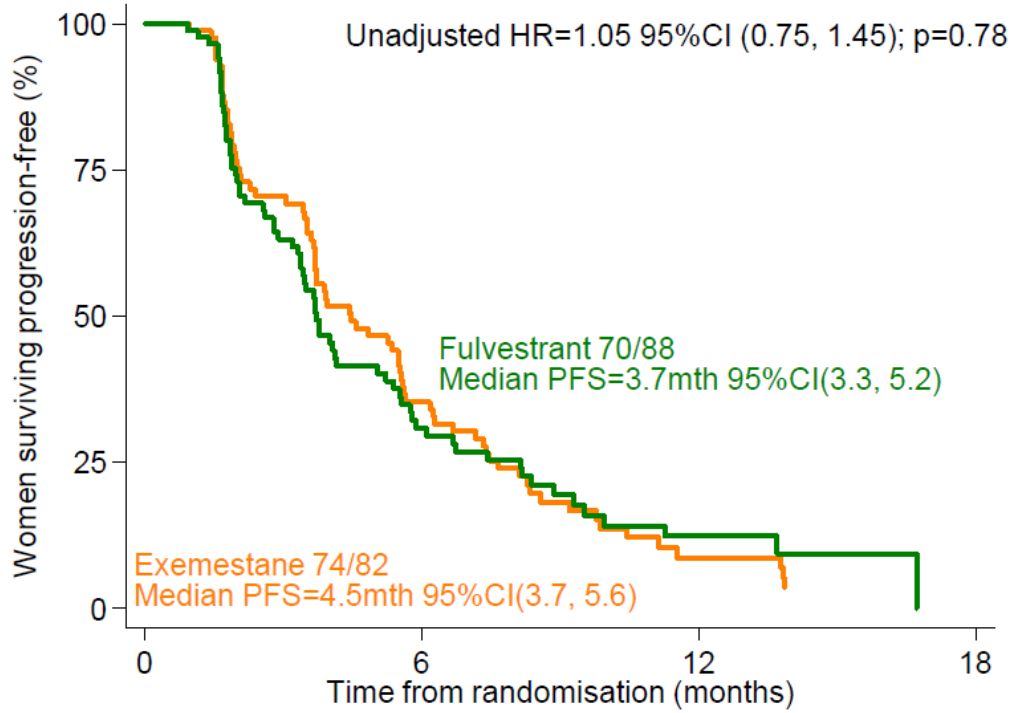
ESR1 Mutant



N at risk (events)

