
بسم الله

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Panel discussion :
Young Breast Cancer Patients

Colleagues:

Dr. M.S.Akbari
Dr. M.Akbari
Dr. M.Hoseyni
Dr. P.Sasanpour
Dr. F.Taghizadeh Hesari
Dr. F.Abbasvandi
Dr. S.Hoseyni
Dr. S.Tabarestani
Dr. A.Pasdar
Dr. L.Nzari

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY striving innovation in oncology

SPECIAL ARTICLE

ESO—ESMO fifth international consensus guidelines for breast cancer in young women (BCY5)

S. Paluch-Shimon[1*†], F. Cardoso[2†], A. H. Partridge[3], O. Abulkhair[4], H. A. Azim[5], G. Bianchi-Micheli[6], M. J. Cardoso[2], G. Curigliano[7,8], K. A. Gelmon[9], O. Gentilini[10], N. Harbeck[11], B. Kaufman[12], S. B. Kim[13], Q. Liu[14], J. Merschdorf[15], P. Poortmans[16], G. Pruneri[17], E. Senkus[18], B. Sirohi[19], T. Spanic[20], V. Sulosaari[21], F. Peccatori[7,22†] & O. Pagani[23†]

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We dedicate this manuscript in memory of a dear friend and colleague Bella Kaufman.

The fifth International Consensus Symposium for Breast Cancer in Young Women (BCY5) took place virtually in October 2020, organized by the European School of Oncology (ESO) and the European Society of Medical Oncology (ESMO). Consensus recommendations for the management of breast cancer in young women were updated from BCY4 with incorporation of new evidence to inform the guidelines. Areas of research priorities as well as specificities in different geographic and minority populations were identified. This manuscript summarizes the ESO—ESMO international consensus recommendations, which are also endorsed by the European Society of Breast Specialists (EUSOMA).

Key words: young women, breast cancer, fertility

❖A 29 Y Female ,Single ,Medical Doctor (Resident) , with R. Breast cancer

❖Triple Negative

❖Core Biopsy : Inv.Ductal Ca (NST)

❖Sono AND Marker: T:23mm ,Axilla And Others :neg

❖BCS is easily feasible

❖BRCA2: Mutant Germline

❖ Next Generation Sequencing NGS:?

❖Fertility Preservation?

What's your recommendation?

1. SR

2. Preop systemic treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

N. Masuda, S.-J. Lee, S. Ohtani, Y.-H. Im, E.-S. Lee, I. Yokota, K. Kuroi, S.-A. Im, B.-W. Park, S.-B. Kim, Y. Yanagita, S. Ohno, S. Takao, K. Aogi, H. Iwata, J. Jeong, A. Kim, K.-H. Park, H. Sasano, Y. Ohashi, and M. Toi

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ABSTRACT

BACKGROUND

Patients who have residual invasive carcinoma after the receipt of neoadjuvant chemotherapy for human epidermal growth factor receptor 2 (HER2)–negative breast cancer have poor prognoses. The benefit of adjuvant chemotherapy in these patients remains unclear.

METHODS

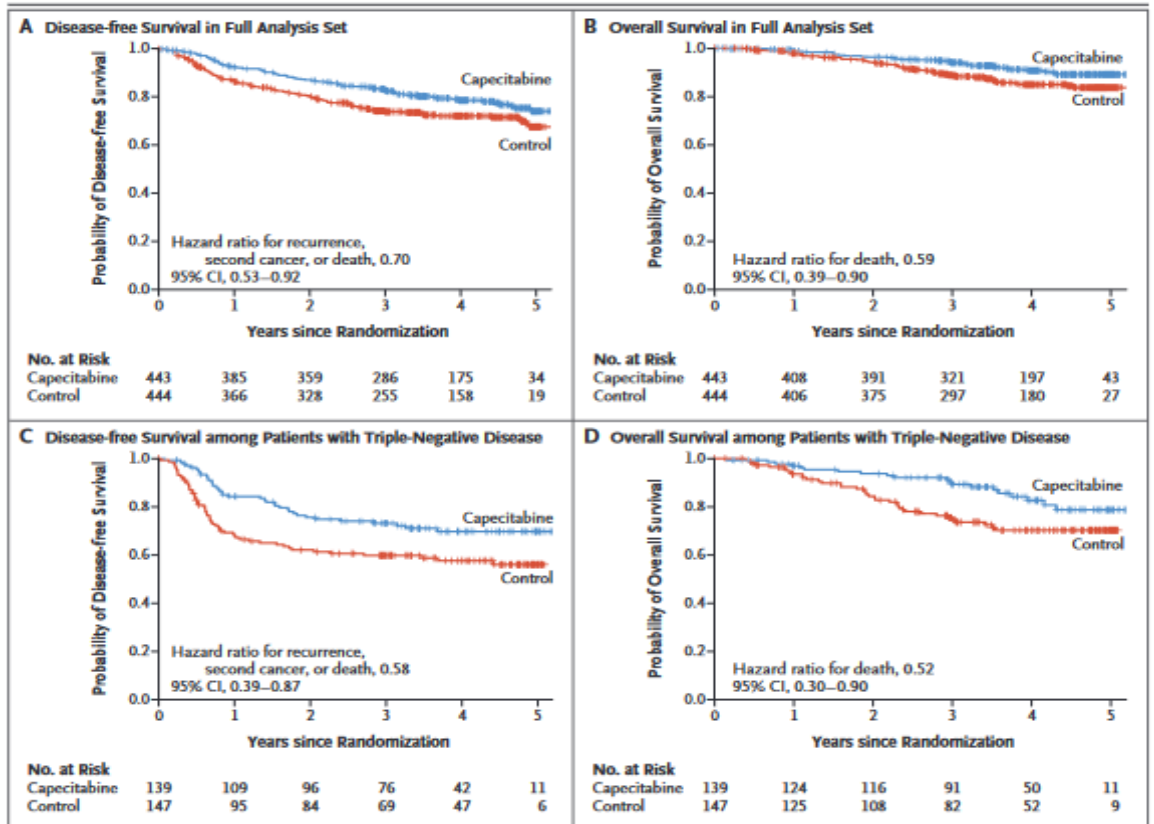
We randomly assigned 910 patients with HER2-negative residual invasive breast cancer after neoadjuvant chemotherapy (containing anthracycline, taxane, or both) to receive standard postsurgical treatment either with capecitabine or without (control). The primary end point was disease-free survival. Secondary end points included overall survival.

