Neoadjuvant endocrine therapy: Who? When? Why?

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What is the role of neoadjuvant endocrine therapy (NET)?

Established role – supported by guidelines

- Disease control for patients who are not good candidates for surgery and/or chemotherapy
- Improve breast conservation rates in postmenopausal women

Prognostic role – evidence based

- Response to NET can provide useful prognostic information on an individual patient level

Research

- NET provides a rich research platform to assess:
  - MOA, PK, PD
  - Mechanisms of resistance
  - Potential platform to test novel agents and combinations in HR+ HER2-negative disease, inform adjuvant trials and patient selection

NET in patients who are not good candidates for chemotherapy and/or surgery

67 women ≥75 y.o
Tamoxifen
RR 73%

BRITISH MEDICAL JOURNAL VOLUME 284 20 MARCH 1982

Tamoxifen as initial sole treatment of localised breast cancer in elderly women: a pilot study

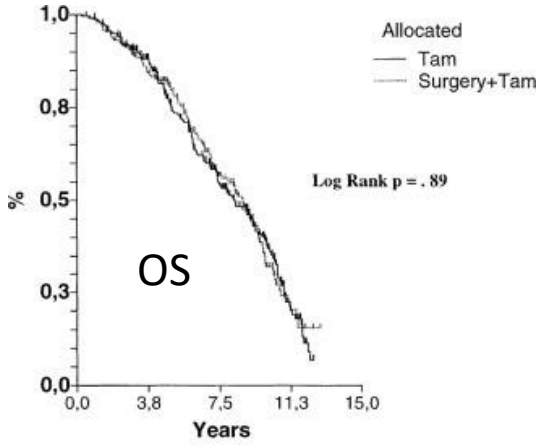
Breast lumps that develop in elderly women are most likely to be mammary carcinomas.[1] Often such women have never been to hospital and the prospect of admission is alarming to them. The presence of intercurrent illnesses in women aged 70 years and over who develop breast cancer is, as might be expected, extremely high, increasing the risk of anaesthesia and surgery.[2] These patients often ask whether, instead of being excised, their breast lumps can be "dispersed." In a four-year pilot study we treated elderly women with apparently localised breast cancer with tamoxifen in view of its proved efficacy in advanced breast cancer in this age group.[3]

GRETA trial

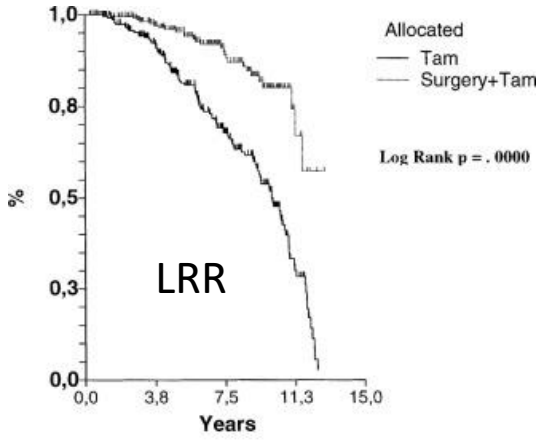
Randomized 474 pts ≥70 y.o.
- Surgery →Tamoxifen vs
- Tamoxifen alone

OS and BCSS: no difference

Higher local recurrence rate in Tam alone arm



Event time (yrs)	0.7	3.5	5.6	8.4	11.2
Nr at risk					
Tam	233	193	141	78	20
Surg+Tam	236	187	141	73	11

