Preoperative Endocrine Therapy in ER positive Breast Cancer

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Selection for Preoperative (Neoadjuvant) Therapy

- Patient who will benefit
  - Locally advanced → Operable
  - Large operable tumors
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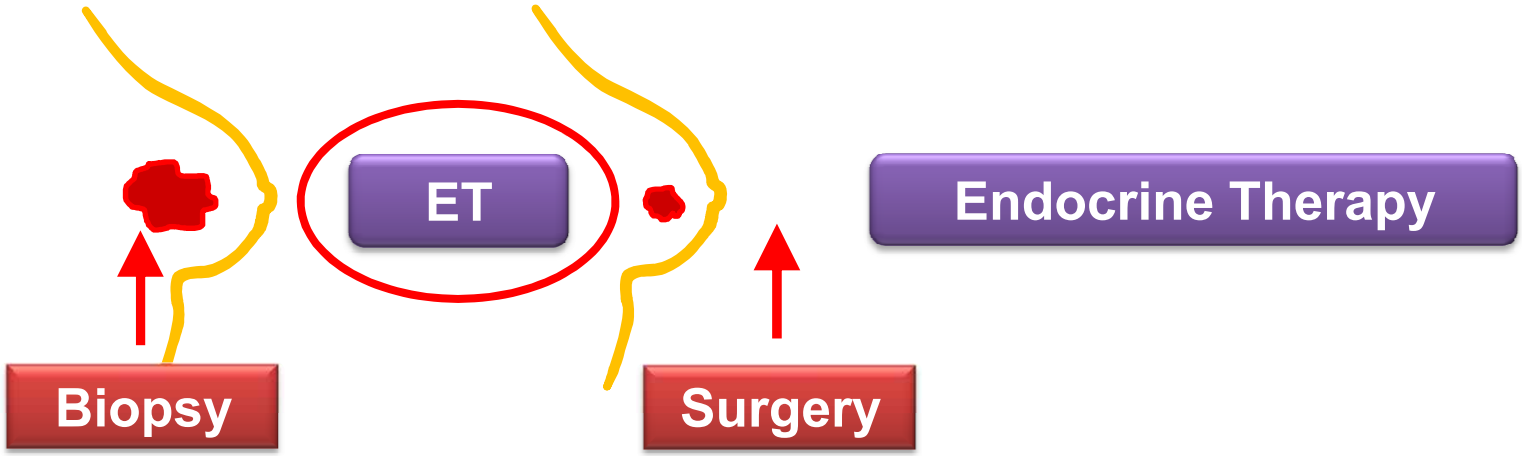
    - BCS → More cosmetic BCS
- Primary therapy : in frail, elderly, and infirm patients

Preoperative endocrine therapy



Clinical Benefits

- Down-staging of tumors
- Knowledge of treatment efficacy

Research Benefits

- Correlation of biomarkers to clinical response
- Sequential access to tumor

Dix JM et al. *Clin Cancer Res* 2000;6:2229-`35

Annals of Oncology Advance Access published June 17, 2009

special article

Annals of Oncology
doi:10.1093/annonc/mdp322

Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009

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Received 12 May 2009; accepted 12 May 2009

➢Neoadjuvant endocrine therapy without chemotherapy was considered reasonable for postmenopausal patients with strongly receptor-positive disease. If used, such treatment should be considered for a duration of 5–8 months or until maximum tumour response.

Annals of Oncology Advance Access published June 17, 2009

Invasive Breast Cancer

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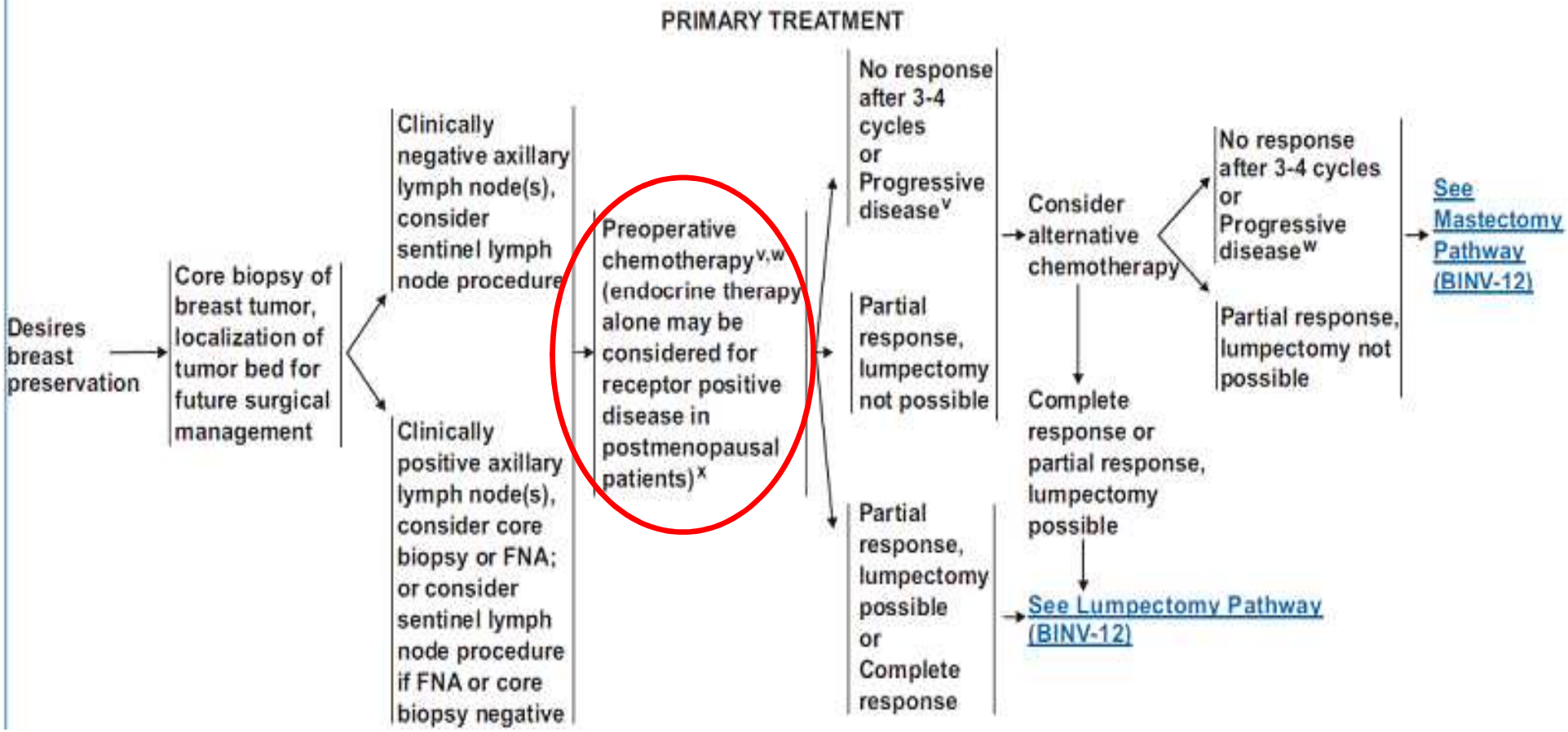
Breast Cancer TOC
Staging, Discussion, References

Preoperative Chemotherapy Guideline



review

Annals of Oncology 18: 1927–1934, 2007
doi:10.1093/annonc/mdm201
Published online 12 November 2007

Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006

M. Kaufmann[1]*, G. von Minckwitz[1,2], H. D. Bear[3], A. Buzdar[4], P. McGale[5], H. Bonnefoi[6], M. Colleoni[7], C. Denkert[8], W. Eiermann[9], R. Jackesz[10], A. Makris[11], W. Miller[12], J.-Y. Pierga[13], V. Semiglazov[14], A. Schneeweiss[15], R. Souchon[16], V. Stearns[17], M. Untch[18] & S. Loibl[1,2]

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Received 5 April 2007; accepted 13 April 2007

- LHRH analogues in premenopausal patients are investigational.
- Primary endocrine therapy with aromatase inhibitors should be offered to postmenopausal women if the tumor is expected to be highly endocrine responsive.

