adjuvant endocrine therapy

postmenopausal

- Women 60 years and older are postmenopausal.
- Women less than 60 years
  - They previously underwent a bilateral oophorectomy.
  - They have not had any menstrual periods for 12 months or more + the serum estradiol.
- They are amenorrheic on tamoxifen + FSH and serum estradiol
- In GnRh setting

AI versus tamoxifen

- Reduced breast cancer recurrence
- Lower 10-year breast cancer mortality
- similar clinical outcomes and tolerability between the aromatase inhibitors

Musculoskeletal pains and stiffness in AI

- Exercise and NSAIDs
- Temporary discontinuation of AI, followed by initiation of a different AI
- Duloxetine
- Switch to tamoxifen, for those who are unable or unwilling to continue treatment with an AI.

Incorporation of adjuvant CDK 4/6 inhibitor in high-risk disease

- Abemaciclib is approved by the US Food and Drug Administration (FDA) as adjuvant therapy in HER2 negative HR positive
- Ki-67 ≥20% plus node positive
  - N1 disease and other high-risk features (T3, high grade),

    or
  - N2 or N3 disease
- for two years, concurrently with the start of endocrine treatment
- the follow-up remains short, the effect on OS is yet unknown
- it is also acceptable to omit

Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2−, Node-Positive, High-Risk, Early Breast Cancer (monarchE)

METHODS This open-label, phase III study included patients with HR+, HER2−, high-risk EBC, who had surgery and, as indicated, radiotherapy and/or adjuvant/neoadjuvant chemotherapy. Patients with four or more positive nodes, or one to three nodes and either tumor size ≥ 5 cm, histologic grade 3, or central Ki-67 ≥ 20%, were eligible and randomly assigned (1:1) to standard-of-care adjuvant endocrine therapy (ET) with or without abemaciclib (150 mg twice daily for 2 years). The primary end point was invasive disease-free survival (IDFS), and secondary end points included distant relapse–free survival, overall survival, and safety.

RESULTS At a preplanned efficacy interim analysis, among 5,637 randomly assigned patients, 323 IDFS events were observed in the intent-to-treat population. Abemaciclib plus ET demonstrated superior IDFS versus ET alone (P = .01; hazard ratio, 0.75; 95% CI, 0.60 to 0.93), with 2-year IDFS rates of 92.2% versus 88.7%, respectively. Safety data were consistent with the known safety profile of abemaciclib.

CONCLUSION Abemaciclib when combined with ET is the first CDK4/6 inhibitor to demonstrate a significant improvement in IDFS in patients with HR+, HER2− node-positive EBC at high risk of early recurrence.

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- High risk was defined as having ≥4 positive nodes; or one to three positive nodes and at least one of the following: tumor size ≥5 cm, histologic grade 3, or central Ki-67 ≥20 percent
- improvement in invasive disease-free survival
  - two-year IDFS rates of 92 versus 89 percent
- The absolute IDFS benefit in the Ki-67 ≥20 percent group was 7.1 percent, versus 4.5 percent in the Ki-67 <20 percent group.
- The FDA approval is only in tumors that are Ki-67 ≥20 percent.

PALLAS trial

- the addition of two years of palbociclib to adjuvant endocrine therapy in patients with stage II or III hormone receptor-positive/HER2-negative breast cancer
- failed to improve three-year IDFS

PENELOPE-B trial

- with residual disease after neoadjuvant chemotherapy
  - the addition of one year of palbociclib to adjuvant endocrine therapy did not improve IDFS

BRCA carriers with high-risk disease OlympiA trial

- Triple-negative disease
- Hormone receptor-positive disease
  - Treated with neoadjuvant chemotherapy
    - with residual disease and a CSP+EG ≥3, we suggest adjuvant Olaparib
  - Treated with adjuvant chemotherapy
    - For patients with hormone receptor-positive disease who were treated with adjuvant chemotherapy and had N2 disease, we suggest adjuvant olaparib.
- patients assigned to the olaparib group had an improvement in three-year DFS relative to the placebo group