RESULTS

The result of the prespecified interim analysis met the primary end point, so this trial was terminated early. The final analysis showed that disease-free survival was longer in the capecitabine group than in the control group (74.1% vs. 67.6% of the patients were alive and free from recurrence or second cancer at 5 years; hazard ratio for recurrence, second cancer, or death, 0.70; 95% confidence interval [CI], 0.53 to 0.92; P=0.01). Overall survival was longer in the capecitabine group than in the control group (89.2% vs. 83.6% of the patients were alive at 5 years; hazard ratio for death, 0.59; 95% CI, 0.39 to 0.90; P=0.01). Among patients with triple-negative disease, the rate of disease-free survival was 69.8% in the capecitabine group versus 56.1% in the control group (hazard ratio for recurrence, second cancer, or death, 0.58; 95% CI, 0.39 to 0.87), and the overall survival rate was 78.8% versus 70.3% (hazard ratio for death, 0.52; 95% CI, 0.30 to 0.90). The hand–foot syndrome, the most common adverse reaction to capecitabine, occurred in 73.4% of the patients in the capecitabine group.

CONCLUSIONS

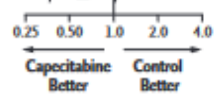
After standard neoadjuvant chemotherapy containing anthracycline, taxane, or both, the addition of adjuvant capecitabine therapy was safe and effective in prolonging disease-free survival and overall survival among patients with HER2-negative breast cancer who had residual invasive disease on pathological testing. (Funded by the Advanced Clinical Research Organization and the Japan Breast Cancer Research Group; CREATE-X UMIN Clinical Trials Registry number, UMIN000000843.)



Kaplan–Meier Estimates of Disease-free Survival and Overall Survival.

Panels A and B show disease-free survival and overall survival, respectively, in the full analysis set (primary analysis). Tick marks indicate censored data. Panels C and D show disease-free survival and overall survival, respectively, in the subgroup of patients with triple-negative breast cancer (i.e., breast cancer that was negative for estrogen receptors, progesterone receptors, and HER2).

Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value
Overall	887	0.70 (0.53–0.92)	0.01
Age			0.85
≤50 yr	532	0.72 (0.50–1.03)	
>50 yr	355	0.68 (0.45–1.04)	
Hormone receptor status			0.21
Estrogen-receptor positive or progesterone-receptor positive	601	0.81 (0.55–1.17)	
Estrogen-receptor negative and progesterone-receptor negative	286	0.58 (0.39–0.87)	
BMI			0.71
<25.0	641	0.67 (0.49–0.93)	
≥25.0	246	0.76 (0.44–1.32)	
BMI among patients with hormone-receptor–negative status			0.66
<25.0	208	0.55 (0.34–0.88)	
≥25.0	78	0.68 (0.30–1.53)	
Tumor size at diagnosis			0.82
≤2 cm	129	0.65 (0.30–1.44)	
>2 cm or cT4	757	0.71 (0.53–0.96)	
Pathological effect grade			0.31
0, 1a, or 1b	484	0.62 (0.44–0.88)	
2 or 3	385	0.84 (0.52–1.34)	
No. of lymph nodes involved on histologic assessment			0.34
0	347	0.87 (0.48–1.60)	
1–3	339	0.54 (0.36–0.83)	
≥4	201	0.81 (0.51–1.28)	
Use of taxane drugs			0.89
Yes	853	0.70 (0.53–0.93)	
No	34	0.80 (0.11–5.70)	
Use of fluorouracil			0.56
Yes	533	0.75 (0.53–1.05)	
No	354	0.63 (0.40–0.99)	
Geographic region			0.57
Japan	599	0.74 (0.53–1.02)	
South Korea	288	0.62 (0.37–1.04)	



Subgroup Analysis of Disease-free Survival in the Full Analysis Set.