Advantages and disadvantages of preoperative endocrine therapy

	Advantages	Disadvantages
Surgical considerations	**May enable conserving surgery** **Gives the option to avoid surgery in elderly patients**	**Delay to definitive surgery might be detrimental in poor responder**
Prognostic considerations	**Allows assessment of response to treatment** **Prognostic value from assessment of PR** **Enables assessment of change in proliferative marker**	**Accurate baseline pathological staging is not obtained**
Comparison with neoadjuvant chemotherapy	**Less toxic, better tolerability** **Cheaper** **Good response rate in postmenopausal, ER/PR (+) pts**	**Ineffective in ER/PR(-)** **Longer time to response** **Lower pCR rate** **Less effective in premenopause**

Studies on primary use of tamoxifen

Study	Treatment	Follow up	Overall survival/Disease -free survival	Time to first locoregional failure	Number or percentage of local progressions or distance metastasis
Tan et al.	T				
Mustacchi et al.					6, p=0.0001
Gazet et al.					NS
Van Dalsen and De Varies	s				%, p<0.005
Bates et al.	Tamoxifen vs tamoxifen + surgery	34 months	NS/NS	ND	ND

Local control rate ; poor

NS: Non-significant / ND: not done

Abrial at al. *The Breast.* 2006:15;9-19.

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New evolution of preoperative endocrine therapy in postmenopausal women with selective aromatase inhibitor

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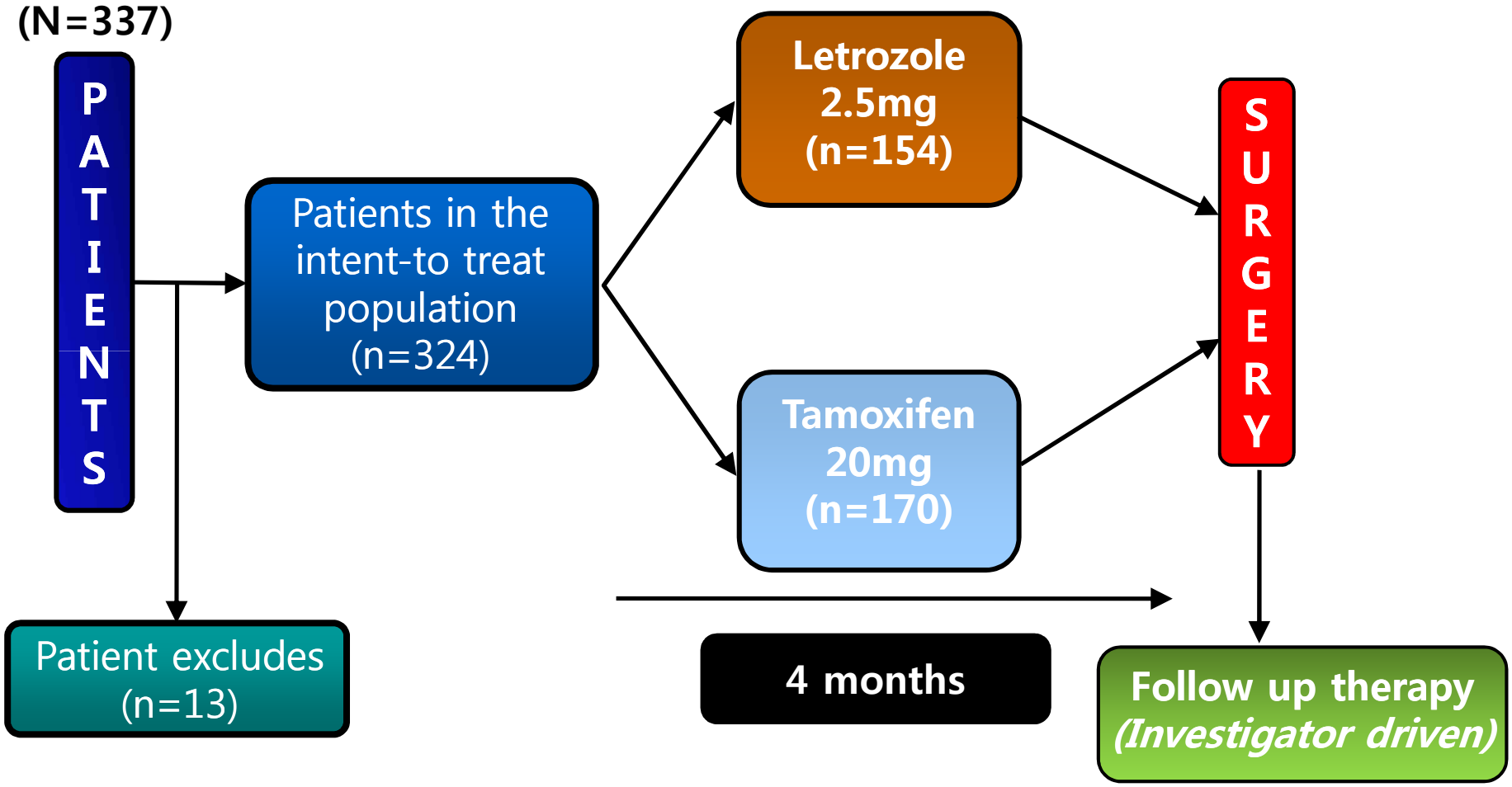
Trials using letrozole in neoadjuvant treatment

Study	Duration of treatment	Treatment	Clinical response	Conser-vative surgery	Pathological complete response
Dixon et al.	3 months	Letrozole 2.5mg vs 10mg	5 CR/7 PR vs 9 PR	ND	8.3% vs 0%
Miller et al.	3 months	Letrozole 2.5mg or 10mg vs Anastrozole 1mg or 10mg vs Tamoxifen 40mg	88% OR vs 70% OR vs 46% OR $p<0.0001$	ND	0% vs 0% vs 0%
Eiermann et al. **(P024 trial)**	4 months	Letrozole 2.5mg vs Tamoxifen 20mg	55% OR vs 36% OR $p<0.001$	45% vs 35% $p=0.022$	ND
Paepke et al.	4-8 months	Letrozole 2.5mg	57% OR vs 80% OR	ND	ND
Renshaw et al.	3-12 months	Letrozole 2.5mg	9.5% CR vs 36% CR	ND	ND
Dixon et al.	3 months	Letrozole 2.5mg	80% OR for Allred 8 74% OR for Allred 6-7	ND	ND

CR: complete response/PR: partial response/OR: objective response (CR + PR)/ND: not done

Abrial at al. *The Breast.* 2006:15;9-19.

P024 trial design



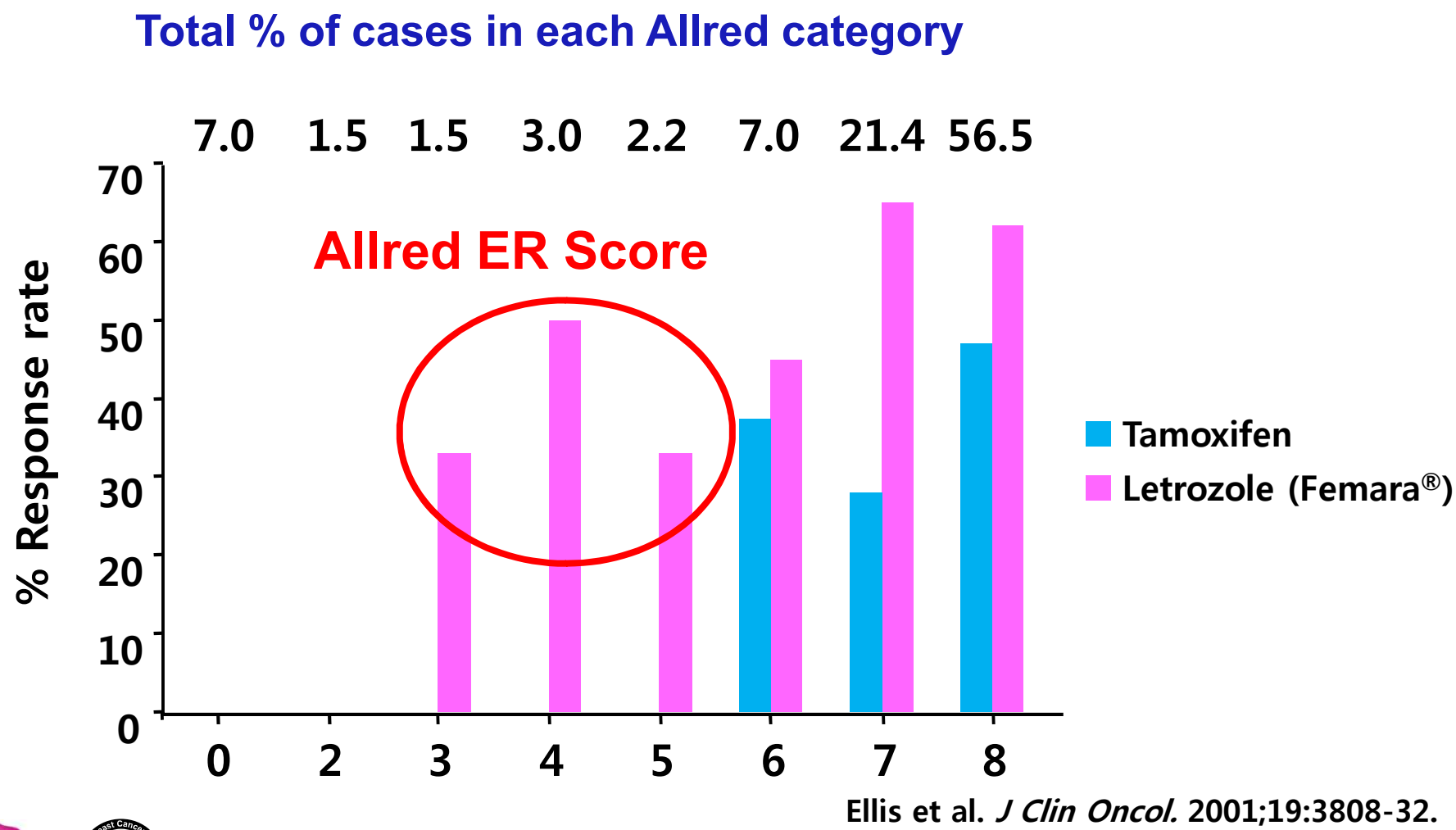
Eiermann et al. *Ann Oncol.* 2001;12:1257-32.