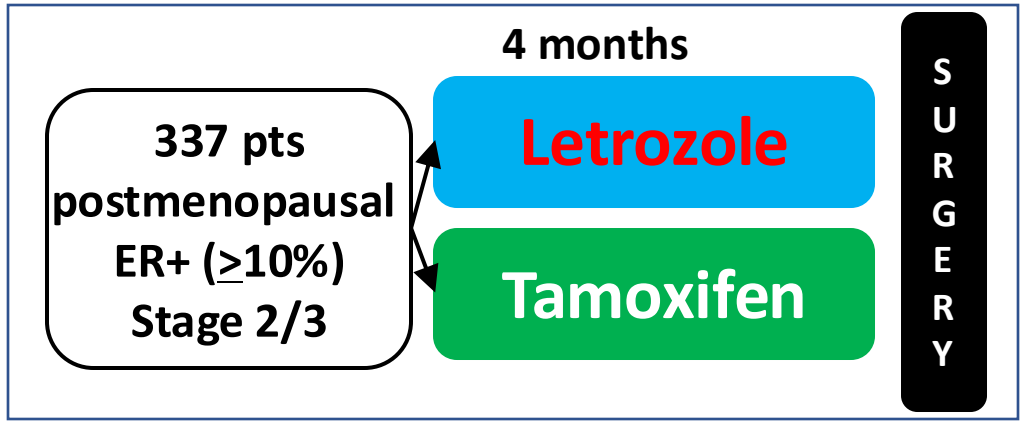


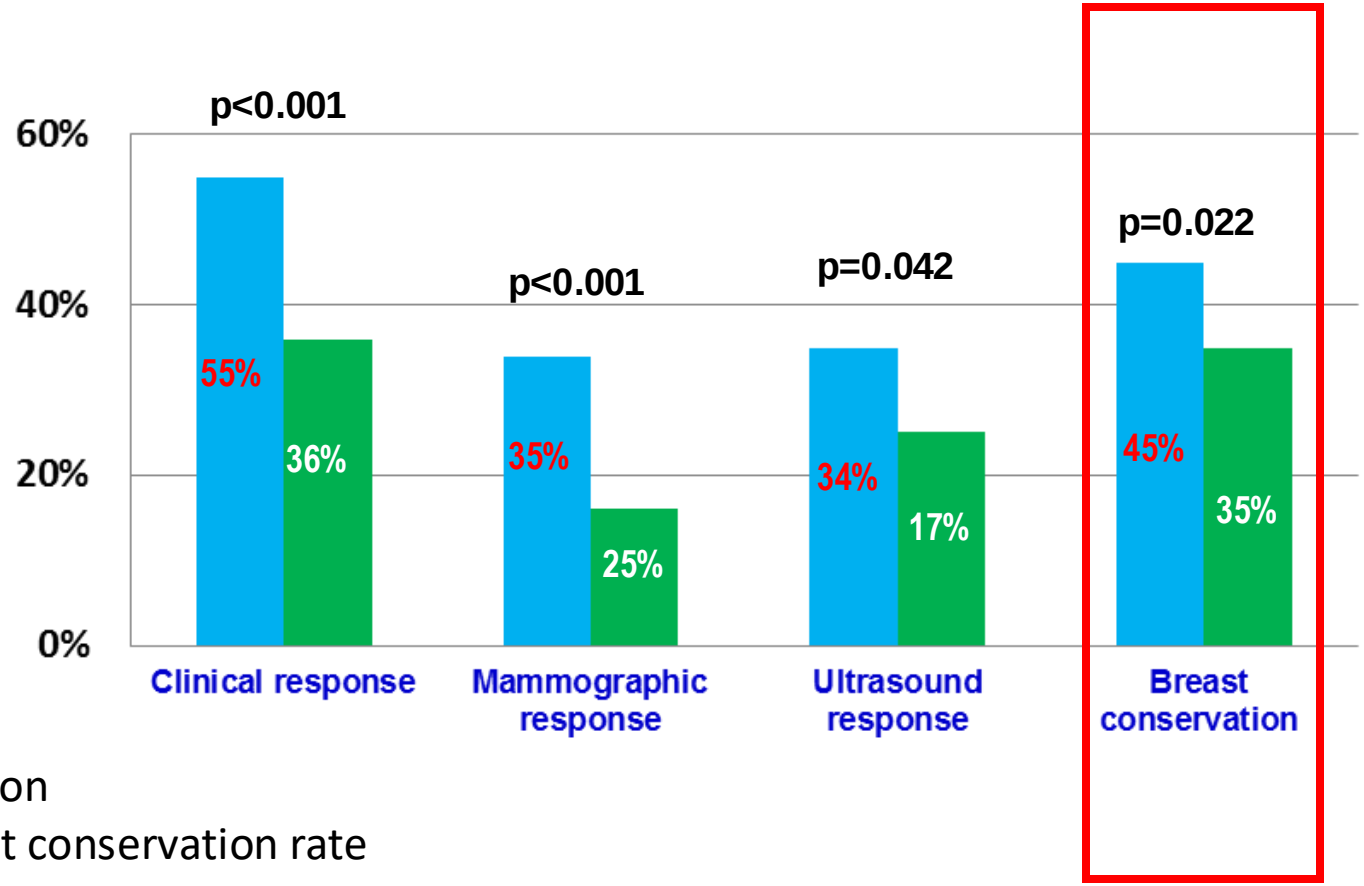
Event time (yrs)	0.7	3.5	5.6	8.4	11.2
Nr at risk					
Tam	232	193	138	78	20
Surg+Tam	228	184	136	73	10

Mustacchi G et al, Ann Oncology, 2003

Neoadjuvant Endocrine Therapy Improves Clinical Response and Breast Conserving Surgery Rate in Postmenopausal Women

P024





Primary endpoint: Objective response by clinical palpation
Secondary endpoints: OR by mammo/ultrasound, breast conservation rate

None of the patients were eligible for breast conservation surgery at baseline

Eiermann W, et al, Ann Oncol 12:1527-32, 2001

ASCO Guidelines: Neoadjuvant Endocrine Therapy in EBC

Recommendations for neoadjuvant ET for ER+ HER2- EBC:

- For postmenopausal women, neoadjuvant ET with an aromatase inhibitor may increase loco-regional options; if no intent for surgery, may be used for disease control
- For premenopausal women, NET should **not** be offered routinely outside a clinical trial

Korde et al, J Clin Oncol Jan 2021

Case

- 52 year-old postmenopausal F
- 4 cm, G
- Clinical
- ER 90/PR 90/HER2-neg
- Ki67 5%
- She is a candidate for breast conservation

Besides breast conservation , what can NET offer?
Can response to NET help inform prognosis and adjuvant decisions?

What do you recommend ?

- hotherapy
- ocrine therapy
- Oncotype or MammaPrint testing

Challenges in conducting NET trials

- What is the biomarker of NET response that serves as a surrogate marker of long-term outcome (ie. pCR for NACT)?
- pCR rates with NET are too low to be that biomarker
  - <5% with 3-6 months of therapy
  - Longer treatment may lead to higher pCR rates
    - 17% pCR with 12 mo

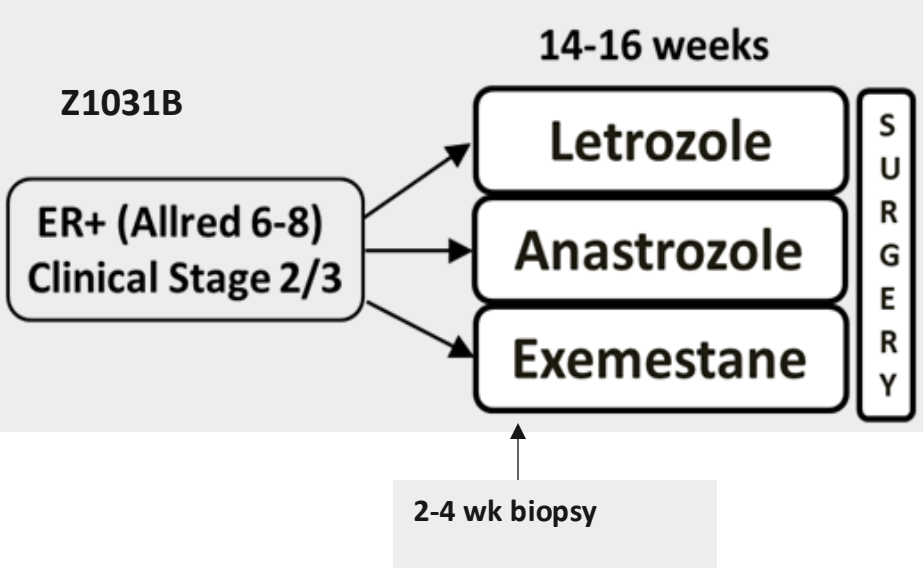
      (Allevi el al, Br J Cancer, 2013)