On the basis of the Cox model, prespecified subgroup analyses for background or prognostic factors were conducted to estimate hazard ratios with 95% confidence intervals and to test for interaction among subgroups with the use

- She had referred 2 months later due to ....
- Sonography showed Suspicious Axillary LN
- Axillary LN FNA was :Positive for malignancy
- ALN marker inserted

What is your Protocol ?

- DDAC → Paclitaxel
- DDAC → Paclitaxel weekly

- Pembrolizumab + Carbo + Paclitaxel→ Pembro+ Epirubicin + Cyclophosphamide (PCP → PEC)

What is Protocol ?

- Preoperative pembrolizumab + chemotherapy
- Pembrolizumab 200 mg IV Day 1
- Paclitaxel 80 mg/m2 IV Days 1, 8, 15
- Carboplatin AUC 5 IV Day 1
- Cycled every 21 days x 4
- Followed by:
- Pembrolizumab 200 mg IV Day 1
- Epirubicin 90 mg/m2 IV Day 1
- Cyclophosphamide 600 mg/m2 IV Day 1 – Cycled every 21 days x 4 cycles (cycles 5–8)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, T. Foukakis, P.A. Fasching, F. Cardoso, M. Untch, L. Jia, V. Karantza, J. Zhao, G. Aktan, R. Dent, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

Previous trials showed promising antitumor activity and an acceptable safety profile associated with pembrolizumab in patients with early triple-negative breast cancer. Whether the addition of pembrolizumab to neoadjuvant chemotherapy would significantly increase the percentage of patients with early triple-negative breast cancer who have a pathological complete response (defined as no invasive cancer in the breast and negative nodes) at definitive surgery is unclear.

METHODS

In this phase 3 trial, we randomly assigned (in a 2:1 ratio) patients with previously untreated stage II or stage III triple-negative breast cancer to receive neoadjuvant therapy with four cycles of pembrolizumab (at a dose of 200 mg) every 3 weeks plus paclitaxel and carboplatin (784 patients; the pembrolizumab–chemotherapy group) or placebo every 3 weeks plus paclitaxel and carboplatin (390 patients; the placebo–chemotherapy group); the two groups then received an additional four cycles of pembrolizumab or placebo, and both groups received doxorubicin–cyclophosphamide or epirubicin–cyclophosphamide. After definitive surgery, the patients received adjuvant pembrolizumab or placebo every 3 weeks for up to nine cycles. The primary end points were a pathological complete response at the time of definitive surgery and event-free survival in the intention-to-treat population.

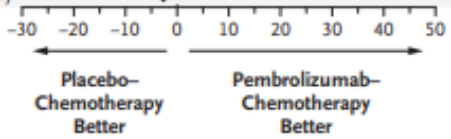
RESULTS

At the first interim analysis, among the first 602 patients who underwent randomization, the percentage of patients with a pathological complete response was 64.8% (95% confidence interval [CI], 59.9 to 69.5) in the pembrolizumab–chemotherapy group and 51.2% (95% CI, 44.1 to 58.3) in the placebo–chemotherapy group (estimated treatment difference, 13.6 percentage points; 95% CI, 5.4 to 21.8; P<0.001). After a median follow-up of 15.5 months (range, 2.7 to 25.0), 58 of 784 patients (7.4%) in the pembrolizumab–chemotherapy group and 46 of 390 patients (11.8%) in the placebo–chemotherapy group had disease progression that precluded definitive surgery, had local or distant recurrence or a second primary tumor, or died from any cause (hazard ratio, 0.63; 95% CI, 0.43 to 0.93). Across all treatment phases, the incidence of treatment-related adverse events of grade 3 or higher was 78.0% in the pembrolizumab–chemotherapy group and 73.0% in the placebo–chemotherapy group, including death in 0.4% (3 patients) and 0.3% (1 patient), respectively.