Exemestane	24	(19)	3	(3)	0	(0)	0
Fulvestrant	28	(20)	7	(6)	0	(0)	0

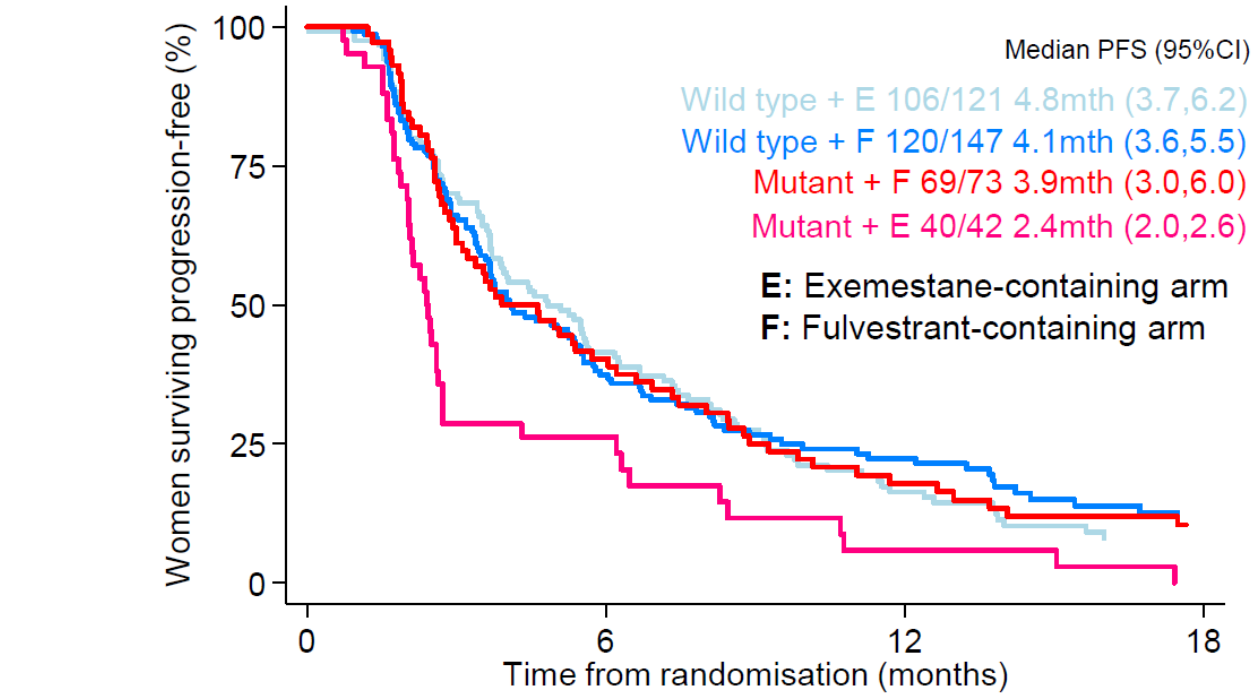
ESR1 Wild type



N at risk (events)

Exemestane	82	(52)	28	(19)	5	(3)	2
Fulvestrant	88	(56)	23	(12)	6	(2)	0

SoFEA and EFECT meta-analysis for baseline detection of ESR1 mutations



N at risk (events)

Wild type + E	121	(70)	49	(28)	17	(8)	7
Wild type + F	147	(87)	50	(19)	25	(10)	8
Mutant + E	42	(31)	9	(7)	2	(2)	0
Mutant + F	73	(43)	29	(16)	12	(5)	6

Patients with ESR1 mutation detected on fulvestrant had improved PFS compared to exemestane (HR=0.59, 95%CI: 0.39, 0.89; p=0.01).
For patients with ESR1 wild type there was no difference in PFS between treatments (HR=1.05, 95%CI: 0.81, 1.37; p=0.69).
Interaction test p=0.02

Endocrine resistance mechanism

PIK3CA mutation

ESR1 mutation

Biomarker of AI resistance

Other therapies to endocrine resistance

HDAC inhibitor (Entinostat)

IGF mAb (Xentuzumab)

Other therapies to endocrine resistance

HDAC inhibitor (Entinostat)

IGF mAb (Xentuzumab)