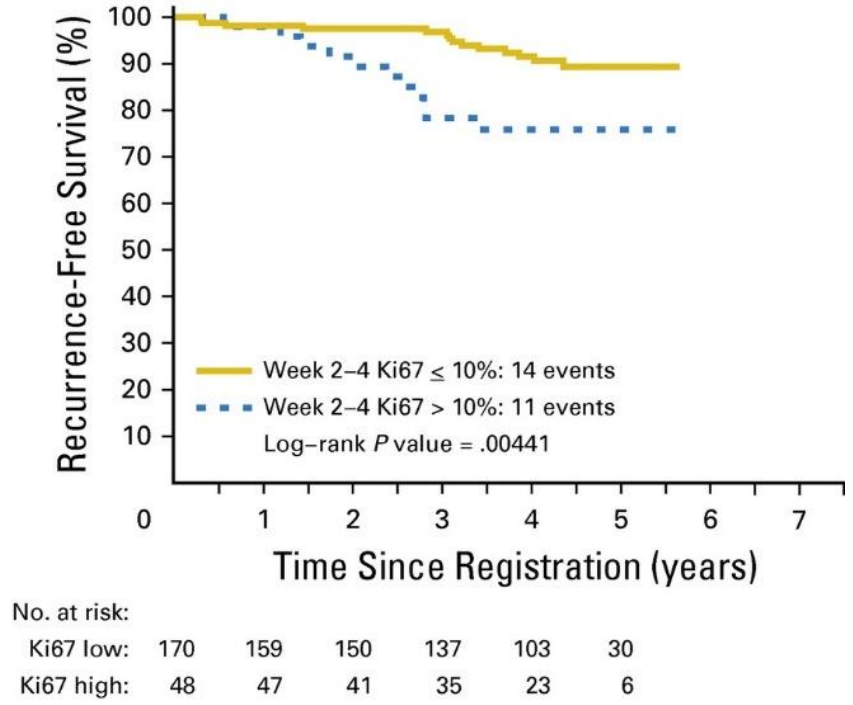
Select NET trials: Primary endpoints

Study	N	Treatment	Primary endpoint
Semiglasov (2007)	239	AI vs chemo	OR by palpation
P024 (2001)	324	AI vs Tam	OR by palpation
IMPACT (2005)	330	Ai vs AI+Tam vs Tam	OR by caliper
STAGE (2012)	197	OS/AI vs OS/Tam	OR by caliper
Baselga et al (2009)	270	AI +/- everolimus	OR by palpation
PALLET (2019)	307	AI +/- palbo	Clinical response, CCCA
neoMONARCH (2020)	224	AI+/- abema	CCCA
NeoPAL (2018)	106	AI+palbo vs chemo	Rate of RCB 0-1
FELINE (2020)	121	AI +/- ribo	Rate of PEPI 0
CORALLEEN (2020)	106	AI+ribo vs. chemo	Rate of ROR-Low
ALTERNATE (2020)	1362	Fulvestrant vs AI vs F+A	ESDR (mPEPI 0)

Ki67 is the most validated biomarker of response to NET

- 2-4 week Ki67 is prognostic for relapse free survival





Ellis MJ et al J Clin Oncol 35:1061-9, 2017

UK POETIC

Postmenopausal women with ER/PgR positive invasive breast cancer

4500 pts
~40% pN+

RANDOMISE
2:1 ratio

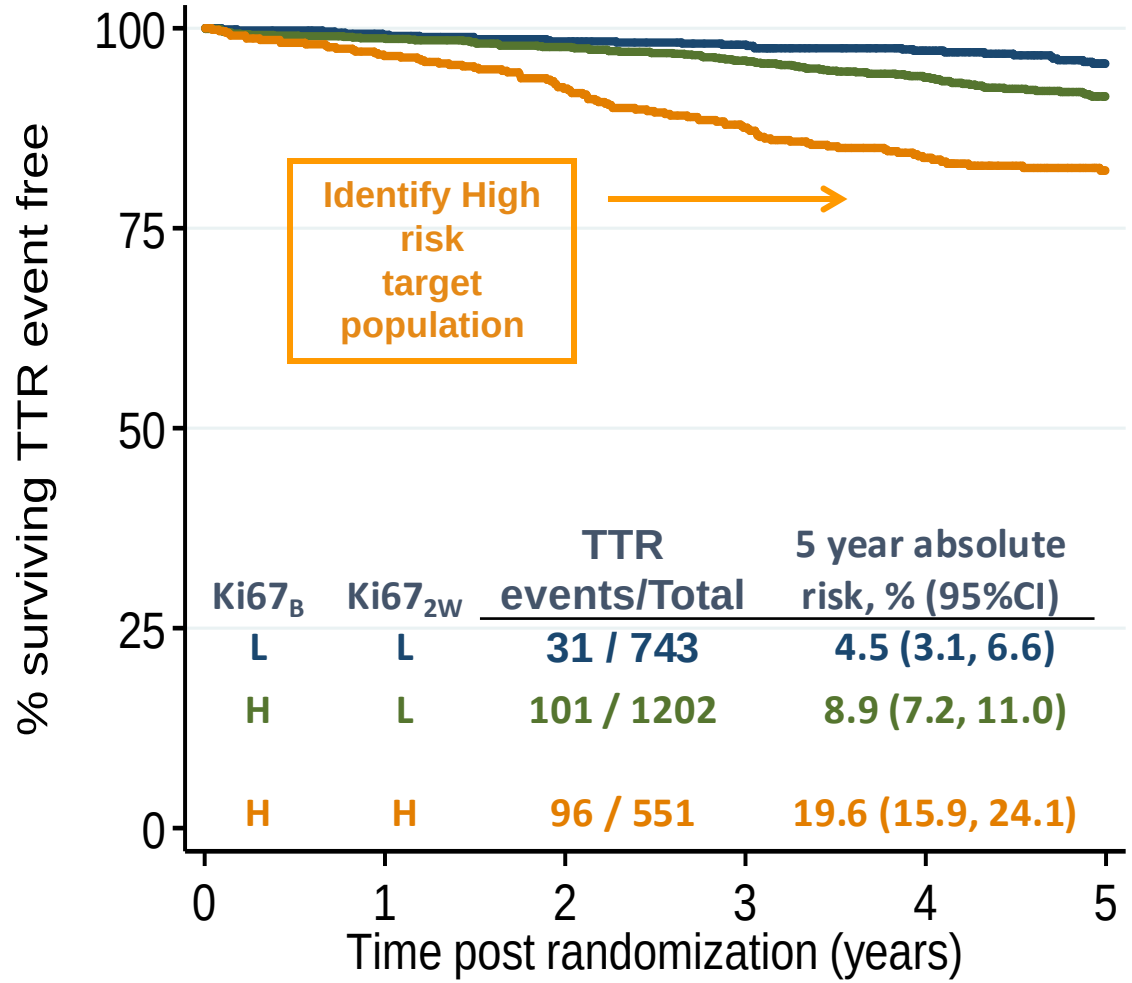
Group I
PERIOPERATIVE THERAPY
AI treatment for 2 weeks
SURGERY