P024 : Results summary

Objective Response	Letrozole (Femara®) n=154	Tamoxifen n=170	*P* Value
Clinical	55%	36%	<0.001
Ultrasound	35%	25%	0.042
Mammography	34%	16%	<0.001
BCS	45%	35%	0.022

Eiermann et al. *Ann Oncol.* 2001;12:1257-32.

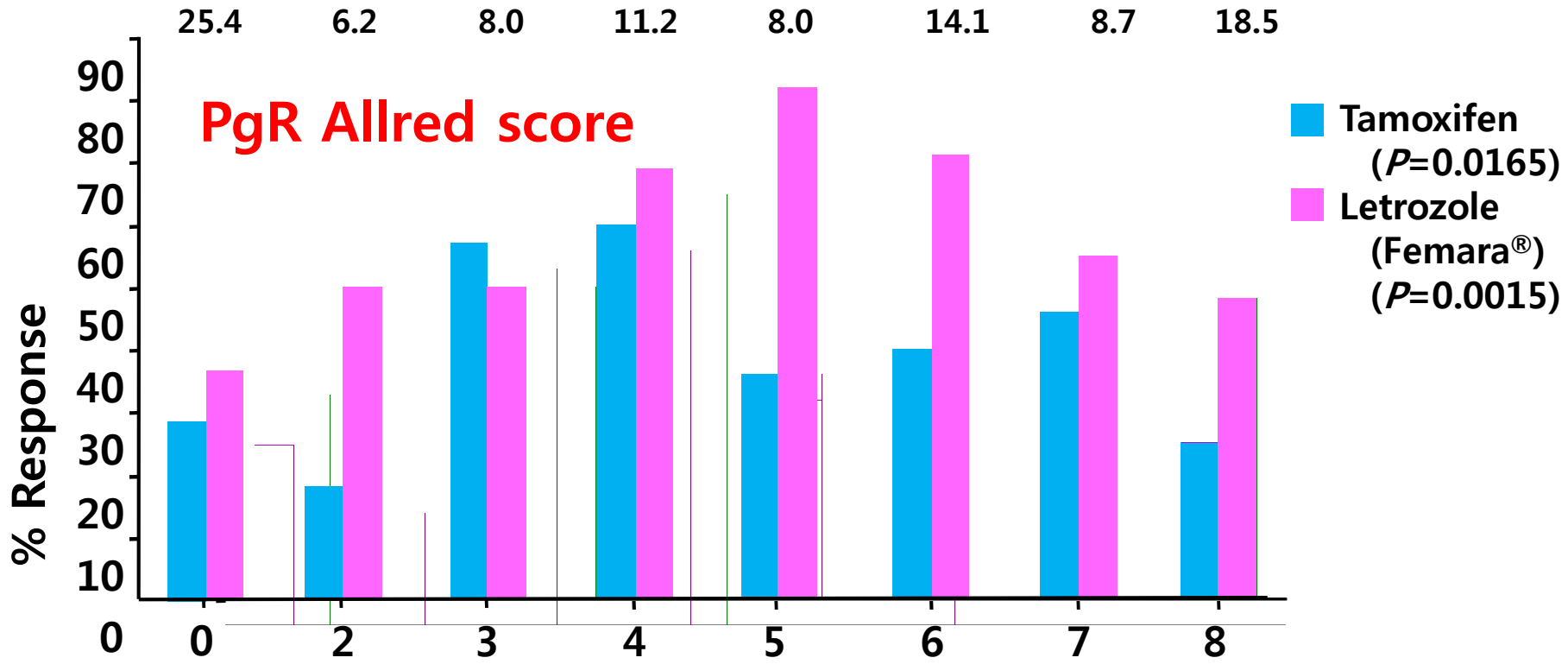
P024 : Response rates and ER expression



Ellis et al. *J Clin Oncol.* 2001;19:3808-32.

P024 : Response by PgR Allred score

Total % of cases in each Allred category



Logistic regression analysis of "inverse V" model

Ellis et al. *J Clin Oncol.* 2001;19:3808-32.

P024 : Response by HER-1/2

➢ Clinical response to Letrozole vs Tamoxifen in HER1+ and/or HER2+ cases that are also ER+

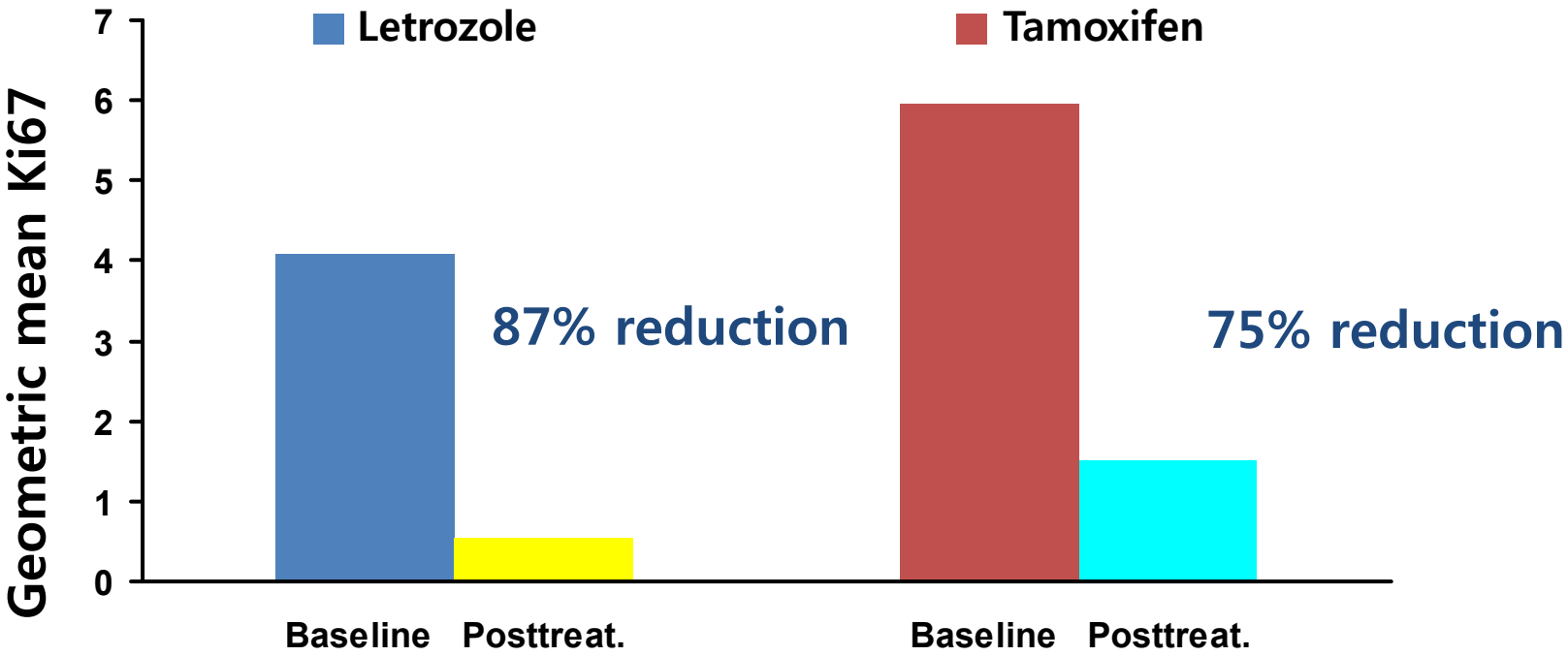
Category	Letrozole	Tamoxifen	Odds Ratio LET vs TAM	*P* Value
HER1/2+ ER+	15/17 (88%)	4/19 (21%)	28 (4.5-177)	0.0004
HER1/2- ER+	55/101 (54%)	42/100 (42%)	1.7 (0.9-2.9)	0.0789