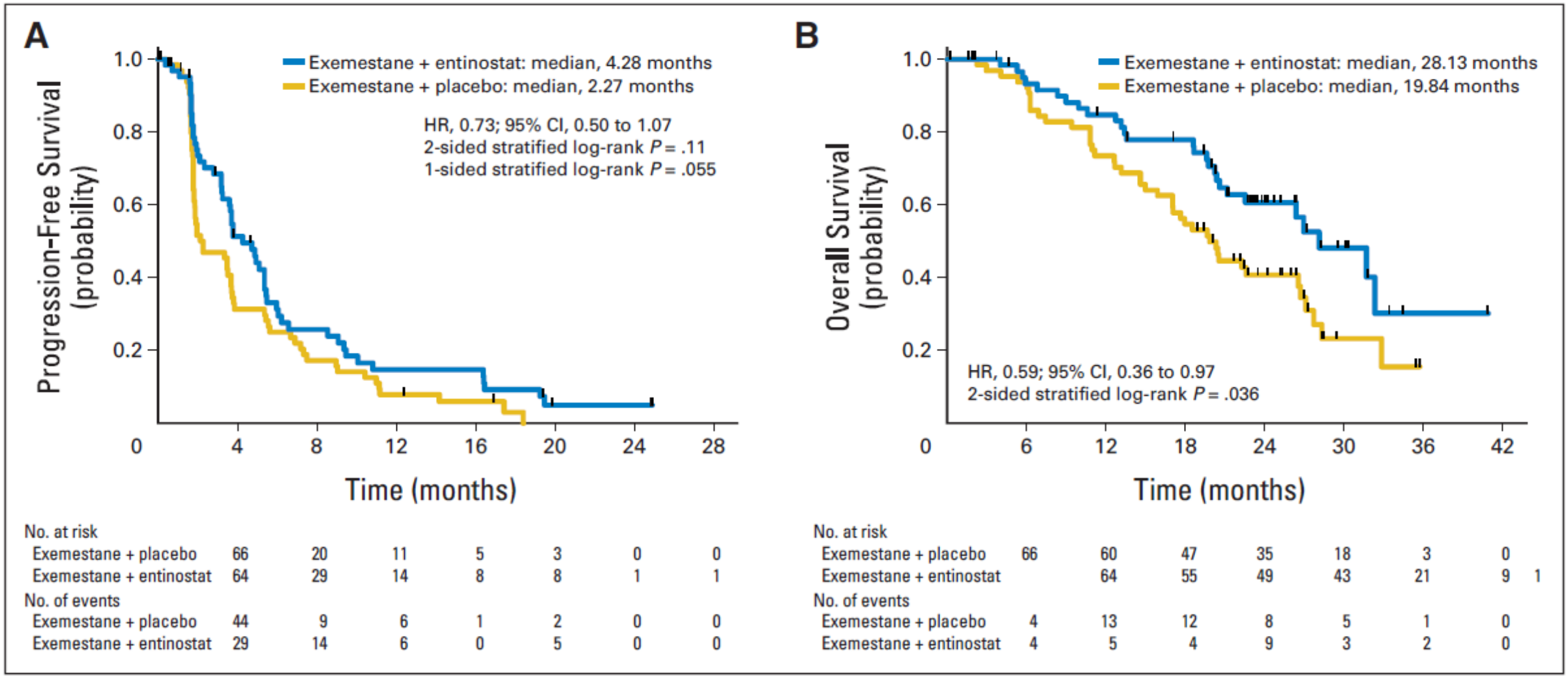
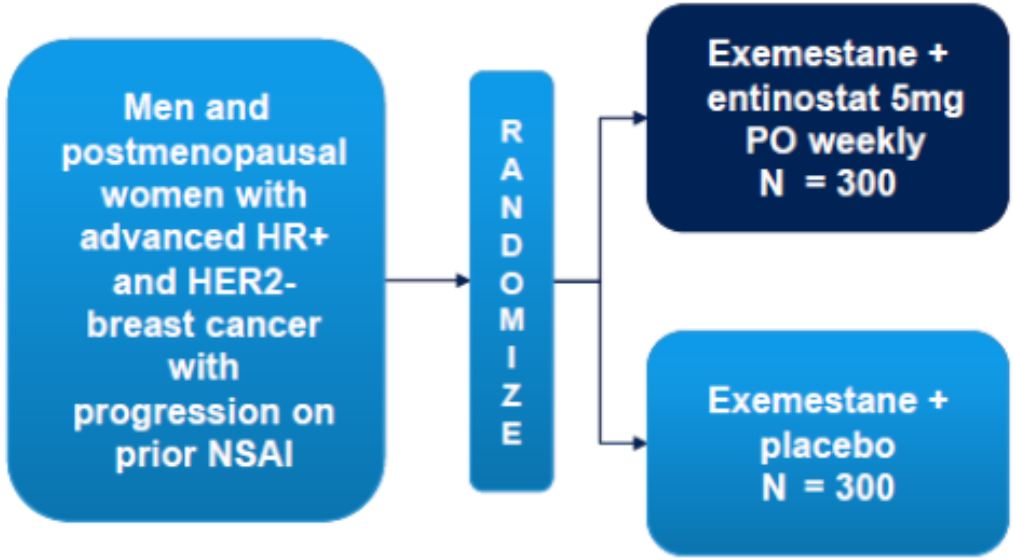


Fig 2. Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS). (A) Vertical tick marks represent the PFS time of patients without progressive disease. (B) Vertical tick marks represent the survival time of patients alive or lost to follow-up as of the last contact.

J Clin Oncol 31:2128-2135. © 2013 by American Society of Clinical Oncology

Global Phase 3

Clinical Trial can be considered successful if either primary endpoint (PFS or OS) is positive



- SPA agreement with FDA in place
- Two primary endpoints: PFS and OS
- Conducted in partnership w/ ECOG and NCI sponsorship