Group II
NO PERIOPERATIVE THERAPY
SURGERY

1st follow up visit post-surgery

Complete trial treatment & continue other treatment in accordance with local practice

POETIC - Time to recurrence by Ki67 at baseline and surgery (2 week)



$Ki67_B$	$Ki67_{2W}$	TTR events/Total	5 year absolute risk, % (95%CI)
L	L	31 / 743	4.5 (3.1, 6.6)
H	L	101 / 1202	8.9 (7.2, 11.0)
H	H	96 / 551	19.6 (15.9, 24.1)

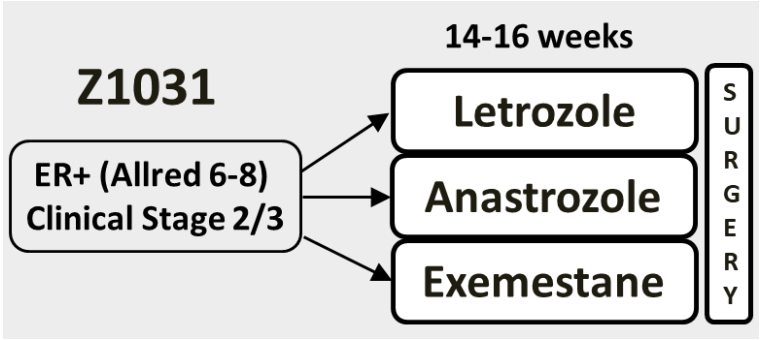
Smith et al., Lancet Oncol. Nov 2020

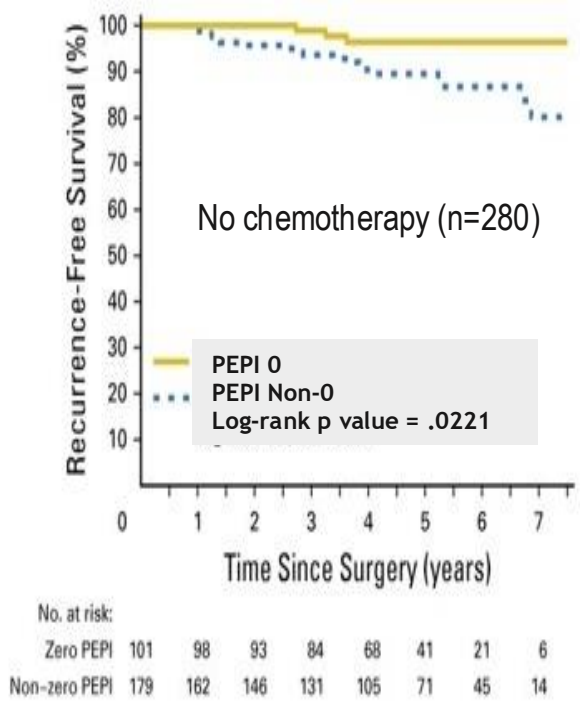
Preoperative Endocrine Prognostic Index: PEPI

PEPI 0
pT1/2 pN0
Ki67 ≤ 2.7%
ER Allred 3-8

Pathology, biomarker status	RFS		BCSS	
	HR	Points	HR	Points
Pathological tumor size				
T1/2	—	0	—	0
T3/4	2.8	3	4.4	3
Node status				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
Ki67 level				
0%–2.7% (0–1†)	—	0	—	0
>2.7%–7.3% (1–2†)	1.3	1	1.4	1
>7.3%–19.7% (2–3†)	1.7	1	2.0	2
>19.7%–53.1% (3–4†)	2.2	2	2.7	3
>53.1% (>4†)	2.9	3	3.8	3
ER status, Allred score				
0–2	2.8	3	7.0	3
3–8	—	0	—	0

All patients (n=460)