CONCLUSIONS

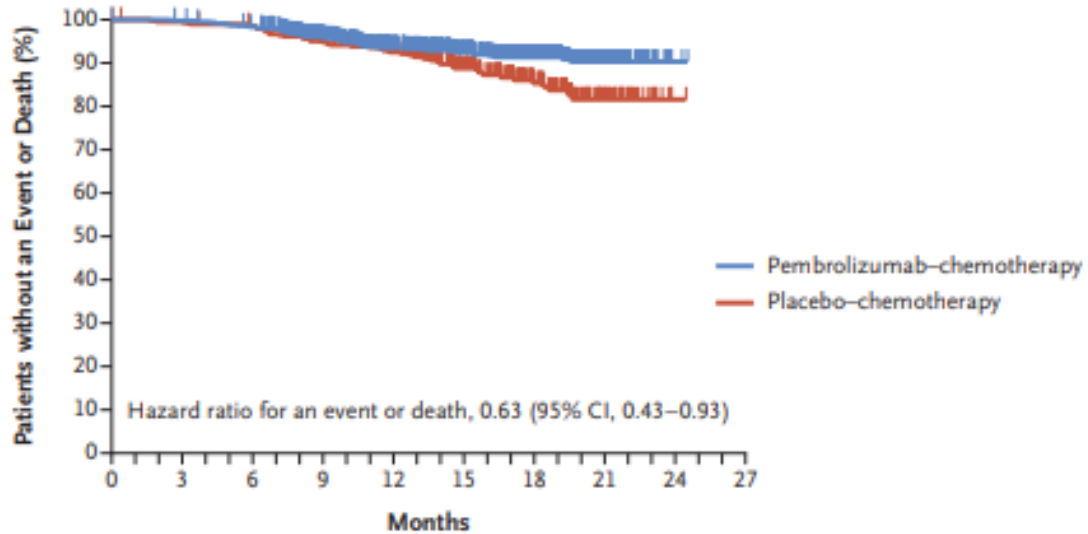
Among patients with early triple-negative breast cancer, the percentage with a pathological complete response was significantly higher among those who received pembrolizumab plus neoadjuvant chemotherapy than among those who received placebo plus neoadjuvant chemotherapy. (Funded by Merck Sharp & Dohme [a subsidiary of Merck]; KEYNOTE-522 ClinicalTrials.gov number, NCT03036488.)

Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Difference in Pathological Complete Response (95% CI)
	no. of patients with response/no. of patients (%)		*percentage points*
Overall	260/401 (64.8)	103/201 (51.2)	13.6 (5.4 to 21.8)
Nodal status			
Positive	136/210 (64.8)	45/102 (44.1)	20.6 (8.9 to 31.9)
Negative	124/191 (64.9)	58/99 (58.6)	6.3 (–5.3 to 18.2)
Tumor size			
T1 to T2	207/295 (70.2)	84/149 (56.4)	13.8 (4.3 to 23.3)
T3 to T4	53/106 (50.0)	19/52 (36.5)	13.5 (–3.1 to 28.8)
Carboplatin schedule			
Every 3 wk	105/165 (63.6)	47/84 (56.0)	7.7 (–5.0 to 20.6)
Weekly	154/231 (66.7)	56/116 (48.3)	18.4 (7.4 to 29.1)
PD-L1 status			
Positive	230/334 (68.9)	90/164 (54.9)	14.2 (5.3 to 23.1)
Negative	29/64 (45.3)	10/33 (30.3)	18.3 (–3.3 to 36.8)
Age			
<65 yr	235/355 (66.2)	95/176 (54.0)	12.2 (3.4 to 21.0)
≥65 yr	25/46 (54.3)	8/25 (32.0)	22.3 (–2.1 to 43.5)
ECOG performance-status score			
0	215/328 (65.5)	85/173 (49.1)	16.4 (7.3 to 25.4)
1	45/73 (61.6)	18/28 (64.3)	–2.6 (–22.1 to 18.9)



Subgroup Analysis of Difference in Percentages of Patients with a Pathological Complete Response (Stage ypT0/Tis ypN0).

An analysis of pathological complete response in key subgroups is shown. For the overall population and the programmed death ligand 1 (PD-L1) subgroups, the analysis is based on the Miettinen and Nurminen method stratified according to nodal status (positive or negative), tumor size (T1 [diameter >1.0 cm to 2.0 cm] to T2 [diameter >2.0 cm to 5.0 cm] or T3 [diameter >5.0 cm] to T4 [locally advanced disease]), and frequency of carboplatin administration (once weekly or once every 3 weeks). For the other subgroups, the analysis is based on the unstratified Miettinen and Nurminen method. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.



No. at Risk

Pembrolizumab–chemotherapy	784	780	765	666	519	376	242	73	2	0
Placebo–chemotherapy	390	386	380	337	264	186	116	35	1	0

Kaplan–Meier Estimates of Event-free Survival, According to Trial Group in the Intention-to-Treat Population.

