2017 San Antonio Breast Cancer Symposium

Publication Number: GS1-01

Title: Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials

Gray R, Bradley R, Braybrooke J, Davies C, Pan H, Peto R, Bliss J, Cameron D, Mackey J, Del Mastro L, Swain S, Untch M, Bergh J, Pritchard K, Norton L and For the EBCTCG. University of Oxford, Oxford, United Kingdom; Institute of Cancer Research, Sutton, United Kingdom; University of Edinburgh, Edinburgh, United Kingdom; University of Alberta, Edmonton, AB, Canada; National Cancer Research Institute, Genoa, Italy; Georgetown University, Washington, DC; HELIOS Klinikum Berlin-Buch, Berlin, Germany; Karolinska Institutet, Stockholm, Sweden; University of Toronto, Toronto, ON, Canada and Memorial Sloan Kettering Cancer Center, New York City, NY.

Body: Background: Much contemporary adjuvant chemotherapy uses conventional 3-weekly scheduling. Yet, cytokinetic modelling suggests that increasing the dose density of cytotoxic therapy by shortening the intervals between courses, or by using sequential rather than concurrent treatment schedules may enhance efficacy.[1] At least 15 randomised trials have directly tested this hypothesis and this meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) brings together the worldwide evidence to clarify the balance of risks and benefits of dose-dense chemotherapy.

Methods: Individual patient data were provided for 98% (21,537/21,944) of women randomised in relevant trials: 7 randomised trials (10,004 women, 2240 breast cancer recurrences, 1481 breast cancer deaths) that compared 2-weekly dose-dense chemotherapy versus the same chemotherapy given 3-weekly, and 9 trials (11,533 women, 2773 breast cancer recurrences, 1711 breast cancer deaths) that compared sequential with concurrent anthracycline and taxane-based chemotherapy. Primary outcomes were time to recurrence and breast cancer mortality.

Results: Highly significant reductions in disease recurrence [rate ratio (RR)=0.83 (95%CI 0.76-0.91), p=0.00004] were seen with 2-weekly compared with 3-weekly chemotherapy, and 10 year breast cancer mortality was 3.0% lower [16.7% vs 19.7%: RR=0.85 (95% CI 0.76-0.95), p=0.003]. Overall survival was also improved [RR=0·86 (95% CI 0·78–0·95), p=0.003]. Similarly, for sequential versus concurrent taxane plus anthracycline chemotherapy the rate ratio for disease recurrence was 0.86 (95% CI 0.79-0.93, p=0.0001), 10-year breast-cancer mortality was 2.3% lower [19.2% vs 21.5%: RR=0.87 (95% CI 0.79-0.96), p=0.005], and overall survival was improved [RR=0·85 (0·78–0·94), p=0.0008]. The proportional reductions in recurrence with dose-dense chemotherapy were similar and highly significant (both p<0.002) in ER-positive and in ER-negative disease, and did not differ significantly by any other patient or tumour characteristics, including age, HER2 status, nodal status, tumour size, or grade. Increasing dose density did not have any material adverse effect on non-breast-cancer mortality, which was similar with 2-weekly and with 3-weekly chemotherapy [RR=0·93 (95% CI 0·74–1·17), p=0.6] and was if anything lower with sequential than with concurrent chemotherapy [RR=0·73 (95% CI 0·55–0·97), p=0.03]. Trial publications also indicate that, with haematopoietic growth factor support, dose-dense chemotherapy does not substantially increase toxicity.

Conclusion: Increasing the dose density of adjuvant chemotherapy is safe and results in fewer disease recurrences and fewer deaths from breast cancer.

Reference:

[1] Norton, L. Evolving concepts in the systemic therapy of breast cancer. Seminars in Oncology, 1997: S10-3 – S10-10.