Statistical Plan

PFS @ 247 events / 360 patients p<0.002 HR=0.58; 88.5% power

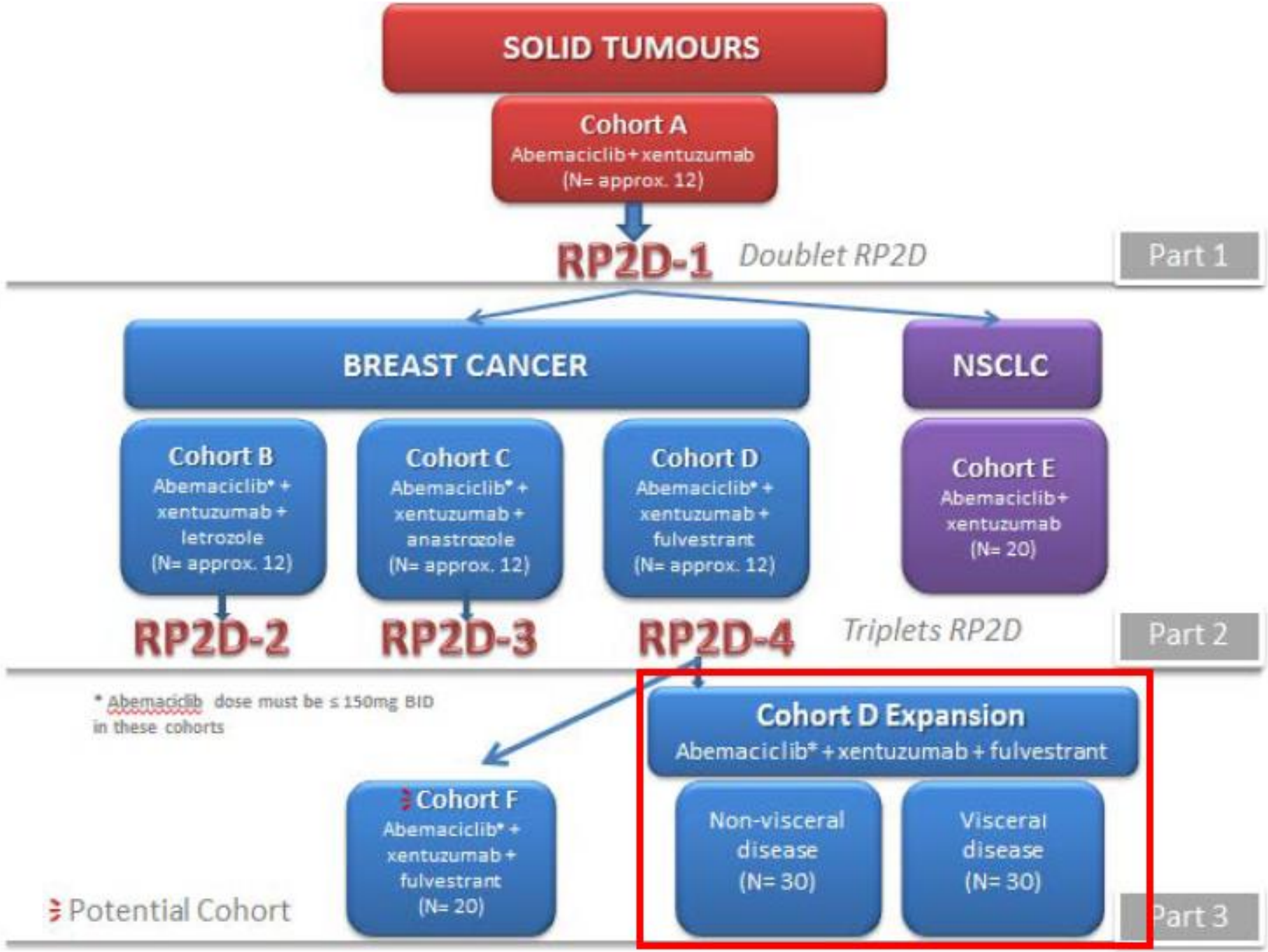
OS @ 410 events / 600 patients p<0.048 HR=0.75; 80% power

Data released to Syndax at full study accrual unless interim OS statistically significant

Other therapies to endocrine resistance

HDAC inhibitor (Entinostat)

IGF mAb (Xentuzumab)