Clinical stage	Score	Pathologic stage	Score	Tumor Marker	Score
Stage I	0	Stage 0	0	ER Negative	1
Stage IIA	0	Stage I	0	Nuclear Grade 3	1
Stage IIB	1	Stage IIA	1		
Stage IIIA	1	Stage IIB	1		
Stage IIIB	2	Stage IIIA	1		
Stage IIIC	2	Stage IIIB	1		
		Stage IIIC	2		

DURATION OF ENDOCRINE TREATMENT extended therapy

1. minimum duration of five years
2. extended therapy: → only improve DFS
3. is an option for all patients

- tumor size
- grade
- Age
- ASCO has not recommended using any of these to guide the decision about extended endocrine therapy at this time.
- gene and protein expression assays have be unlikely to benefit

Durations of extended endocrine therapy

- For women with higher-risk disease (eg, stage II or stage III disease), we suggest extended endocrine treatment (Grade 2B), total duration between 7 and 10 years is appropriate,
- For women with smaller, node-negative tumors (ie, stage I disease),
  - Women who are tolerating endocrine treatment well and wish to decrease their likelihood of new breast cancers or recurrences may reasonably choose extended endocrine therapy. 7 years

Patients with mucinous or tubular/cribriform histologies

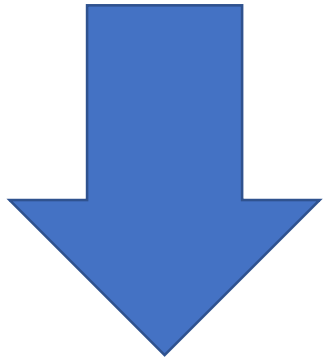
- Because prospective data are limited for mucinous and tubular/cribriform histologies, our treatment approach for these entities is the same as for more common histologies.

adjuvant endocrine therapy for premenopausal women

HIGH-RISK, HORMONE RECEPTOR-POSITIVE CANCERS

- patients in whom chemotherapy is indicated and age ≤35 years

  node-positive breast cancer, large tumor size, high tumor grade, lymphovascular invasion, and/or high risk of recurrence based on a genomic assay; and younger women, <35 years of age



adding of ovarian function suppression (OFS)/ablation

start with a GnRHa and proceed to oophorectomy if OFS is tolerated.