Tick marks indicate data censored at the last time the patient was known to be alive and without an event (disease progression that precludes definitive surgery; local or distant recurrence or a second primary tumor; or death from any cause). The hazard ratio and confidence interval were analyzed with the use of a Cox regression model with treatment as a covariate stratified according to the randomization stratification factors of nodal status (positive or negative), tumor size (T1 to T2 or T3 to T4), and frequency of carboplatin administration (once weekly or once every 3 weeks).

A 29 Y Breast cancer
R. Breast cancer
Triple Negative
Core Biopsy : Inv.Ductal Ca (NST)
T: 23 mm, LN :(+)
Germ Line BRCA 2 : Mutant

- SR: Right BCS or Right MRM or Plus Prophylactic Left Mastectomy

A 29 Y Breast cancer
R. Breast cancer
Triple Negative
Core Biopsy : Inv.Ductal Ca (NST)
T: 23 mm, LN :(+)
Germ Line BRCA 2 : Mutant

- Surgery : BCS , SLNB (+) : ypT0 , LN+ : 5/11

A 29 Y Breast cancer
R. Breast cancer
Triple Negative
Core Biopsy : Inv.Ductal Ca (NST)
T: 23 mm, LN :(+)
Germ Line BRCA 2 : Mutant

- EBRT :
- Hypofractione RT ?
- Conventional RT?

A 29 Y Breast cancer
R. Breast cancer
Triple Negative
Core Biopsy : Inv.Ductal Ca (NST)
T: 23 mm, LN :(+)
Germ Line BRCA 2 : Mutant

- EBRT : 40 Gy / 15 F → Boost: 10 Gy / 5 F

- A 29 Y Breast cancer
  R. Breast cancer
  Triple Negative
  Core Biopsy : Inv.Ductal Ca (NST)
  T: 23 mm, LN :(+)
  Germ Line BRCA 2 : Mutant

- What's your choice?

- Adj Pembrolizumab
- Adj Olaparib
- Adj Capecitabine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R.D. Gelber, E. de Azambuja, A. Fielding, J. Balmaña, S.M. Domchek,

BACKGROUND

Poly(adenosine diphosphate–ribose) polymerase inhibitors target cancers with defects in homologous recombination repair by synthetic lethality. New therapies are needed to reduce recurrence in patients with *BRCA1* or *BRCA2* germline mutation–associated early breast cancer.

METHODS

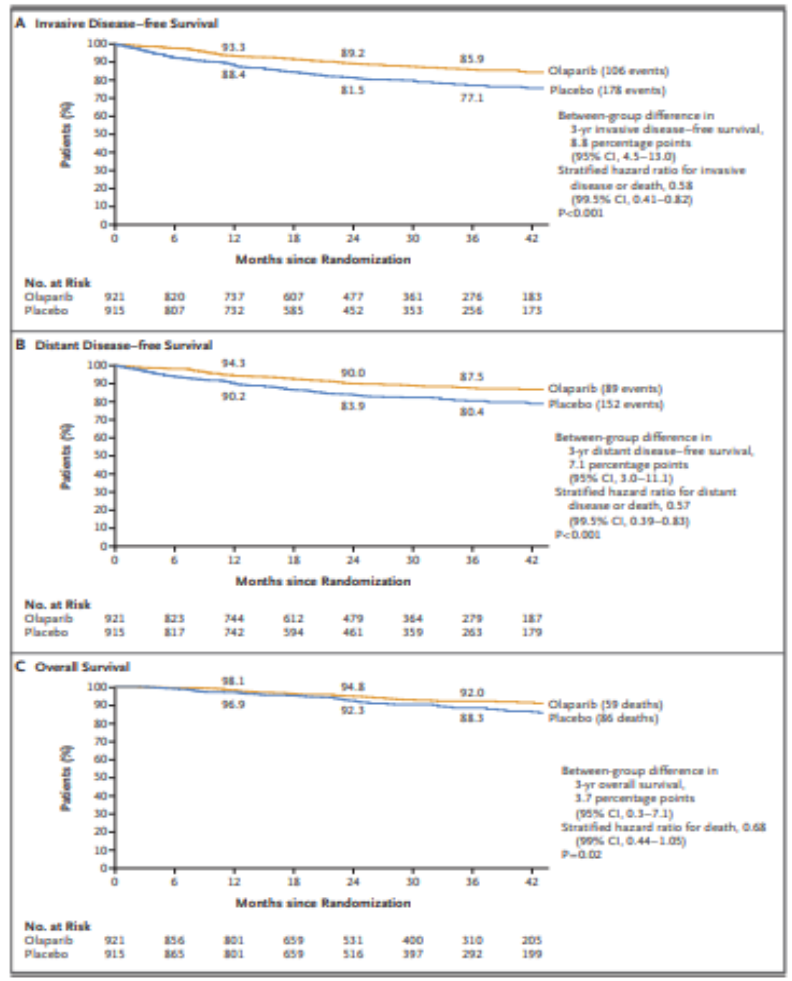
We conducted a phase 3, double-blind, randomized trial involving patients with human epidermal growth factor receptor 2 (HER2)–negative early breast cancer with *BRCA1* or *BRCA2* germline pathogenic or likely pathogenic variants and high-risk clinicopathological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy. Patients were randomly assigned (in a 1:1 ratio) to 1 year of oral olaparib or placebo. The primary end point was invasive disease–free survival.