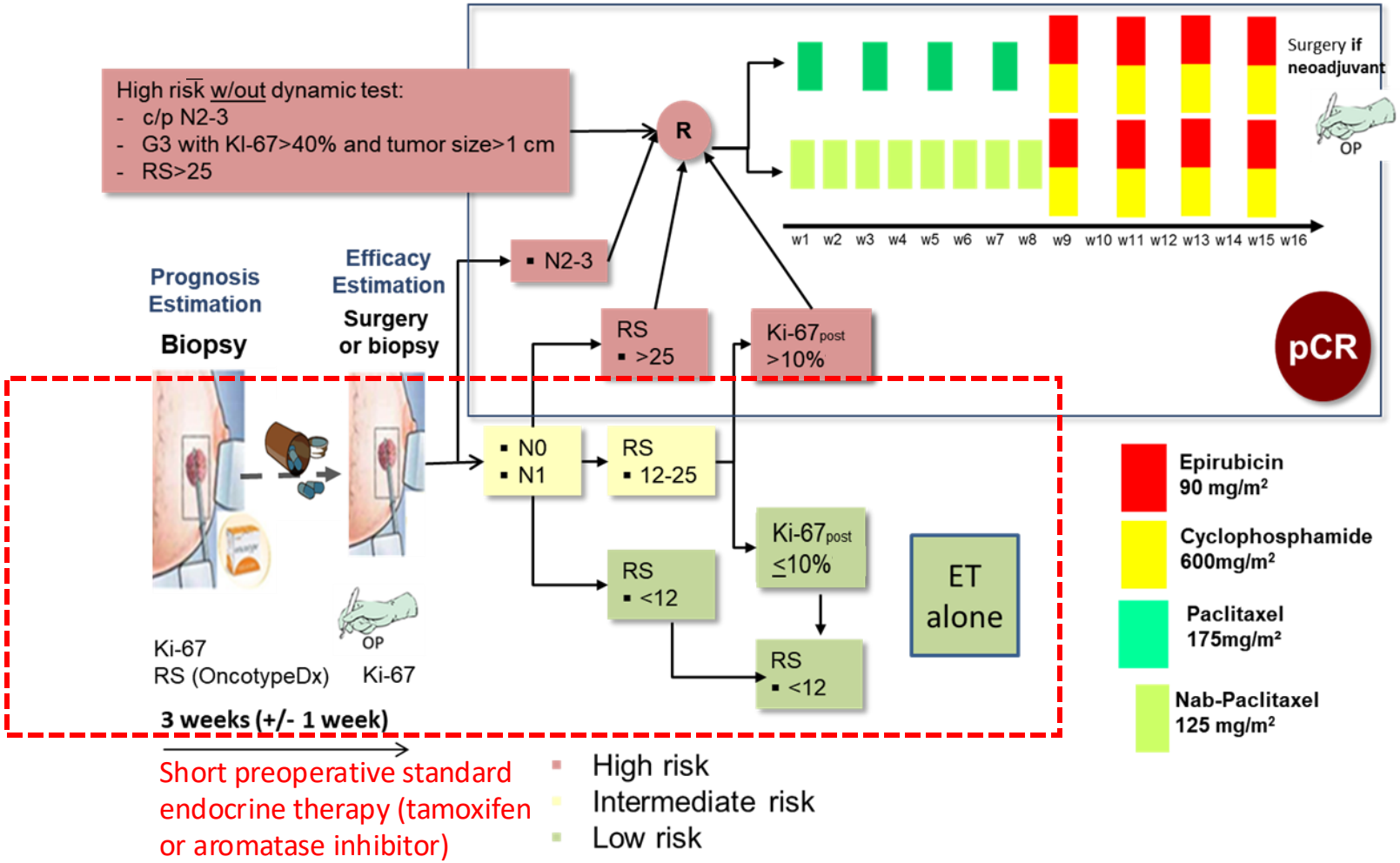




Eiermann W, et al, Ann Oncol 12:1527-32, 2001; Smith IE, et al, J Clin Oncol 23:5108-16, 2005; Ellis MJ, et al, J Natl Cancer Inst 100:1380-8, 2008, *Ellis MJ et al J Clin Oncol 35:1061-9, 2017*

ADAPT HR+/HER2- Study Design (included premenopausal women)

- Female patients ≥18 years
- ER and/or PR positive (≥1%)/ HER2-negative unilateral EBC
- cT1-4c, cN0-3
- **Candidates for adjuvant chemotherapy by conventional prognostic criteria:** cT2 or G3 or Ki67≥15% or <35 years old or cN+