LET = letrozole; TAM = tamoxifen.

Ellis et al. *J Clin Oncol.* 2001;19:3808-32.

P024: Percentage change in Ki67

➢ Letrozole (Femara®) Is a more effective anti-proliferative agent than Tamoxifen



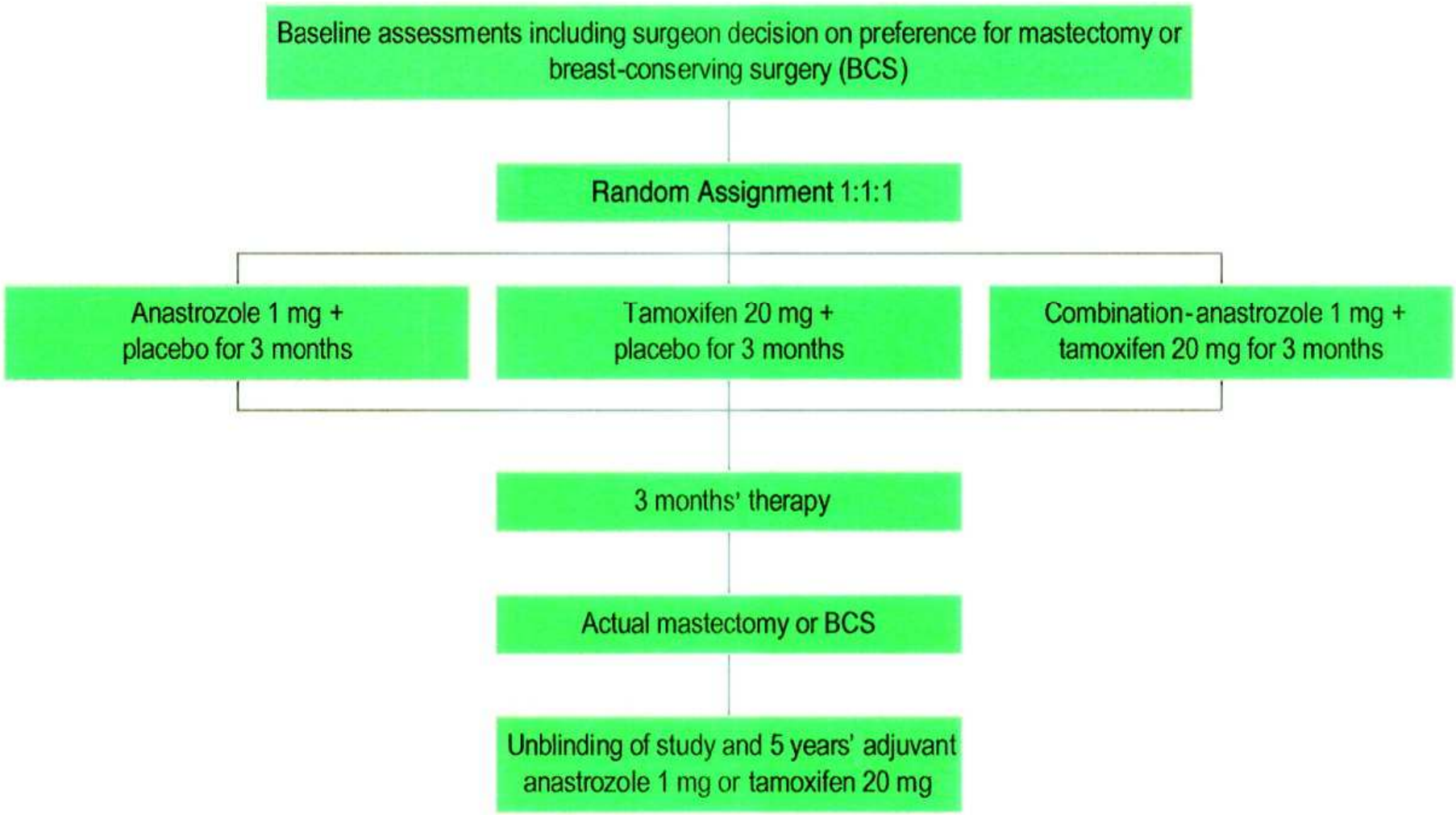
Post-treatment geometric mean is lower after Letrozole than Tamoxifen, *P*=0.0009 by ANCOVA (analysis of covariance of logged values with baseline adjustment).

Ellis et al. *Cancer Res.* 2003;63:6523.

Trials using anastrozole in neoadjuvant treatment

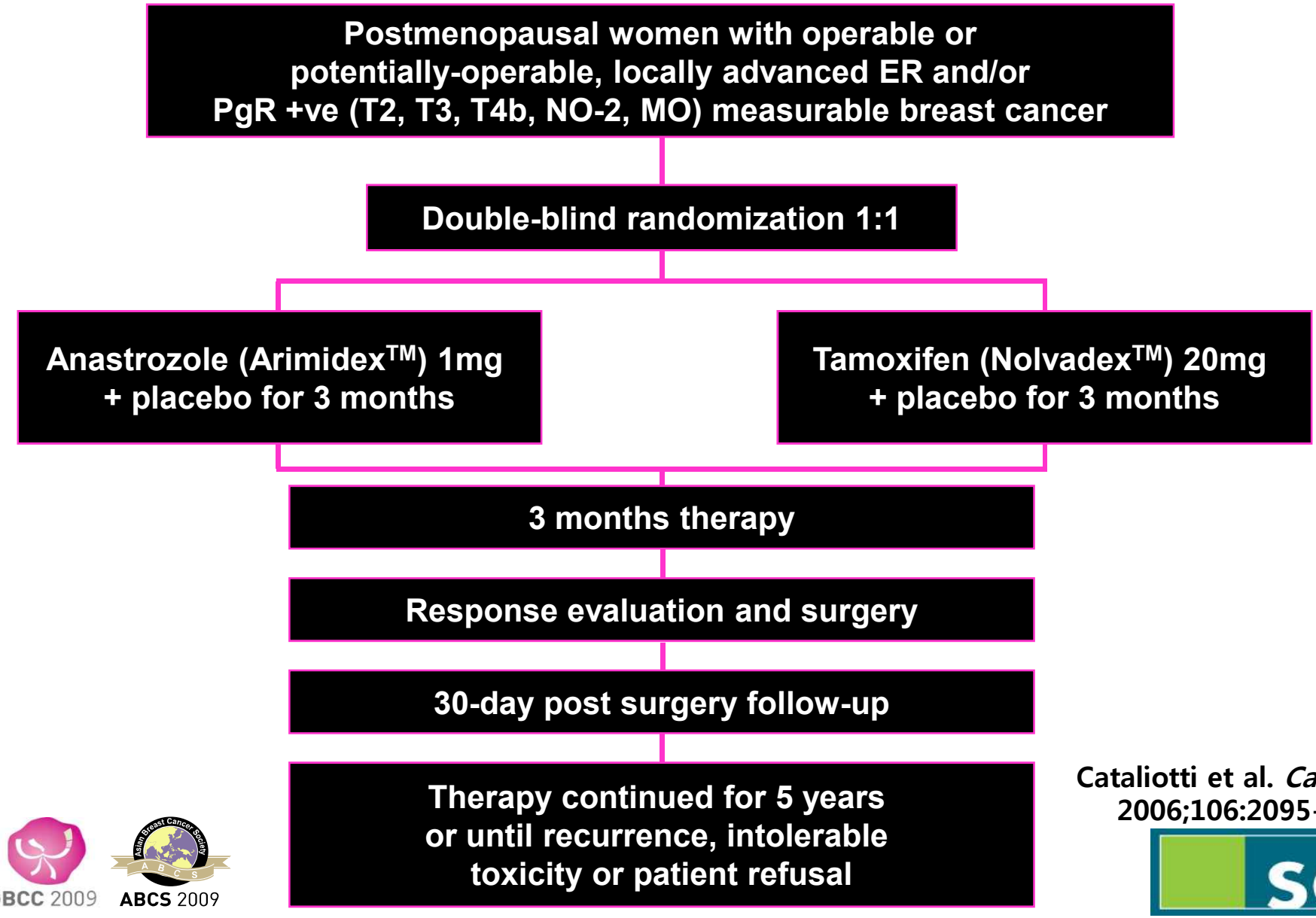
Study	Duration of treatment	Treatment	Clinical response	Conser-vative surgery	Pathological complete response
Dixon et al.	3 months	Anastrozole 1mg vs 10mg	Median reduction ultrasound : 80.5% vs 69.6%	91.6%	ND
Milla-Santos et al.	3 months	Anastrozole 1mg	55% CR & 29% PR	0%	12%
Smith and Dowsett **(IMPACT)**	3 months	Anastrozole 1mg vs tamoxifen 20mg vs anastrozole + tamoxifen	37% OR vs 36% OR vs 39% OR	46% vs 22% p=0.03	ND
Cataliotti et al **(PROACT)**	3 months	Anastrozole 1mg vs tamoxifen 20mg	39.5% shrinkage > 30% vs 35.4% p=0.29	ND	ND
CR: complete response/PR: partial response/OR: objective response (CR + PR)/ND: not node				**Abrial at al. *The Breast.* 2006:15;9-19.**	