2017 San Antonio Breast Cancer Symposium

Publication Number: GS1-02

Title: NSABP B-47 (NRG oncology): Phase III randomized trial comparing adjuvant chemotherapy with adriamycin (A) and cyclophosphamide (C) → weekly paclitaxel (WP), or docetaxel (T) and C with or without a year of trastuzumab (H) in women with node-positive or high-risk node-negative invasive breast cancer (IBC) expressing HER2 staining intensity of IHC 1+ or 2+ with negative FISH (HER2-Low IBC)

Fehrenbacher L, Cecchini RS S, Geyer CE E, Rastogi P, Costantino JP P, Atkins JN N, Polikoff J, Boileau J-F, Provencher L, Stokoe C, Moore TD D, Robidoux A, Borges V, Albain KS S, Swain SM M, Paik S, Mamounas EP P and Wolmark N. NSABP/NRG Oncology; Kaiser Permanente, Northern California; NRG Oncology; University of Pittsburgh; Virginia Commonwealth University, Massey Cancer Center; University of Pittsburgh Cancer Institute; SCOR - NCORP; Kaiser Permanente, San Diego California; Jewish General Hospital Segal Cancer Center, McGill University; CHU de Québec-Université Laval; Texas Oncology Plano East; The Columbus CCOP; Centre Hopitalier de l'Université de Montréal; University of Colorado; Loyola University Chicago Stritch School of Medicine; Georgetown Lombardi Comprehensive Cancer Center (current); Washington MedStar (Where Research Was Conducted); Yonsei University College of Medicine; UF Health and Allegheny Health Network Cancer Institute.

Body: Background: Adjuvant trastuzumab (H) reduces cancer recurrence and improves survival in patients (pts) with HER2-amplified or overexpressing (IHC 3+ staining intensity) IBC. Two of the landmark trials that demonstrated the efficacy of H-based eligibility on HER2 testing performed at local site laboratories were found to contain a cohort of pts without amplification or IHC overexpression on tissue submitted for central testing. These HER2-low cohorts appeared to benefit from the addition of H, and efforts at external HER2 testing validation and laboratory explorations did not negate these findings. NSABP B-47 was performed to determine if these findings would be confirmed in a large prospective randomized trial. The primary aim was to determine whether the addition of H to chemotherapy (CT) regimens of AC→WP or TC (choice per investigator discretion) would improve invasive disease-free survival (IDFS).

Methods: From 2/8/2011 to 2/10/2015, 3270 women were enrolled with 1630 pts randomly assigned to Arm 1 [TC: docetaxel 75mg/m2, cyclophosphamide 600 mg/m2 every 3 weeks x 6 cycles; or AC→WP: doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 every 2 or 3 weeks x 4 cycles followed by paclitaxel 80 mg/m2 every week x 12], and 1640 pts to Arm 2 [same CT regimens + 12 months of H]. Pts were stratified by IHC score (1+ vs 2+), number of positive nodes (0-3, 4-9, ≥10), hormone receptor status (ER or PgR positive vs both negative), and CT (TC vs AC→WP). Overall 58.5% were ≥50 years, 57% had tumors with IHC 1+, 17.3% were ER- and PgR-, 19.9% were node negative, and 27.4% had ≥4 positive nodes. TC was the intended CT regimen for 44.2%.

Results: As of 7/31/2017, the median follow-up time was 46.1 months. We observed 264 IDFS events, which triggered the definitive analysis for the primary endpoint. The addition of H to CT showed a 5-year IDFS of 89.6% compared to 89.2% for CT alone (HR 0.98; 95%CI 0.77-1.26; P=0.90). The findings did not differ by level of HER2 IHC expression, level of lymph node involvement, or hormone receptor status. 5-year point estimates for RFI were 92.0% for CT+H compared to 92.2% for CT alone (HR 0.995; 95%CI 0.75-1.32; P=0.97). 5-year estimates for DRFI were 92.7% for CT+H and 93.5% for CT alone (HR 1.10; 95%CI 0.81-1.49; P=0.55). The addition of H did not change OS significantly with 5-year point estimates of 94.8% in CT+H vs 96.2% in CT alone (HR 1.33; 95%CI 0.91-1.94; P=0.14). 4.3% of women in the CT arm experienced Grade 4 or 5 toxicities compared to 5.0% in CT+H.

Conclusion: The addition of H to CT did not demonstrate a reduction in IDFS, RFI, or DRFI in women with non-overexpressing but IHC measurable HER2 IBC. This prospective study did not confirm the retrospective findings in NSABP B-31 or N9831. The threshold of HER2 expression or genetic amplification for H benefit remains unchanged.