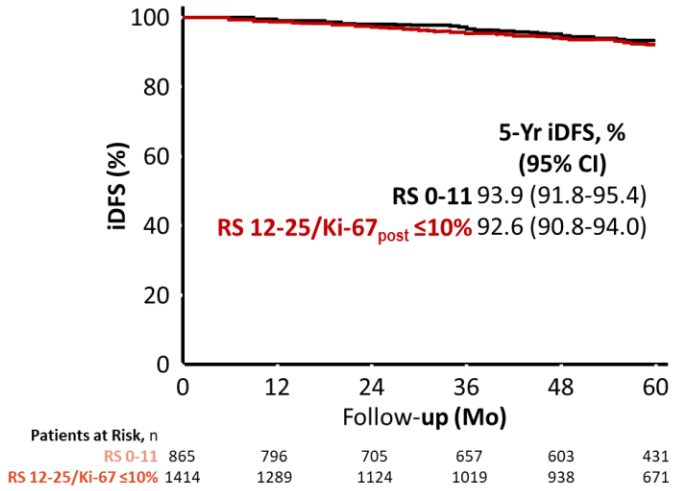


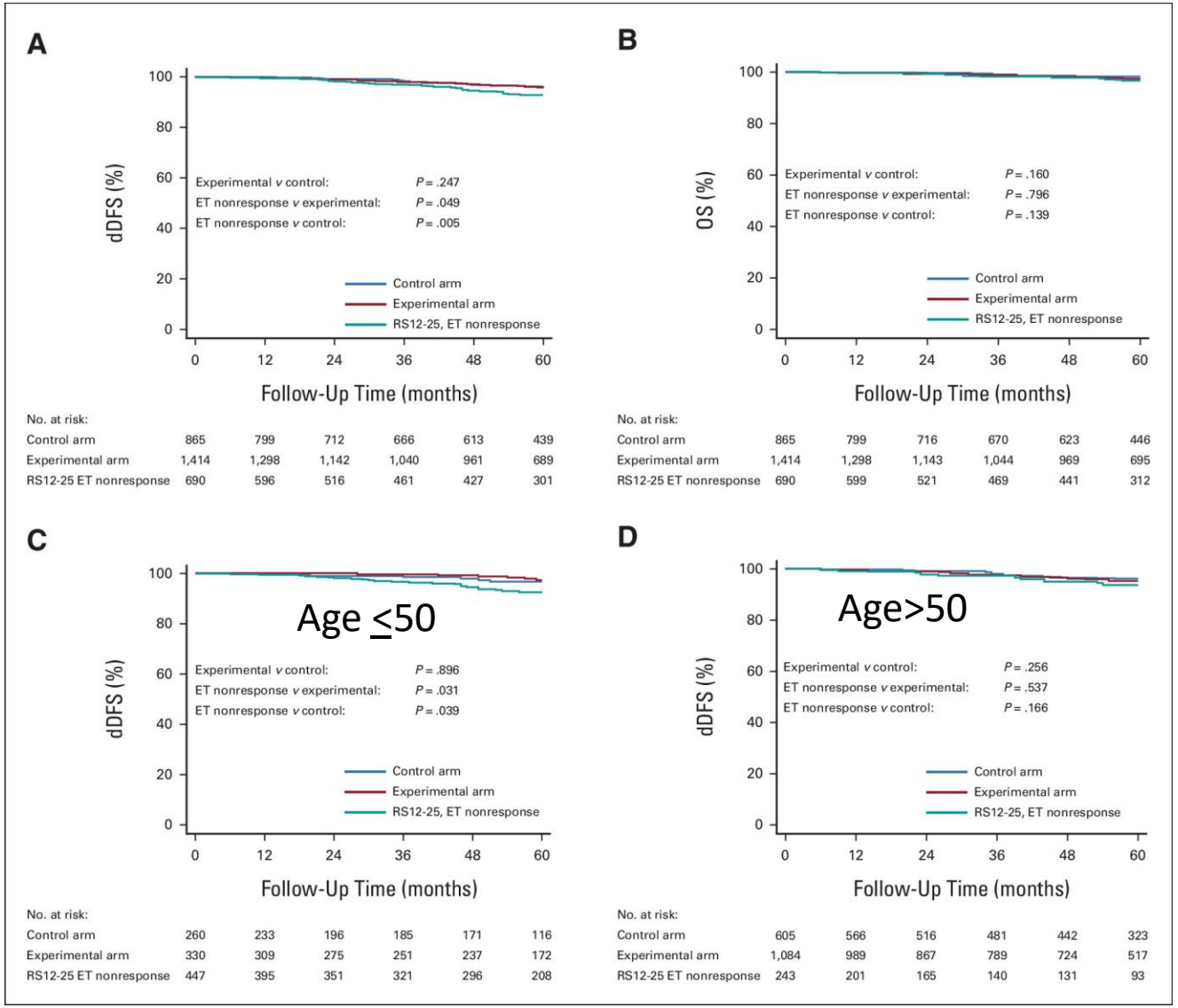
Harbeck et al SABCS 2020 GS04-04

ADAPT HR+/HER2-: 5-Yr iDFS (Primary Endpoint), dDFS, OS

Characteristic	ITT: ET Alone (n = 2290)	
	Control (n = 868)	Experimental (n = 1422)
Median age, yr	57	58
▪ ≤50 yr of age, n (%)	260 (30.0)	332 (23.3)
Premenopausal, n (%)	300 (34.6)	374 (26.3)
Tumor stage pT2-4, n (%)	300 (34.6)	543 (38.2)
Nodal status pN1, n (%)	208 (24.0)	389 (27.4)
Grade 3, n (%)	114 (13.1)	306 (21.5)
Median Ki-67, %	15	15
Positive PgR, n (%)	823 (94.8)	1251 (88.0)

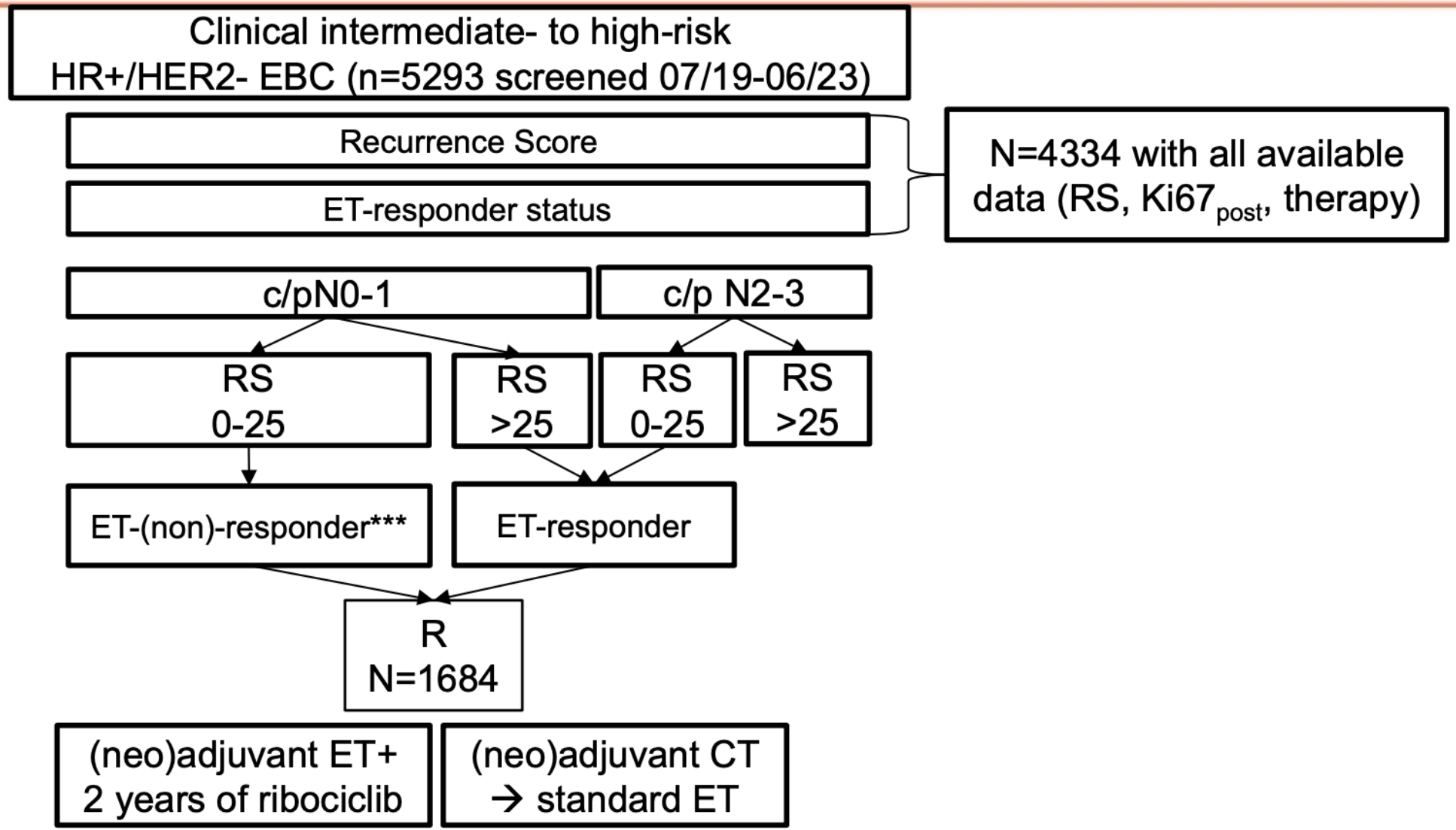
Median follow-up: 60 mos (range: 0-91)