The IMmediate Preoperative Anastrozole, tamoxifen, or Combination with Tamoxifen (IMPACT) trial design



Smith et al. *J Clin Oncol.* 2005;23:5108-16.

The PRe-Operative "Armidex" Compaired to Tamoxifen (PROACT) trial design



Cataliotti et al. *Cancer.* 2006;106:2095-103.

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Outcomes from IMPACT and PROACT studies of 3 months preoperative anastorozole or tamoxifen

Outcomes	IMPACT (n=330)			PROACT (n=314, Hormonal only)		
	Anastrozole (%)	Tamoxifen (%)	P-value	Anastrozole(%)	Tamoxifen (%)	P-value
Ultrasound ORR	24	20	0.53	36.2	26.5	0.07
Clinical ORR	37	36	0.87	49.7	39.7	0.08
Breast-conserving surgery	46	22	0.03*	43.0	30.8	0.04**

* For feasible surgery at 3 months (n=220)
** In hormonal only mastectomy or inoperable baseline (n=262)

Smith et al. *J Clin Oncol.* 2005;23:5108-16.
Cataliotti et al. *Cancer.* 2006;106:2095-103.

Summary of anastrozole studies

- There was significantly higher ORR in favor of anastrozole in those patients initially assessed as requiring mastectomy.

- There was no statistical significant reduction but feasible tumor shrinkage than tamoxifen and actual surgery in those patients whose tumors were thought to require a mastectomy or who were inoperable at initial assessment.

Trials with exemestane in neoadjuvant setting

Study	Included study	Response rate	pCR	Down staging	BCS-rate
Miller et al.	Locally advanced	85% reduction of tumor volume	NR	NR	80%
Krainick et al.	T < 2cm	37%	0	51%	52%
Tubiana-Hulin et al.	Operable T2-4	76%	18%	45%	45%
Semiglazov et al.	NR	76% 64% 60%	3%	NR	36%
Gil et al.	T2-4a-b > 3cm non BCS	45%	2%	NR	38%
Mustacchi et al.		60%	0	NR	76%
Mlineritsch et al.	T2-4a-b	34%	3%	45%	76%

pCR: pathologic complete response/BCS: breast conserving surgery/NR: not reported

Mlineritsch et al. *Breast Cancer Res Treat.* 2008;112:203-13.

Summary of exemestane studies

- There was substantial response rate, a valuable downsizing and breast-conserving surgery rate in post-menopausal women with HR-positive tumors.

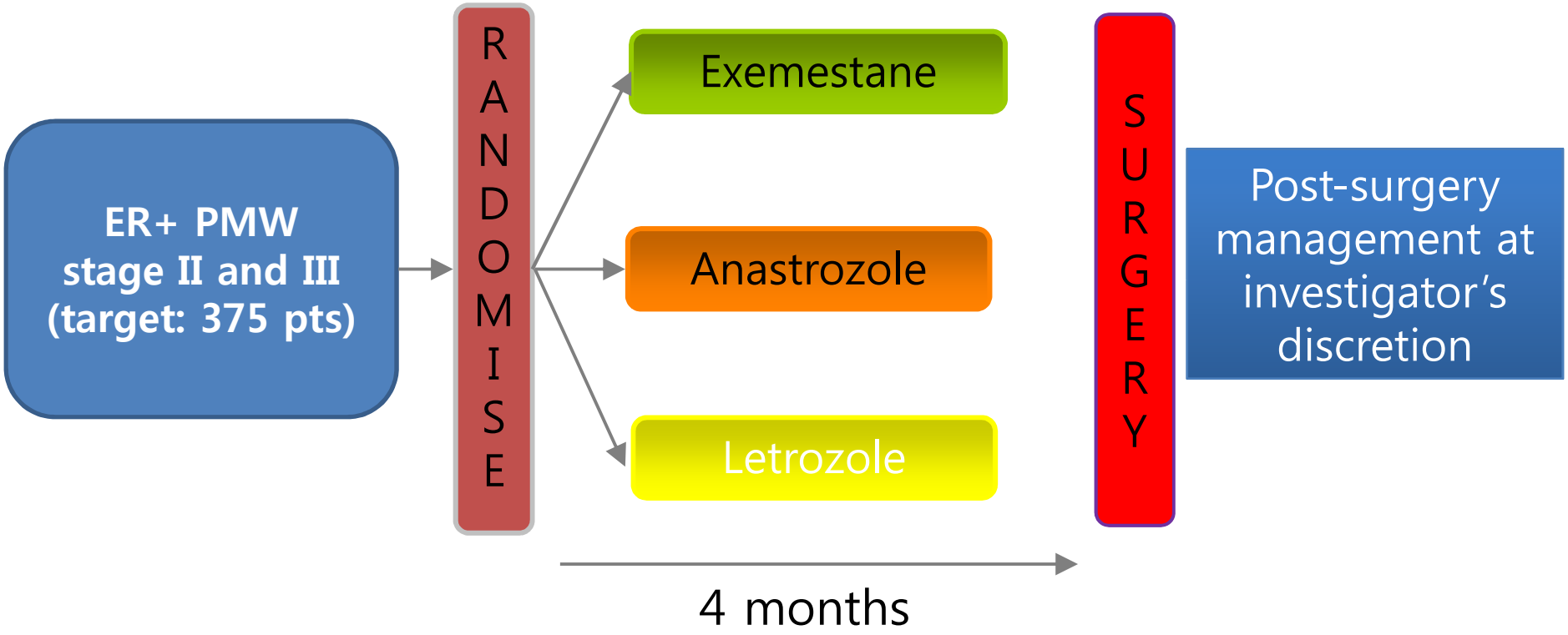
- The efficacy results on neoadjuvant exemestane are at least closely similar to those of non-steroidal AIs and also taxane/anthracycline combination chemotherapies in HR-positive patients.

Mlineritsch et al. *Breast Cancer Res Treat*. 2008;112:203-13.