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2017 San Antonio Breast Cancer Symposium

Publication Number: GS2-05

Title: First-line ribociclib vs placebo with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: results from the randomized Phase III MONALEESA-7 trial

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Background: Endocrine therapy (ET) with ovarian function suppression is an established first-line treatment for pre- and peri-menopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC). Addition of ribociclib (orally bioavailable, selective cyclin-dependent kinase [CDK] 4/6 inhibitor) to first-line ET prolonged progression-free survival (PFS) in a Phase III trial of postmenopausal women with HR+, HER2– ABC (MONALEESA-2). Here we report results from MONALEESA-7 (NCT02278120), the first double-blind, randomized, Phase III trial evaluating ribociclib + tamoxifen/non-steroidal aromatase inhibitor (NSAI) and goserelin specifically in pre- and peri-menopausal patients.

Methods: Pre- or peri-menopausal women with HR+, HER2– ABC who had received ≤1 line of chemotherapy and no prior ET for ABC were randomized (1:1) to ribociclib (600 mg/day, 3-weeks-on/1-week-off) or placebo in combination with either tamoxifen (20 mg/day) or an NSAI (letrozole [2.5 mg/day] or anastrozole [1 mg/day]) + goserelin (3.6 mg every 28 days). The primary endpoint was locally assessed PFS. Secondary endpoints included overall response rate (ORR), clinical benefit rate (CBR), and safety.

Results: 672 patients were enrolled. Baseline patient characteristics were balanced between treatment arms. The primary analysis was conducted after 318 events had occurred; median time from randomization to data cut-off date was 19.2 months. The study met its primary objective: PFS was significantly improved in the ribociclib arm (median PFS = 23.8 months; 95% CI: 19.2–not reached) vs the placebo arm (median PFS = 13.0 months; 95% CI: 11.0–16.4), with a hazard ratio of 0.553 (95% CI: 0.441–0.694; $p=9.83\times10^{-8}$). Subgroup analyses demonstrated consistent PFS benefits for ribociclib vs placebo. In patients with measurable disease at baseline, ORR was 51% vs 36% (ribociclib vs placebo arm; $p=3.17\times10^{-4}$) and CBR was 80% vs 67% ($p=3.40\times10^{-4}$). The most frequent all-grade adverse events (AEs; ≥25% of patients; ribociclib vs placebo arm) were neutropenia (76% vs 8%), hot flush (34% vs 34%), nausea (32% vs 20%), leukopenia (31% vs 6%), and arthralgia (30% vs 27%). Of these, neutropenia (61% vs 4%) and leukopenia (14% vs 1%) were the only Grade 3/4 events reported in ≥5% of patients (ribociclib vs placebo arm). Febrile neutropenia (ribociclib vs placebo arm) occurred in 2% vs <1% of patients. Grade 3/4 QT prolongation (ribociclib vs placebo arm) was reported in 1% vs <1% of patients. AEs leading to permanent discontinuation of ribociclib + tamoxifen/NSAI + goserelin vs placebo + tamoxifen/NSAI + goserelin occurred in 4% vs 3% of patients.

Conclusions: MONALEESA-7, the first dedicated trial investigating a CDK4/6 inhibitor in pre- and peri-menopausal women with HR+, HER2– ABC, demonstrated that addition of ribociclib to first-line ET (tamoxifen/NSAI + goserelin) significantly prolonged PFS and had a manageable safety profile. The trial validates the clinical utility of ribociclib with multiple endocrine therapies, including tamoxifen, in premenopausal women with HR+, HER2– ABC.

2017 San Antonio Breast Cancer Symposium

Publication Number: GS2-06

Title: Phase Ib/II study evaluating safety and efficacy of pembrolizumab and trastuzumab in patients with trastuzumab-resistant HER2-positive metastatic breast cancer: Results from the PANACEA (IBCSG 45-13/BIG 4-13/KEYNOTE-014) study

Loi S, Giobbe-Hurder A, Gombos A, Bachelot T, Hui R, Curigliano G, Campone M, Biganzoli L, Bonnefoi H, Jerusalem G, Bartsch R, Rabaglio-Poretti M, Kammler R, Maibach R, Smyth MJ J, Di Leo A, Colleoni M, Viale G, Regan MM M and Andre F.
International Breast Cancer Study Group and Breast International Group.