RESULTS

A total of 1836 patients underwent randomization. At a prespecified event-driven interim analysis with a median follow-up of 2.5 years, the 3-year invasive disease–free survival was 85.9% in the olaparib group and 77.1% in the placebo group (difference, 8.8 percentage points; 95% confidence interval [CI], 4.5 to 13.0; hazard ratio for invasive disease or death, 0.58; 99.5% CI, 0.41 to 0.82; P<0.001). The 3-year distant disease–free survival was 87.5% in the olaparib group and 80.4% in the placebo group (difference, 7.1 percentage points; 95% CI, 3.0 to 11.1; hazard ratio for distant disease or death, 0.57; 99.5% CI, 0.39 to 0.83; P<0.001). Olaparib was associated with fewer deaths than placebo (59 and 86, respectively) (hazard ratio, 0.68; 99% CI, 0.44 to 1.05; P=0.02); however, the between-group difference was not significant at an interim-analysis boundary of a P value of less than 0.01. Safety data were consistent with known side effects of olaparib, with no excess serious adverse events or adverse events of special interest.

CONCLUSIONS

Among patients with high-risk, HER2-negative early breast cancer and germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variants, adjuvant olaparib after completion of local treatment and neoadjuvant or adjuvant chemotherapy was associated with significantly longer survival free of invasive or distant disease than was placebo. Olaparib had limited effects on global patient-reported quality of life. (Funded by the National Cancer Institute and AstraZeneca; OlympiA ClinicalTrials.gov number, NCT02032823.)



at 3 years was 85.9% in the olaparib group and 77.1% in the placebo group (difference, 8.8 percentage points; 95% confidence interval [CI], 4.5 to 13.0). Invasive disease–free survival was significantly longer among patients assigned to receive olaparib than among those assigned to receive placebo (hazard ratio, 0.58; 99.5% CI, 0.41 to 0.82; P<0.001) (Fig. 1A). Events of invasive disease or death were reported in 106 patients in the olaparib group and 178 patients in

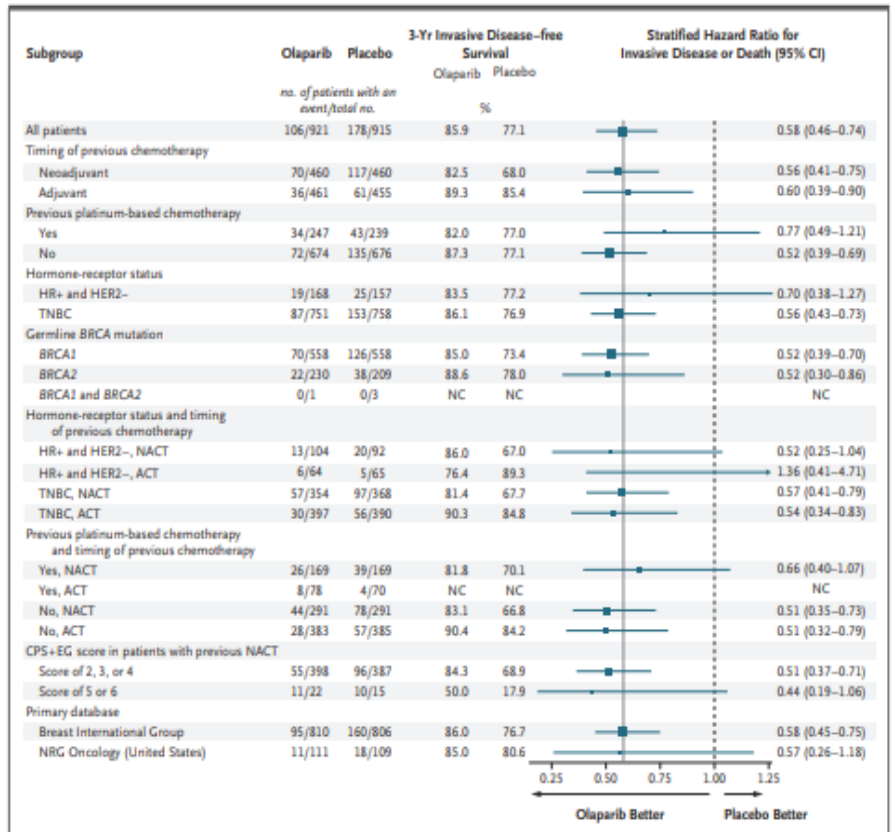


Figure 2. Subgroup Analysis of Invasive Disease–free Survival.