SOLID TUMOURS
Cohort A
Abemaciclib + xentuzumab
(N= approx. 12)
RP2D-1
Doublet RP2D
Part 1
BREAST CANCER
NSCLC
Cohort B
Abemaciclib* + xentuzumab + letrozole
(N= approx. 12)
Cohort C
Abemaciclib* + xentuzumab + anastrozole
(N= approx. 12)
Cohort D
Abemaciclib* + xentuzumab + fulvestrant
(N= approx. 12)
Cohort E
Abemaciclib + xentuzumab
(N= 20)
RP2D-2
RP2D-3
RP2D-4
Triplets RP2D
Part 2
* Abemaciclib dose must be ≤ 150mg BID in these cohorts
Cohort D Expansion
Abemaciclib* + xentuzumab + fulvestrant
Cohort F
Abemaciclib* + xentuzumab + fulvestrant
(N= 20)
Non-visceral disease
(N= 30)
Visceral disease
(N= 30)
Potential Cohort
Part 3

Review Article

Frontiers in Medicine

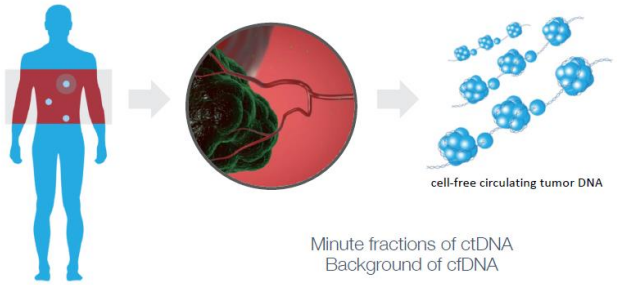
Application of Cell-free DNA Analysis to Cancer Treatment

Ryan B. Corcoran, M.D., Ph.D., and Bruce A. Chabner, M.D.

Tumor biopsies represent the standard for cancer DNA (cfDNA) diagnosis and the primary method for molecular testing to guide the selection of from plasma, are rapidly emerging as an important and minimally invasive adjunct to standard tumor biopsies and, in some cases, even a potential alternative approach. Liquid biopsy is becoming a valuable tool for molecular testing, for new insights into tumor heterogeneity, and for cancer detection and monitoring. Here, we review the current and potential clinical applications of cfDNA analysis in patients with cancer (see video).

NEJM 379;18 November 1, 2018

Tumor DNA is Present in Blood at Exceedingly Low Concentrations



Minute fractions of ctDNA
Background of cfDNA

All NCCN Somatic Genomic Targets with a Single Test

Version 2.10-11/8/2016

Point Mutations – 73 Genes

AKT1	*ALK*	***APC***	***AR***	*ARAF*	*ARID1A*	*ATM*	***BRAF***	***BRCA1***	***BRCA2***
CCND1	*CCND2*	*CCNE1*	*CDH1*	*CDK4*	*CDK6*	*CDKN2A*	*CTNNB1*	*DDR2*	***EGFR***
ERBB2 (HER2)	*ESR1*	*EZH2*	*FBXW7*	*FGFR1*	*FGFR2*	*FGFR3*	*GATA3*	*GNA11*	*GNAQ*
GNAS	*NF1A*	***HRAS***	*IDH1*	*IDH2*	*JAK2*	*JAK3*	***KIT***	***KRAS***	*MAP2K1 (MEK1)*
MAP2K2 (MEK2)	***MAPK1 (ERK2)***	***MAPK3 (ERK1)***	***MET***	*MLH1*	*MPL*	*MTOR*	***MYC***	*NF1*	*NFE2L2*
NOTCH1	*NPM1*	***NRAS***	*NTRK1*	*NTRK3*	*PDGFRA*	***PIK3CA***	*PTEN*	*PTPN11*	*RAF1*
RB1	*RET*	*RHEB*	*RHOA*	*RIT1*	*ROS1*	*SMAD4*	*SMO*	***STK11***	*TERT***
TP53	*TSC1*	*VHL*					** Includes *TERT* promoter region		

Indels – 23 Genes

ATM	*APC*	*ARID1A*	*BRCA1*	*BRCA2*	*CDH1*	*CDKN2A*	*EGFR*	*ERBB2*	*GATA3*
KIT	*MET ex14*	*MLH1*	*MTOR*	*NF1*	*PDGFRA*	*PTEN*	*RB1*	*SMAD4*	*STK11*
TP53	*TSC1*	*VHL*							

Amplifications – 18 Genes

AR	*BRAF*	*CCND1*	*CCND2*	*CCNE1*	*CDK4*	*CDK6*	*EGFR*	*ERBB2*
FGFR1	*FGFR2*	*KIT*	*KRAS*	*MET*	*MYC*	*PDGFRA*	*PIK3CA*	*RAF1*