Nitz et al, JCO, 2022

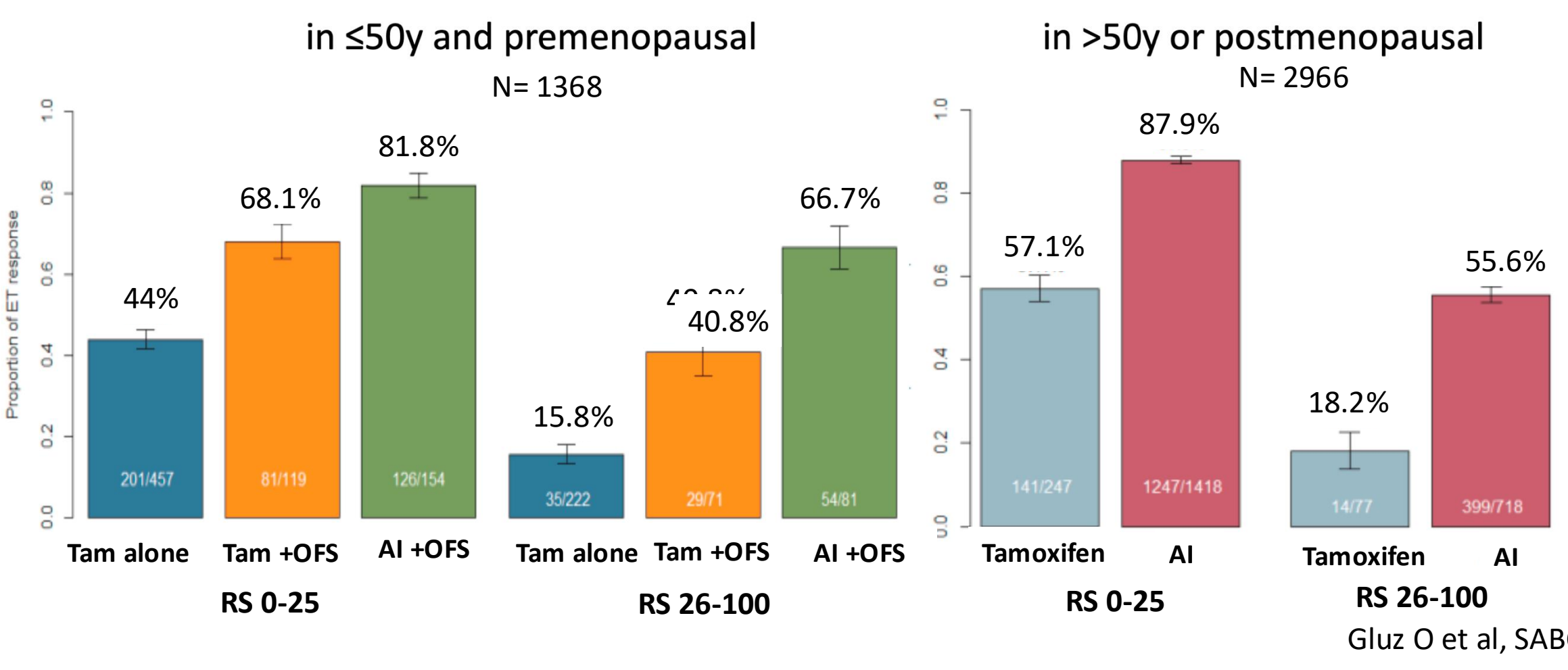
ADAPTcycle



*** Participation of premenopausal N1 and N0 with RS 16-25 irrespective of ET-responder status allowed by investigator's decison, postmenopausal only if several risk factors

ADAPTcycle screening cohort (4334 patients)

ET Response: 2-4 week Ki67 ≤10%
OFS +AI started simultaneously C1D1



Gluz O et al, SABCS 2023

Randomized Ph3 trial of NCT vs NET in premenopausal women

Phase 3 study
Randomized to NCT vs NET x 6 months
N=187

- Premenopausal
- ER+ (Allred score ≥3)/HER2-, LN+

Primary endpoint: Clinical response by RECIST by MRI
Secondary endpoints: pCR, change in Ki67, BCS rate, QoL