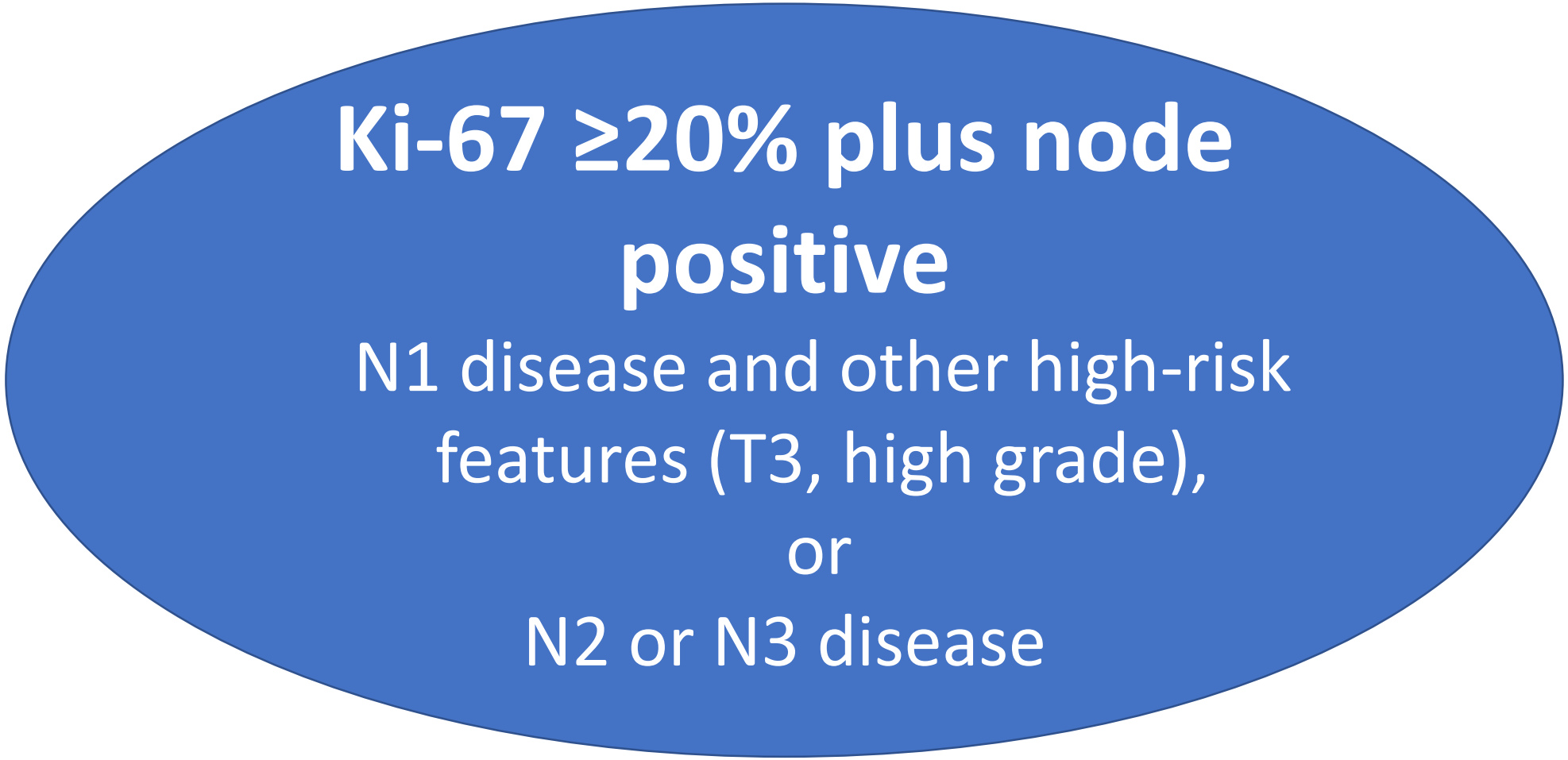
addition of OFS to either tamoxifen or AI

- modest DFS benefit but not OS
- but may not justify the more intensive side effects for many average-risk patients.

Sequencing

1. start GnRHa after chemotherapy and add AIs two to three months later
2. others initiate OFS and AIs in tandem, according to the SOFT/TEXT trials discussed above
3. For those who will be treated with tamoxifen and OFS, they are initiated concurrently.

Addition of CDK 4/6 inhibitor same as postmenopausal



- some women on OFS and AIs do not achieve consistently low estradiol levels
- the SOFT Estrogen Suppression Study (SOFT-EST), estradiol levels were measured in a central laboratory at several time points during the first year of therapy with triptorelin
- 17 percent of the women were found to have levels above those that have been reported in postmenopausal

two years Vs five years

- One trial has evaluated a shorter course of OFS (two years), with promising results, but two versus five years have not been compared in a head-to-head fashion, and we would therefore stop at two years only for those not tolerating treatment.

Take home message

1. Stage 1 in pre or postmenopusal → 5 to 7 years treatment
2. Stage 2 in pre or postmenopusal → 7 to 10 years treatment
3. Abemaciclib in pre or postmenopausalhigh risk patients:
   - Ki-67 ≥20% plus node
     a. positive N1 disease and other high-risk features (T3, high grade),
     b. N2 or N3 disease
4. Olaparib in high risk BRCA+ patients
   a. Treated with neoadjuvant chemotherapy with residual disease and a CSP+EG ≥3,
   b. Treated with adjuvant chemotherapy and had N2 disease

Take home message

- adding of ovarian function suppression (OFS)/ablation in
  - patients in whom chemotherapy is indicated and age ≤35 years
  - two years Vs five years
- All of the above changes can not be superior OS than 5 years tamoxifen alone