Body: Background Preclinical and clinical data suggest that HER2-positive (HER2+) breast cancer (BC) will be amendable to immunotherapeutic approaches. We evaluated pembrolizumab with trastuzumab in patients (pts) with trastuzumab-resistant HER2+, PD-L1 positive (PD-L1pos), unresectable loco-regional or metastatic BC and a parallel cohort of pts with HER2+, PD-L1 negative (PD-L1neg) BC during the phase II study.
Methods: Pts with advanced BC and progression on prior trastuzumab-based therapies, ECOG 0-1, and a metastatic tumor biopsy in the last year were eligible. HER2 positivity and quantity of tumor-infiltrating lymphocytes (TILs) on H&E slide were centrally evaluated. PD-L1 score was assessed by Merck central lab. Tumor imaging was performed at weeks 12, 18, 24 and every 12 weeks, thereafter. Primary endpoints were safety of the combination (phase Ib) and objective response rate (ORR) per RECIST 1.1 (phase II). Secondary endpoints were PFS, duration of response, and OS. Phase Ib was a 3+3 dose-escalation of 2 pembrolizumab doses (2mg/kg, 10mg/kg) Q3W. In phase II, pts received pembrolizumab 200mg Q3W for 24 months or until disease progression. Clinically stable pts with progression were allowed to continue pembrolizumab until confirmation on subsequent assessment. Pts with isolated CNS progression were also allowed to continue pembrolizumab after local treatment. Planned total enrollment was 61 pts. For the phase II PD-L1pos cohort, a Simon two-stage design (N=40; proceed if ≥2/17 respond) was used which had 85% power to compare ORR of 7% vs. 22% (1-sided α=0.05). For the PD-L1neg cohort, a single-stage design with 15 pts had >95% power to compare ORR of 1% vs. 20% (1-sided α=0.14). Clinicaltrials.gov: NCT02129556.
Results: 6 pts enrolled in phase Ib between April and July 2015; no DLTs were observed. The PD-L1pos cohort enrolled 40 pts between August 2015 and September 2016. The PD-L1neg cohort enrolled May 2016 to April 2017, stopping after 12 pts due to low rate of PD-L1 negativity, maintaining >90% power to detect the target difference in ORR. PD-L1 testing labs changed in April 2016. Prior to this time, QualTek PD-L1 positive was defined as ≥1% on tumor or TILs. Using the Dako 22C3 antibody, positive was defined as tumor PD-L1 combined positive score (CPS)≥1%.
146 pts were screened to enroll 58 pts. Of screened pts, median stromal TILs was 1% (mean: 4.8%, SD: 9.1%, range: 0 to 60%; n=127); 52% of pts were PD-L1pos, with higher positivity rates while using the Dako assay compared with Qualtek (65% vs. 43%, p=0.009). Median TILs of pts in the PD-L1pos cohort was 2% (mean: 8.1%, SD: 11.2%, range: 0 to 40%) and 0% (mean: 1.2%, SD: 2.2%, range: 0 to 5%) in the PD-L1neg cohort.
Of enrolled pts, median age was 51yrs (range: 28-72), 69% had visceral metastases. 29% of pts received prior pertuzumab, 72% had prior T-DM1, 40% prior lapatinib. 38% of pts were ER-positive, 62% were ER-negative. Median TILs in enrolled ER pos and ER neg pts were 1.5% and 2.0%, respectively. PD-L1 positivity rates were also not significantly different by ER status (p=0.5). Final safety data and efficacy results will be presented at the meeting.

2017 San Antonio Breast Cancer Symposium

Publication Number: GS3-01

Title: A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial

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Body: Background: While extended adjuvant therapy with aromatase inhibitors (AI) after initial tamoxifen has been demonstrated to improve disease-free-survival (DFS) of postmenopausal patients with hormone-receptor positive breast cancer, the optimal duration of extended AI is unknown. Moreover, it remains unclear whether patients after AI in the first 5 years benefit similarly from extended adjuvant AI therapy as patients after Tamoxifen.