Fusions – 6 Genes

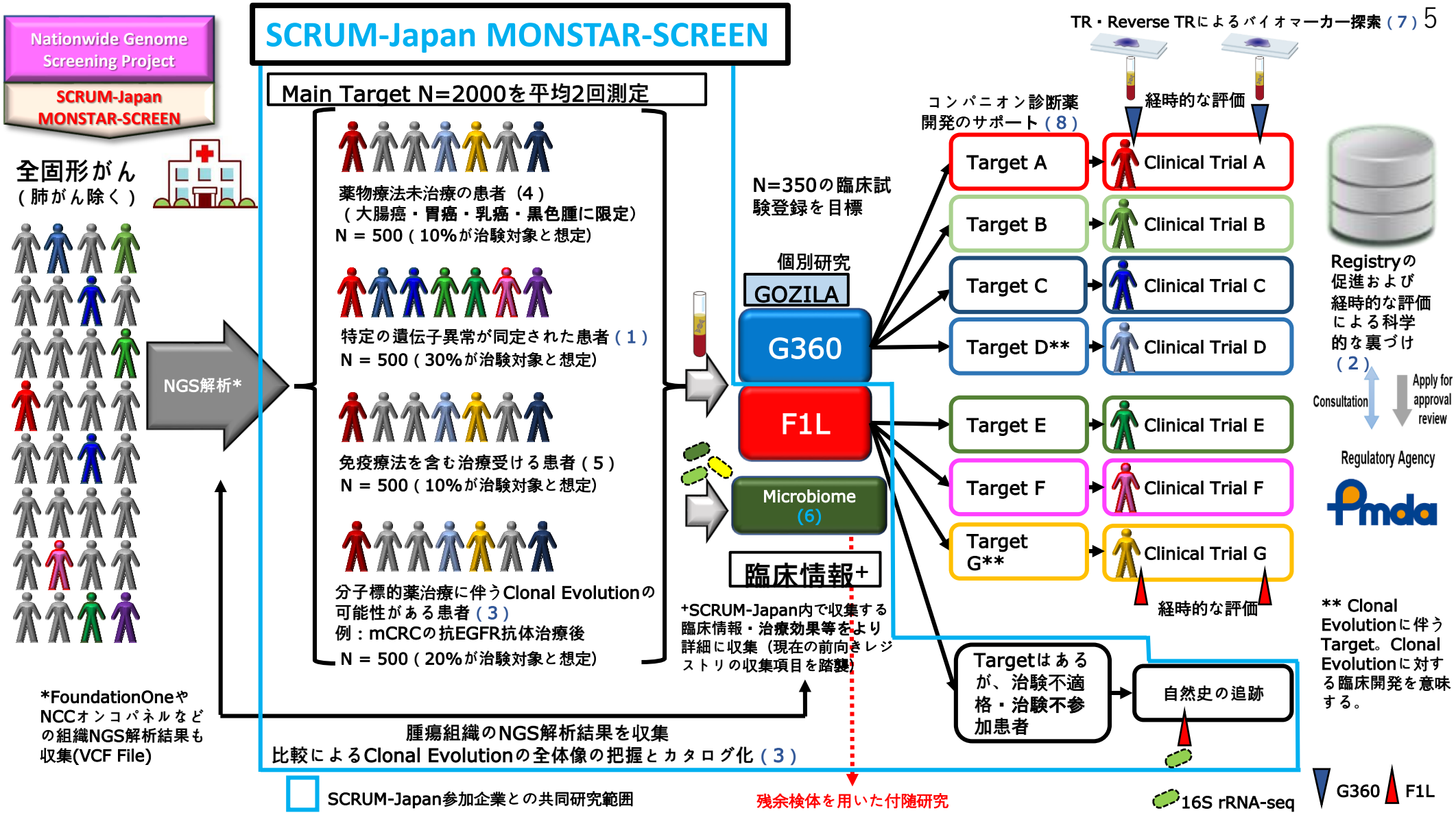
ALK	*FGFR2*	*FGFR3*	*RET*	*ROS1*	*NTRK1*

MSI: High/Low

 GUARDANT

Treatment decision according to liquid biopsy for MBC

Overall Picture



Conclusion to near future

- New approach based on response-guide therapy for PBC
- New approach based on innovative technology and new drug development for MBC