The solid vertical line indicates the overall hazard-ratio estimate, and the dashed vertical line indicates a hazard ratio of 1.00, as recommended by Cuzick.[21] The size of the blue squares corresponds to the number of events contributing to the estimate of the treatment effect. Even without correcting for multiple comparisons, none of the tests for heterogeneity reached statistical significance. *BRCA* mutation data reflect central Myriad testing results only. The CPS+EG score is a staging system for disease-specific survival among patients with breast cancer treated with neoadjuvant chemotherapy (NACT).[20] This incorporates pretreatment clinical stage, estrogen-receptor status, nuclear grade, and postneoadjuvant chemotherapy pathological stage. Patients who were enrolled had scores ranging from 2 to 6, with higher scores indicating worse prognosis. The prespecified subgroup analysis of the CPS+EG score in patients with previous NACT was performed in all the patients who had received NACT, whether they had hormone-receptor–positive (HR+) disease or triple-negative breast cancer (TNBC). ACT denotes adjuvant chemotherapy, HER2 human epidermal growth factor receptor 2, and NC not calculated.

JAMA | Original Investigation

Effect of Capecitabine Maintenance Therapy Using Lower Dosage and Higher Frequency vs Observation on Disease-Free Survival Among Patients With Early-Stage Triple-Negative Breast Cancer Who Had Received Standard Treatment

The SYSUCC-001 Randomized Clinical Trial

Xi Wang, MD; Shu-Sen Wang, MD; Heng Huang, MD; Li Cai, MD; Li Zhao, MD; Rou-Jun Peng, MD; Ying Lin, MD; Jun Tang, MD; Jian Zeng, MD;

IMPORTANCE Among all subtypes of breast cancer, triple-negative breast cancer has a relatively high relapse rate and poor outcome after standard treatment. Effective strategies to reduce the risk of relapse and death are needed.

OBJECTIVE To evaluate the efficacy and adverse effects of low-dose capecitabine maintenance after standard adjuvant chemotherapy in early-stage triple-negative breast cancer.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at 13 academic centers and clinical sites in China from April 2010 to December 2016 and final date of follow-up was April 30, 2020. Patients (n = 443) had early-stage triple-negative breast cancer and had completed standard adjuvant chemotherapy.

INTERVENTIONS Eligible patients were randomized 1:1 to receive capecitabine (n = 222) at a dose of 650 mg/m^2 twice a day by mouth for 1 year without interruption or to observation (n = 221) after completion of standard adjuvant chemotherapy.

MAIN OUTCOMES AND MEASURES The primary end point was disease-free survival. Secondary end points included distant disease-free survival, overall survival, locoregional recurrence-free survival, and adverse events.

RESULTS Among 443 women who were randomized, 434 were included in the full analysis set (mean [SD] age, 46 [9.9] years; T1/T2 stage, 93.1%; node-negative, 61.8%) (98.0% completed the trial). After a median follow-up of 61 months (interquartile range, 44-82), 94 events were observed, including 38 events (37 recurrences and 32 deaths) in the capecitabine group and 56 events (56 recurrences and 40 deaths) in the observation group. The estimated 5-year disease-free survival was 82.8% in the capecitabine group and 73.0% in the observation group (hazard ratio [HR] for risk of recurrence or death, 0.64 [95% CI, 0.42-0.95]; P = .03). In the capecitabine group vs the observation group, the estimated 5-year distant disease-free survival was 85.8% vs 75.8% (HR for risk of distant metastasis or death, 0.60 [95% CI, 0.38-0.92]; P = .02), the estimated 5-year overall survival was 85.5% vs 81.3% (HR for risk of death, 0.75 [95% CI, 0.47-1.19]; P = .22), and the estimated 5-year locoregional recurrence-free survival was 85.0% vs 80.8% (HR for risk of locoregional recurrence or death, 0.72 [95% CI, 0.46-1.13]; P = .15). The most common capecitabine-related adverse event was hand-foot syndrome (45.2%), with 7.7% of patients experiencing a grade 3 event.

CONCLUSIONS AND RELEVANCE Among women with early-stage triple-negative breast cancer who received standard adjuvant treatment, low-dose capecitabine maintenance therapy for 1 year, compared with observation, resulted in significantly improved 5-year disease-free survival.

TRIAL REGISTRATION ClinicalTrials.

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

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PURPOSE Many patients with HR+, HER2− early breast cancer (EBC) will not experience recurrence or have distant recurrence with currently available standard therapies. However, up to 30% of patients with high risk clinical and/or pathologic features may experience distant recurrence, many in the first few years. Superior treatment options are needed to prevent early recurrence and development of metastases for this group of patients. Abemaciclib is an oral, continuously dosed, CDK4/6 inhibitor approved for HR+, HER2− advanced breast cancer (ABC). Efficacy and safety of abemaciclib in ABC supported evaluation in the adjuvant setting.