Methods: From February 2004 to June 2010, 3484 women with postmenopausal stage I-III hormone-receptor positive early breast cancer were randomized in 71 centers in Austria to receive either 2 years or 5 years of additional Anastrozole (1 mg daily) as extended adjuvant therapy, after initial 5 years of adjuvant endocrine treatment. Eligible patients had to be recurrence-free at 60 months of initial adjuvant therapy with Tamoxifen (Tam) or AI or Tam→AI, and younger than 80 years of age. Stratification factors were tumor stage, nodal status, initial endocrine therapy, adjuvant chemotherapy, and quantitative hormone receptors. Patients were followed-up at least annually. Primary end point of ABCSG-16 was DFS, secondary end points included overall survival (OS), fractures, contralateral breast cancer, and toxicity.

Results: As of June 30, 2016, the median follow-up of the 3468 patients included in the analysis of ABCSG-16 was 105.9 months (IQR 102.2-110.3 months) after randomization (i.e. approx. 14 years after diagnosis). Median patient age was 64 years, 2507 (72%) patients had tumors smaller than 2 cm, 2301 (66%) patients were node-negative, 674 (19%) patients had high-grade tumors, 2683 (77%) patients had tumors both ER and PR positive. 2764 (80%) patients were treated with breast conserving surgery. Before randomization into ABCSG-16, 1000 (29%) patients had undergone (neo)adjuvant chemotherapy, 1774 (51%) patients had received 5 years of Tamoxifen, whereas 1688 (49%) patients had received other (AI containing) regimens in the first five years.

As of June 30, 2016, 757 DFS events have been recorded, 377 (22%) in the 2-year group, and 380 (22%) in the 5-year group. There was no significant difference in DFS (HR 0.997, 95%CI 0.86-1.15, log rank p=0.982), in OS, time to secondary carcinoma and time to contralateral breast cancer. With respect to drug adherence, 81.2% of patients in the 2-year arm were taking the study drug still at 2 years, and 80.1% at 2 years in the 5-year arm. At 5 years, 65.6% of patients in the 5-year arm were still on the assigned medication. Bone fractures were more frequent in the 5-year arm (i.e. years 3 to 5 after randomization: 6% vs 4 %, HR=1.405, 95%CI 1.03-1.91, p=0.029).

Conclusion: After 5 years of adjuvant endocrine therapy (Tamoxifen or AI or Sequence), 2 additional years of Anastrozole are sufficient for extended adjuvant therapy – a further extension to 5 additional years did not yield additional outcome benefit but added toxicity.

Support: AstraZeneca

2017 San Antonio Breast Cancer Symposium

Publication Number: GS3-04

Title: A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer (the SOLD study)

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Body: Background: The optimal duration of trastuzumab (T), when given together with chemotherapy and after chemotherapy as adjuvant treatment in patients with HER2+ breast cancer (BC), is unknown. Whilst the international standard is 12 months of T, the benefits and harms of T treatment continued beyond the chemotherapy are unclear.
Methods: Women with histologically confirmed node-negative or node-positive HER2+ BC were eligible for the trial (NCT00593697). The primary tumor diameter was required to be >5 mm in node-negative cancer. Patients with distant metastases, inflammatory cancer, clinically significant cardiac disease, left ventricular ejection fraction (LVEF) <50%, unknown estrogen receptor (ER) status, World Health Organization performance status >1, and those who had received neoadjuvant systemic cancer therapy were excluded. Patients were randomly assigned to 2 groups prior to starting systemic cancer therapy. The initial systemic treatment was identical in the groups consisting of 3 cycles of 3-weekly docetaxel plus T followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide (FE75C). Thereafter, no further T or chemotherapy was administered in Arm A, whereas in Arm B single-agent T was administered 3-weekly for 14 cycles to complete 1 year of T treatment. The docetaxel dose was either 80 mg/m2 or 100 mg/m2 (prespecified for each center). Radiation therapy and endocrine therapy (for patients with ER+ cancer) were given according to the institutional practice; the minimum scheduled duration of endocrine therapy was 5 years. The LVEF was measured pretreatment, and on study weeks 18, 31, 43, and 61 and month 36. The primary endpoint was disease-free survival (DFS) compared between the groups using a Cox model and the non-inferiority approach.
Results: A total of 2,176 patients were entered into the study from 63 centers in 7 countries from Jan. 3, 2008 to Dec.16, 2014. The median follow-up time was 5.2 years at data collection closure (Dec. 31, 2016). The efficacy and safety data will be presented at the meeting.