Trial comparing preoperative AIs vs Tamoxifen

Trial	Design	Patients	Results		p value
			AI	Tam	
p024	Let vs Tam 4 months	337	CR 55%	CR 36%	<0.001
IMPACT	Ana vs Tam vs Combine 12 weeks	330	CR 37% BCS 44%	CR 36% BCS 31%	0.87 0.23
PROACT	Ana vs Tam 3 months	314	RR 36.2% BCS 43%	RR 26.5% BCS 31%	0.07 0.04
Exemestane	Exe vs Tam 3 months	151	RR 76% BCS 37%	RR 40% BCS 20%	0.05 0.05

ACOSOG Z1031: Randomised Neoadjuvant AI Protocol



ACOSOG = American College of Surgeons Oncology Group; AI = aromatase inhibitor; ER = estrogen receptor; PMW = postmenopausal women.

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Neoadjuvant use of fulvestrant

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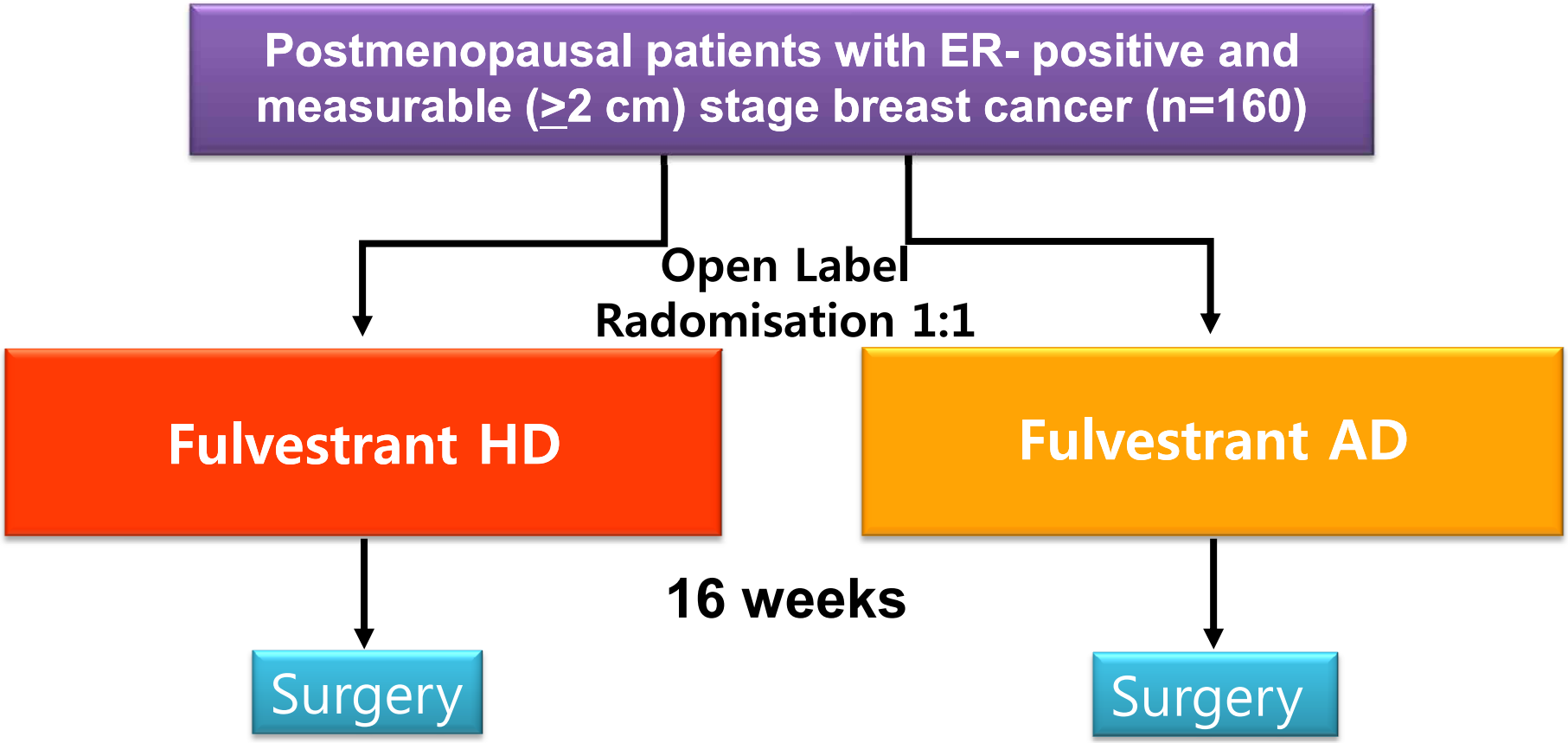
Neoadjuvant Endocrine Therapy for Women with Endocrine Sensitive Tumours

Phase II, Randomised Trial



Core biopsy at baseline and 4 weeks for correlative studies, surgery performed at 16 weeks

Kuter I et al. *SABCS*. 2007.

High dose: rationale

- Clinical data have shown that fulvestrant 125 mg is less effective than 250 mg
- Fulvestrant induces dose-related reductions in estrogen receptor (ER), progesterone receptor (PgR) and Ki67
- Pharmacokinetic data suggest that higher fulvestrant plasma concentrations may
  - lead to higher ER downregulation (and thus may improve overall efficacy)
  - reduce time to steady state

NEWEST – results summary

- NEWEST is the first study to compare the biological and clinical activity of fulvestrant HD and AD regimens
- At week 4 fulvestrant HD:
  - reduced Ki67 LI to a significantly greater extent ($p<0.0001$) than AD (primary endpoint)
  - reduced ER levels significantly more ($p<0.0003$) than AD and reduced PgR expression
- Similar reductions were also observed for HD vs AD at week 16
- All other efficacy parameters were numerically in favour of the HD regimen
- Both doses were well tolerated
  - AEs consistent with known toxicity profile of fulvestrant
  - no adverse effects on bone markers or endometrium

Kuter et al. SABCS newsletter; Issue 1, December 13 2007: 13

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Neoadjuvant use of combined therapy

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Preoperative bevacizumab combined with letrozole and chemotherapy in locally advanced ER(+) and/or PgR(+) breast cancer

- Antiangiogenic agent bevacizumab showed a synergic effect when combined with chemotherapy and endocrine therapy
- Investigated the bevacizumab in combination with chemotherapy (capecitabine and vinorelbine) and endocrine therapy (letrozole) (+triptorelin in premenopausal women)

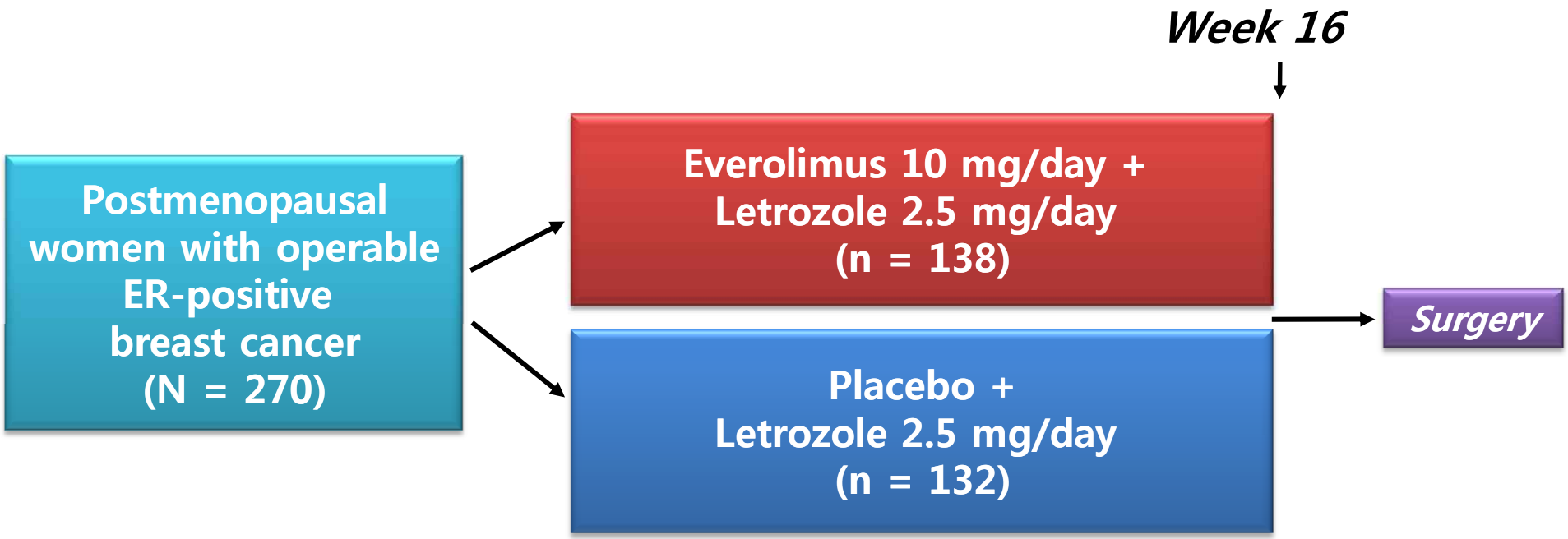
Torrisi R, et al. *Br J Cancer*. 2008;99:1564-71.