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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Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background ExteNET showed that 1 year of neratinib, an irreversible pan-HER tyrosine kinase inhibitor, significantly improves 2-year invasive disease-free survival after trastuzumab-based adjuvant therapy in women with HER2-positive breast cancer. We report updated efficacy outcomes from a protocol-defined 5-year follow-up sensitivity analysis and long-term toxicity findings.

Methods In this ongoing randomised, double-blind, placebo-controlled, phase 3 trial, eligible women aged 18 years or older (≥20 years in Japan) with stage 1–3c (modified to stage 2–3c in February, 2010) operable breast cancer, who had completed neoadjuvant and adjuvant chemotherapy plus trastuzumab with no evidence of disease recurrence or metastatic disease at study entry. Patients who were eligible patients were randomly assigned (1:1) via permuted blocks stratified according to hormone receptor status (hormone receptor-positive *vs* hormone receptor-negative), nodal status (0 *vs* 1–3 *vs* or ≥4 positive nodes), and trastuzumab adjuvant regimen (given sequentially *vs* concurrently with chemotherapy), then implemented centrally via an interactive voice and web-response system, to receive 1 year of oral neratinib 240 mg/day or matching placebo. Treatment was given continuously for 1 year, unless disease recurrence or new breast cancer, intolerable adverse events, or consent withdrawal occurred. Patients, investigators, and trial funder were masked to treatment allocation. The predefined endpoint of the 5-year analysis was invasive disease-free survival, analysed by intention to treat. ExteNET is registered with ClinicalTrials.gov, number NCT00878709, and is closed to new participants.

Findings Between July 9, 2009, and Oct 24, 2011, 2840 eligible women with early HER2-positive breast cancer were recruited from community-based and academic institutions in 40 countries and randomly assigned to receive neratinib (n=1420) or placebo (n=1420). After a median follow-up of 5·2 years (IQR 2·1–5·3), patients in the neratinib group had significantly fewer invasive disease-free survival events than those in the placebo group (116 *vs* 163 events; stratified hazard ratio 0·73, 95% CI 0·57–0·92, p=0·0083). The 5-year invasive disease-free survival was 90·2% (95% CI 88·3–91·8) in the neratinib group and 87·7% (85·7–89·4) in the placebo group. Without diarrhoea prophylaxis, the most common grade 3–4 adverse events in the neratinib group, compared with the placebo group, were diarrhoea (561 [40%] grade 3 and one [<1%] grade 4 with neratinib *vs* 23 [2%] grade 3 with placebo), vomiting (grade 3: 47 [3%] *vs* five [<1%]), and nausea (grade 3: 26 [2%] *vs* two [<1%]). Treatment-emergent serious adverse events occurred in 103 (7%) women in the neratinib group and 85 (6%) women in the placebo group. No evidence of increased risk of long-term toxicity or long-term adverse consequences of neratinib-associated diarrhoea were identified with neratinib compared with placebo.

Interpretation At the 5-year follow-up, 1 year of extended adjuvant therapy with neratinib, administered after chemotherapy and trastuzumab, significantly reduced the proportion of clinically relevant breast cancer relapses—ie, those that might lead to death, such as distant and locoregional relapses outside the preserved breast—without increasing the risk of long-term toxicity. An analysis of overall survival is planned after 248 events.

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بسم الله

بیمار خانم 32 ساله با:

- R Breast Cancer (NST) پس از جراحی BCS ،
- ER:80% LN+: 5/11 T:22mm
- HER-2: - Ki67: 40 – 50 %
- BRCA 2 : Mutant
- مجدد تمایل به حفظ باروری دارند.

شیمی درمانی اجوانت:

DD AC → Paclitaxel weekly *12

Breast cancer woman patient, 32 years old
R Breast cancer
BCS , ER: 80% , HER2 : - , Ki67 : 40 – 50 %
LN+ : 5/11 T : 22 mm
BRCA 2 : Mutant

- What's your choice?

- 40 Gy / 15F (Hypofraction RT) + Boost 12 Gy/ 6F
- 50 Gy/ 25F (Conventional RT) + Boost 12Gy/ 6F

Breast cancer woman patient, 32 years old
R Breast cancer
BCS , ER: 80% , HER2 : - , Ki67 : 40 – 50 %
LN+ : 5/11 T : 22 mm
BRCA 2 : Mutant

- GnRH agonist + Letrozole

Plan:

1- Abemaciclib

2- Palbociclib

3- Ribociclib

4- Olaparib

Breast cancer woman patient, 32 years old
R Breast cancer
BCS , ER: 80% , HER2 : - , Ki67 : 40 – 50 %
LN+ : 5/11 T : 22 mm
BRCA 2 : Mutant

Abemaciclib Or Olaparib can be given