2017 San Antonio Breast Cancer Symposium

Publication Number: GS4-01

Title: Pooled analysis of five randomized trials investigating temporary ovarian suppression with gonadotropin-releasing hormone analogs during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal early breast cancer patients

Lambertini M, Moore HCF CF, Leonard RCF CF, Loibl S, Munster P, Bruzzone M, Boni L, Unger JM M, Anderson RA A, Mehta K, Minton S, Poggio F, Albain KS S, Adamson DJA JA, Gerber B, Cripps A, Bertelli G, Seiler S, Ceppi M, Partridge AH H and Del Mastro L. Institut Jules Bordet, Brussels, Belgium; Cleveland Clinic Foundation, Cleveland, OH; Imperial College, London, United Kingdom; GBG - German Breast Group, Neu-Isenburg, Germany; UCSF - University of California, San Francisco, CA; IRCCS AOU San Martino-IST, Genova, Italy; AOU Careggi and Istituto Toscano Tumori, Florence, Italy; SWOG - Fred Hutchinson Cancer Research Center, Seattle, WA; University of Edinburgh, Edinburgh, United Kingdom; Moffitt Cancer Center, Tampa, FL; Loyola University Medical Center, Cardinal Bernardin Cancer Center, Maywood, IL; Tayside Cancer Centre, Ninewells Hospital, Dundee, United Kingdom; University Hospital Rostock, Rostock, Germany; Nexgen Oncology, Dallas, TX; Singleton Hospital, Swansea, United Kingdom and Dana-Farber Cancer Institute, Boston, MA.

Body: Background
The role of temporary ovarian suppression with gonadotropin-releasing hormone analogs (GnRHa) during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal early breast cancer patients remains highly controversial. This option is considered experimental by the ASCO and ESMO guidelines on fertility preservation in cancer patients. The present pooled analysis aimed at elucidating the efficacy and safety of temporary ovarian suppression with GnRHa during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal early breast cancer patients.
Patients and methods
This study included individual patient data from 5 trials (PROMISE-GIM6, POEMS/SWOG S0230, Anglo Celtic Group OPTION, GBG-37 ZORO, Moffitt-led trial) in which premenopausal women with early breast cancer were randomized to receive (neo)adjuvant chemotherapy alone or with concurrent administration of GnRHa.
Efficacy endpoints were premature ovarian insufficiency (POI, according to the definition used as primary endpoint in the included trials), 1- and 2-year amenorrhea rates and post-treatment pregnancy rate. Safety endpoints were disease-free survival (DFS) and overall survival (OS). Odds ratio (OR), incidence rate ratio (IRR) and hazard ratio (HR) with 95% confidence intervals (CI) were calculated for the effect of adding GnRHa to chemotherapy alone. As each study represents a cluster, statistical analysis has been performed using a random effects model.
The study is registered with the PROSPERO registration number CRD42014015638.