Conclusion

➢ Bebacizumab is feasible and active in association with primary chemo-endocrine therapy for ER-positive tumors in terms of proliferation inhibition, clinical response and antiangiogenic activity.

Torrisi R, et al. *Br J Cancer*. 2008;99:1564-71.

Neoadjuvant Everolimus + Letrozole in ER-positive breast cancer



Baselga J, et al. *J Clin Oncol*. 2009;27:2630-7.

Conclusion of neoadjuvant Everolimus + Letrozole in ER-positive breast cancer

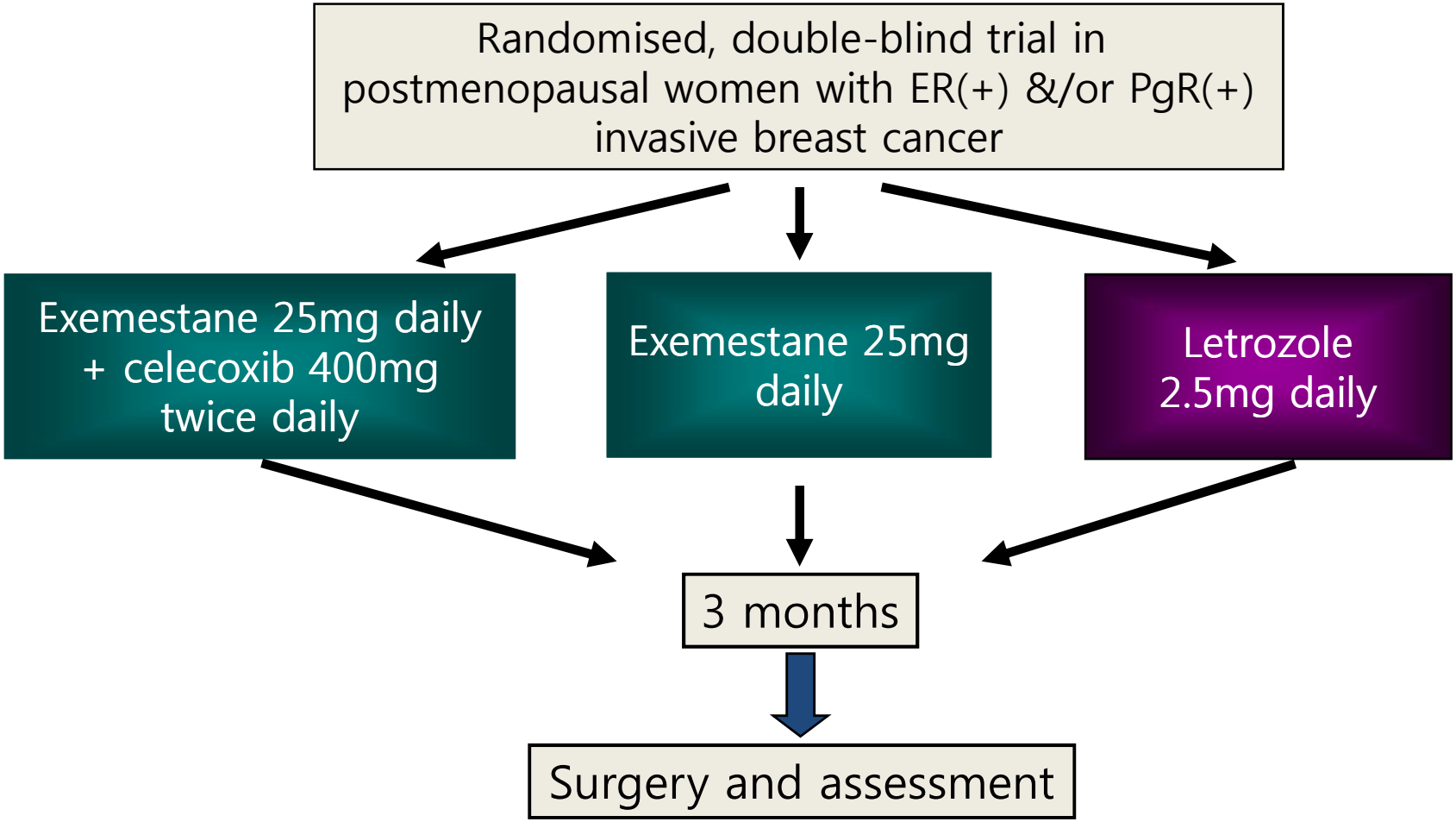
- Everolimus significantly increased the efficacy of letrozole in the treatment of newly diagnosed, ER-positive breast cancer in terms of both clinical and antiproliferative response.

- The safety profile of the combination is acceptable, and toxicity in the everolimus arm was consistent with historical data.

- The benefit/risk assessment calls for additional evaluation of the potential value of the combination.

Baselga J, et al. *J Clin Oncol*. 2009;27:2630-7.

Celecoxib anti-aromatase neoadjuvant (CANN) trial for locally advanced breast cancer



Chow L , et al. *J Steroid Biochem Mol Biol*. 2008;111:13-17.

Conclusion of CANN trial

- Three anti-aromatase therapies are effective and safe
- Serum levels of CA15.3 dropped more significantly when combined with celecoxib

Chow L , et al. *J Steroid Biochem Mol Biol*. 2008;111:13-17.

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Neoadjuvant use of premenopausal patients

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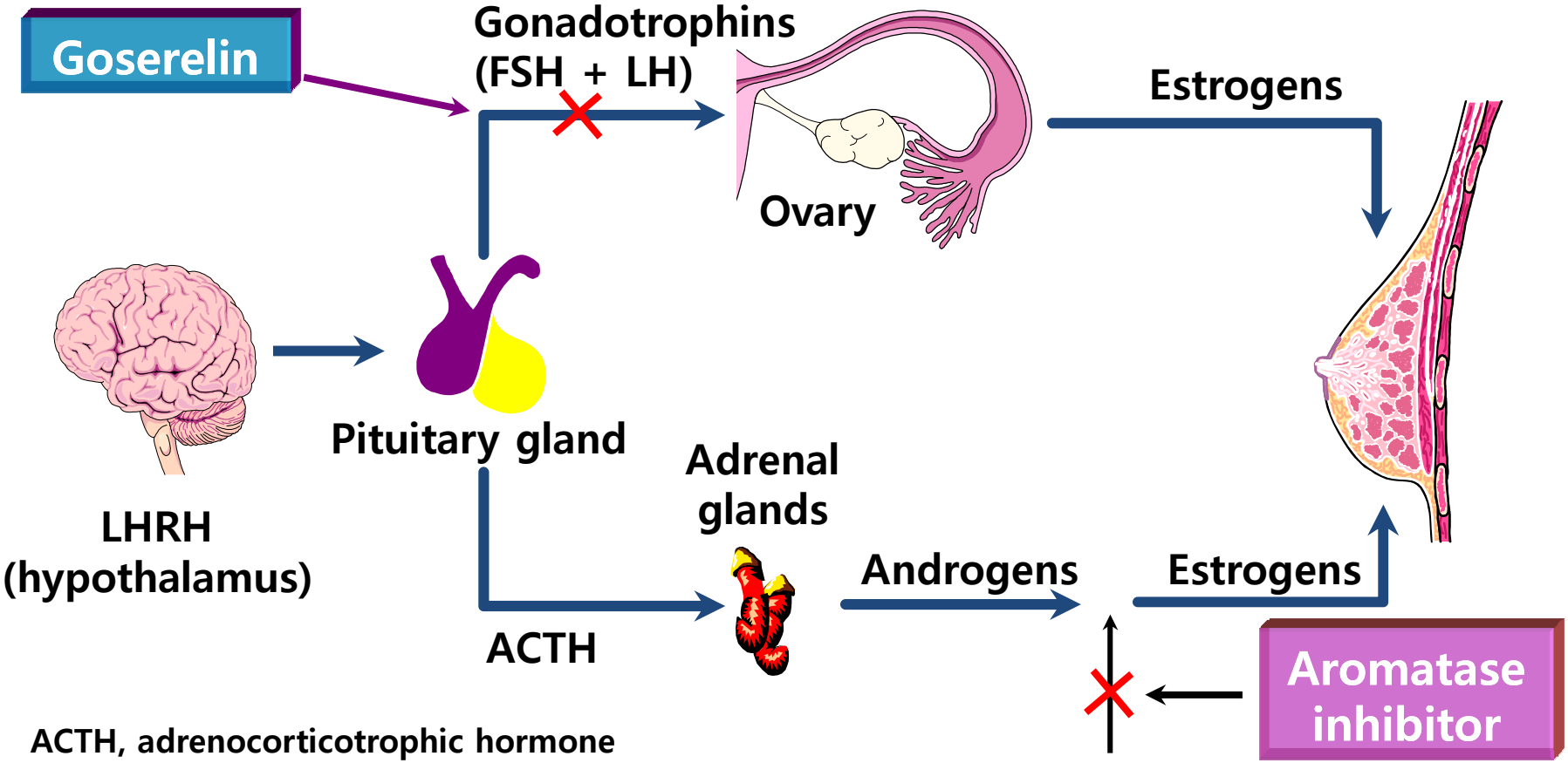
Rationale for Combination Therapy