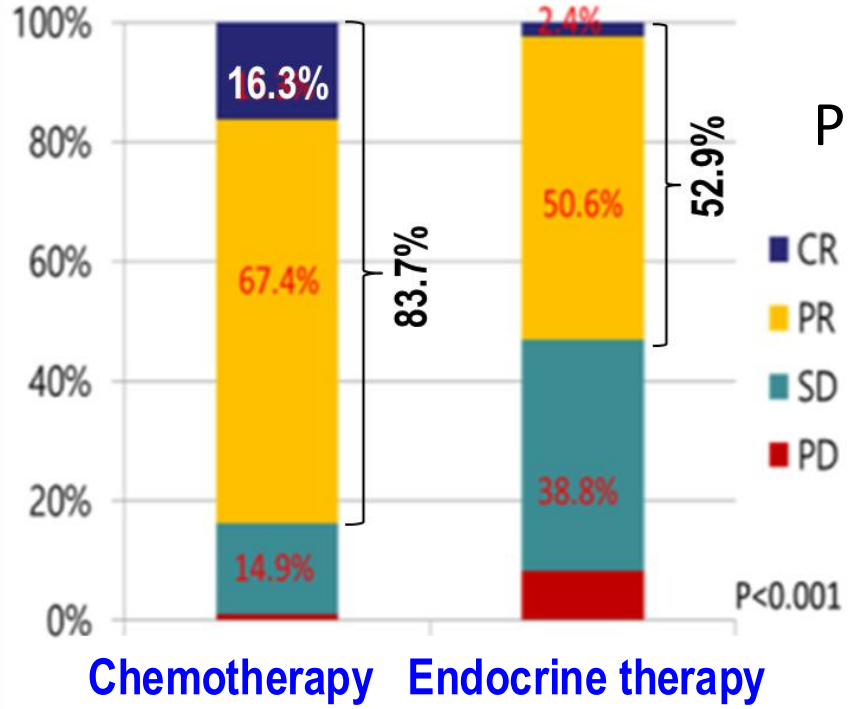
Treatment Regimen:
Chemotherapy: AC x 4 followed by T x 4 (q3w)
Endocrine therapy: goserelin + tamoxifen 6 months

The BCS rate was not different between the two groups (13.8% vs 11.5%; P = .53).

No difference between Ki67 change between the 2 groups

(N=187)

Clinical response measure by MRI



P<0.001

Kim et al. Breast Cancer Research (2020) 22:54

Neoadjuvant endocrine therapy trials with CDK 4/6i

Trial	Phase II design	Treatment and Duration	N	Primary Endpoint	Other Endpoints
Adding CDK4/6i to ET					
NeoPalAna	• Single arm, 2 cohorts by PIK3CA^{mut} status	Anastrozole (ANA) 28 d (C0) → ANA+PAL 16 wks (C1-C4) → ANA+PAL 12d (C5) until Surg	50	**Ki67 ≤ 2.7% (CCCA) C1D15**	ORR, pCR rate, genomic correlates with Ki67
PALLET	• Randomized	Grp A: Letrozole (LET) 14 wks Grp B: LET 2wks → LET+PAL 14wks Grp C: PAL 2wks→ LET+PAL 14wks Grp D: LET+PAL 14 wks	307	Comparing A vs B+C+D • **Ki67↓ at 14 wk** • **ORR**	• Comparing Ki67↓ at 2 wk vs 14 wk • Cleaved PARP • CCCA 14 wks
N007	• S				n
NeoMonarch	• R				tives
FELINE	• R				
CDK4/6i vs Chen					
NeoPal	• Randomized LumB, or LumA/N+	• LET+PAL 19wks • FEC → T	106	• Residual Cancer Burden **(RCB) 0-1 rate**	ORR, Ki67
CORALLEEN	• Randomized LumB	• LET+Ribo 24 wks, Surg off Ribo 1 wk • AC → T	101	• **PAM50 ROR low rate**	pCR, RCB, PEPI, ORR, Ki67, correlatives

- CDK 4/6i increase rates of Ki67 suppression and complete cell cycle arrest
- No increase in pCR, PEPI-0, or ORR
- Ki67 is not validated as a prognostic marker in the setting of CDK 4/6i. Need alternative biomarkers!

Select neoadjuvant trials of oral SERDs and other novel endocrine agents

Trial	Agent	Patients	Treatment	Primary Endpoint	Other endpoints	Reference
CooPERA	Giredestrant (G)	221pts postmenopausal	G 2wks →G+palbo vs. AI+palob	2 week Ki67 change	2 week CCA ORR< safety	Hurvitz S et al, Lancet Oncology 2023
Ember-2	Imlunestrant	87 pts postmenopausal	200 mg, 400mg, 800mg imlunestrant	Change in ER	PR, Ki67, PK, safety	Neven P et al, ESMO 2023
I-SPY2 EOP	Amcenestrant (A)	74 pts pre/post	A, A+AI, A+abema	feasibility	Ki67, MRI FTV, mPEPI 0, ctDNA	Chien et al., Asco 2024
Serena-3	Camizestrant	130 pts postmenopausal	75mg , 150 mg, 300 mg	Change in ER	Ki67	Robertson J, SABCS 2023
I-SPY2 EOP	Lasofoxifene	20 pts pre/post	Lasofoxifene 5 mg	feasibility	Ki67, MRI FTV, PEPI 0, ctDNA	Wei et al, Rise Up 2024
Evangeline	Endoxifen	162 pts	OFS+Endoxifen 40 mg vs OFS+AI	4 week ESDR (Ki67<=10%)	PK	Goetz et al, AACR 2024
I-SPY EOP	Vepdegestrant (V)	120 pre/post	V, V+AI, V+ Abema	feasibility	Ki67, MRI FTV, PEPI 0, ctDNA	Ongoing

Conclusions

- NET can be used to increase surgical options in postmenopausal pts and in those who are poor candidates for surgery and chemotherapy
- Ki67 and PEPI 0 are the only 2 biomarkers currently validated to be prognostic for 5-year EFS.
- Few NET studies included premenopausal women.
  - Similar Ki67 suppression between pre- and postmenopausal pts
  - ADAPT HR+/HER2- shows similar 5-year dDFS in pre- and postmenopausal ET responders
- NET trials should be further leveraged to test novel agents/combinations, MOA, resistance mechanisms
  - Potential to inform adjuvant trials and patient selection
  - Identifying and validating novel biomarkers of response to NET is a high priority