Results
A total of 873 patients from 5 randomized trials were included. Median age was 38 years (interquartile range: 34-42 years). POI rate was 14.1% in the GnRHa group and 30.9% in the control group (adjusted OR 0.38; 95% CI 0.26-0.57; $p < 0.001$). The incidence of 1-year amenorrhea was 36.8% in the GnRHa group and 40.4% in the control group (adjusted OR 0.92; 95% CI 0.66-1.28; $p = 0.623$). The incidence of 2-year amenorrhea was 18.2% in the GnRHa group and 30.0% in the control group (adjusted OR 0.51; 95% CI 0.31-0.85; $p = 0.009$). A total of 37 patients had at least one post-treatment pregnancy in the GnRHa group and 20 in the control group (IRR 1.83; 95% CI 1.06-3.15; $p = 0.030$).
There were no significant differences in DFS (adjusted HR 1.01; 95% CI 0.72-1.42; $p = 0.999$) or OS (adjusted HR 0.67; 95% CI 0.42-1.06; $p = 0.083$) between the GnRHa and control groups.
Subgroup analyses of both efficacy and safety endpoints according to age of the patients, hormone receptor status, type and duration of chemotherapy will be presented at the conference.
Conclusions
This study provides level 1A of evidence for the efficacy and safety of temporary ovarian suppression with GnRHa during chemotherapy in premenopausal early breast cancer patients. Given the findings of this pooled analysis, temporary ovarian suppression with GnRHa during chemotherapy should be considered as a new standard option to reduce the likelihood of chemotherapy-induced POF and possibly improve future fertility in premenopausal early breast cancer patients.

2017 San Antonio Breast Cancer Symposium

Publication Number: GS4-04

Title: Randomized blinded sham- and waitlist-controlled trial of acupuncture for joint symptoms related to aromatase inhibitors in women with early stage breast cancer (S1200)

Hershman DL L, Unger JM M, Greenlee H, Capodice J, Lew DL L, Kengla AT T, Melnik MK K, Jorgensen CW W, Kreisle WH H, Minasian LM M, Fisch MJ J, Henry L and Crew KD D. Columbia University Medical Center, New York, NY; Fred Hutchinson Cancer Research Center, Seattle, WA; Mount Sinai Hospital, New York, NY; Kaiser Permanente Medical Center, Walnut Creek, CA; Spectrum Health Medical Group, Grand Rapids, MI; NCORP of the Carolinas (Greenville Health System), Greenville, SC; St. Luke's Mountain States Tumor Institute, Boise, ID; National Cancer Institute, Bethesda, MD; AIM Specialty Health, Chicago, IL and University of Utah Huntsman Cancer Institute, Salt Lake City, UT.

Body: Background: Musculoskeletal symptoms are the most common side effect of aromatase inhibitors (AIs) and can result in decreased quality of life and discontinuation of therapy. Pilot data from two prior single institution studies showed that acupuncture decreased AI-induced joint symptoms in breast cancer (BC) patients.
Methods: We conducted a SWOG multicenter randomized controlled trial among postmenopausal women with early stage BC. Patients taking an AI for ≥30 days and having a worst pain score of ≥3 out of 10 using the Brief Pain Inventory (BPI-WP) were eligible. Subjects were randomized at a 2:1:1 ratio to true acupuncture (TA) vs. sham acupuncture (SA) vs. waitlist control (WC). The TA protocol used a standardized protocol of body and auricular acupoints tailored to joint symptoms. The similarly standardized SA protocol utilized superficial needling of non-acupoints. Both the TA and SA protocols consisted of a 12 week intervention, with 12 sessions administered over 6 weeks, followed by 1 session per week for 6 additional weeks. The primary endpoint was change in the BPI-WP (worst pain) score at 6 weeks. Secondary outcomes included other BPI scores, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for the hips and knees, the Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands (M-SACRAH), and functional testing with grip strength and "Timed Get Up and Go" (TGUG). The design specified alpha=.025 two-sided tests to account for two independent comparisons (TA vs. SA and TA vs. WC).
Results: Among 226 patients registered, 110 were randomized to TA, 59 to SA and 57 to WC. Baseline characteristics were similar between the groups. In a linear regression adjusting for the baseline score and stratification factors, 6-week mean BPI-WP scores were 0.92 points lower (correlating with less pain) in the TA compared to SA arm (95% CI: 0.20-1.65, p=.01), and were 0.96 points lower in the TA compared to WC arm (95% CI: 0.24-1.67, p=.01). The proportion of patients experiencing a clinically meaningful (>2) reduction (i.e. improvement) in BPI-WP was 58% for TA compared to 33% on SA and 31% on WC. Patients randomized to TA had improved symptoms compared to SA at week 6 according to all other BPI pain measures (average pain, p=.04; pain interference, p=.02; pain severity, p=.05; worst stiffness, p=.02). Results were similar compared to WC. Patients randomized to TA compared to SA or WC had statistically significant or marginally statistically significant improvements in BPI pain measures at week 12. Patients randomized to TA had generally improved symptoms compared to SA or WC at week 6 and at week 12 according to the M-SACRAH and WOMAC measures ($p<0.05$). With regard to adverse events, more patients on the TA arm experienced Grade 1 bruising compared to SA (47% vs. 25%, p=.01). No other differences by arm for selected adverse events were observed.
Conclusions: This study was the first large multicenter trial to investigate the effect of acupuncture in treating AI-induced joint symptoms in BC patients. According to multiple measures, TA generated better outcomes than either SA or WC with minimal toxicity.