ACTH, adrenocorticotrophic hormone
FSH, follicle-stimulating hormone
LH, luteinising hormone
LHRH, LH-releasing hormone

Summary of preoperative endocrine therapy in premenopause patients

- In interim analysis of results indicate that therapy with AIs, in combination with a GnRH analogue, is safe and effective in pre-menopausal women with locally advanced breast cancer.

- A biological response, in terms of down-regulation of the estrogenic signaling, was observed in all patients.

- The trend to improved response rate observed with longer duration in selected populations of premenopausal patients with endocrine-responsive tumors.

Torrisi et al. *Br J Cancer.* 2007;97:802-8.

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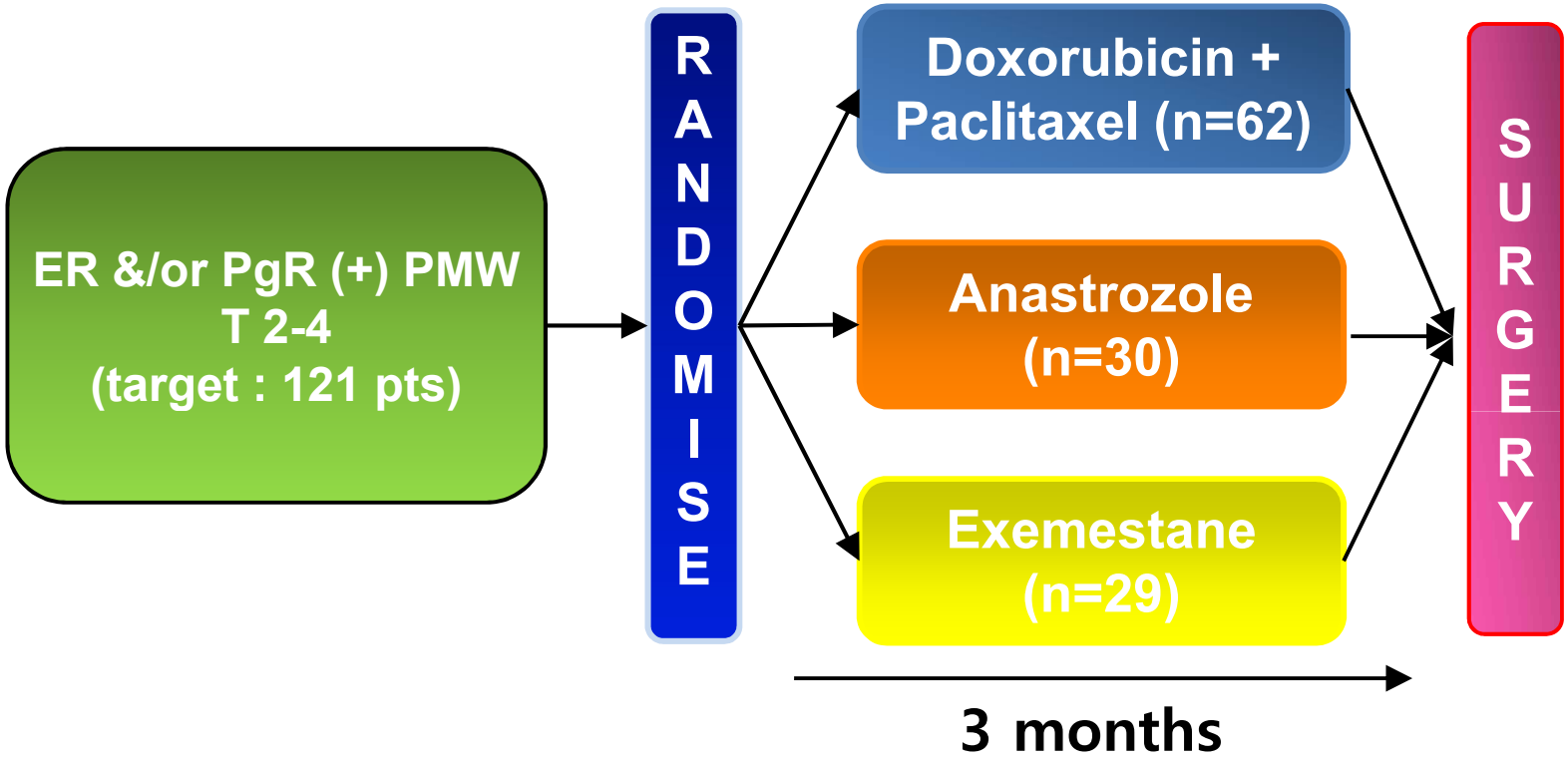
Direct comparison of chemotherapy

Unpublished Pilot Russian Study



ER = estrogen receptor; PgR = progesterone receptor; PMW = post-menopausal women; T = tumor size; pts = patients.

Proc Am Soc Clin Oncol 2004;22(14s):519

Results

- Clinical and mammographic objective response rates (ORR) were similar for endocrine therapy and chemotherapy, and there was a trend for increasing rates of breast-conserving surgery in favor of endocrine therapy with no significant differences in local recurrence rates.

Proc Am Soc Clin Oncol 2004;22(14s):519

Neoadjuvant endocrine *versus* chemotherapy

	Neoadjuvant Chemotherapy	Neoadjuvant Endocrine Therapy
Regimen	Anthracycline based	Letrozole
Median volume decreased	78%	75%
Responses	85%	88.7%
pCR	18%	1.9%
Central scars	4%	58.5%
Breast-conserving surgery	32%	86.7%

Dixon M, Histology Vol 51 (2007)
ER+, 31/50 (CTx), All in 53 Letrozole

Conclusion

- Neoadjuvant endocrine therapy was better tolerated than chemotherapy: the most common adverse events reported were hot flushes, fatigue, vaginal spotting, and arthralgia.

- This data confirms that endocrine therapy is a safe alternative to chemotherapy, with similar response rates but less toxicity.

Proc Am Soc Clin Oncol 2004;22(14s):519

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Conclusion and Take Home Message

Conclusion and Take Home Message

- Neoadjuvant hormone therapy is effective at down-staging tumors, particularly large tumors, initially thought to be inoperable or requiring mastectomy.

- Aromatase inhibitors are superior to tamoxifen in terms of clinical response.

- When compared with neoadjuvant chemotherapy, aromatase inhibitors have similar ORR and rates of local recurrence after down-staging and breast-conserving treatment, but are better tolerated because of their much lower toxicity.

Conclusion and Take Home Message

- The aromatase inhibitors are clinically and biologically effective in both HER2 positive and negative tumors, whereas HER2 positive tumors show a level of resistance to tamoxifen.

- In neoadjuvant studies comparing aromatase inhibitors with tamoxifen, the duration of use has been 3-4 months, by which time any response is usually evident, but optimum duration of treatment has yet to be identified.

Thank You for Your Attention !

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