2017 San Antonio Breast Cancer Symposium

Publication Number: GS5-06

Title: A U.S. food and drug administration pooled analysis of outcomes of older women with hormone-receptor positive metastatic breast cancer treated with a CDK4/6 inhibitor as initial endocrine based therapy

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Body: Background: With recent FDA approvals of inhibitors of Cyclin Dependent Kinases 4 and 6 (CDK 4/6) in combination with endocrine therapy for the treatment of postmenopausal women with hormone-receptor positive metastatic breast cancer (MBC), an increasing number of older adults will be treated with this class of agents. An improved understanding of the safety and efficacy of CDK 4/6 inhibitors in this population is important to inform clinical decision making for the treatment of older patients.
Methods: Data from two prospective randomized controlled studies (n=1334) of different CDK 4/6 inhibitors in combination with an aromatase inhibitor for the initial treatment of postmenopausal patients with hormone-receptor positive MBC were pooled and analyzed. The effect of age on progression free survival (PFS) was explored using Kaplan Meier (KM) estimates and a Cox-proportional hazard model. Safety analysis included adverse events up to 30 days after last administration of drug based on standardized adverse event datasets.
Results: Age was balanced between the two studies, and between treatment arms within each study. The median age of women was 62 (range 23-91). Of the 1334 total patients, 42% were ≥65, and 24% were ≥ 70. For patients ≥70 who were treated with a CDK4/6 inhibitor in combination with an aromatase inhibitor, the estimated PFS was not reached (95% CI: 25.1months, NR) vs an estimated 18 months (95% CI: 13.8, 31.3) for those treated only with an aromatase inhibitor. For patients <70 treated with a CDK4/6 inhibitor, the estimated PFS was 23.5 months (95% CI: 21.4, 25.7) vs an estimated 13.8 months (95% CI: 12.9, 16.5) for those treated only with an aromatase inhibitor.
Safety was evaluated in the 778 patients who received at least one dose of CDK4/6 inhibitor.

Adverse Events by Age in Patients Treated with a CDK4/6 Inhibitor

	Patients < 65 years	**Patients≥65 years**	**Patients≥70 years**
	N=447	N=331	N=187
	n (%)	n (%)	n (%)
Grade 1-2 Adverse Events	437 (98)	324 (98)	185 (99)
Grade 3-4 Adverse Events	340 (76)	276 (83)	159 (85)
Serious Adverse Events	72 (16)	88 (27)	50 (27)
Adverse Events Leading to Discontinuation	35 (8)	56 (17)	38 (20)
Adverse Events leading to dose reduction and/or interruption	323 (72)	253 (76)	147 (79)
Selected Adverse Events			
Neutropenia (all grades)	341 (76)	256 (77)	150 (80)
Grade 3-4 neutropenia	292 (65)	228 (69)	134 (72)
Infections (all grades)	190 (43)	165 (50)	100 (53)
Hepatotoxicty (all grades)	79 (18)	51 (15)	34 (18)
Grade 3-4 hepatotoxicity	32 (7)	16 (5)	12 (6)
Fatigue (all grades)	195 (44)	153 (46)	89 (48)
Grade 3 fatigue	11 (2)	11 (3)	7 (4)

Conclusions: This exploratory analysis suggests the use of a CDK4/6 inhibitor in combination with an aromatase inhibitor for the

first line treatment of HR+ MBC in older women results in similar efficacy benefit as seen in younger women. Although incidence and severity of Grade 1-4 adverse reactions appeared similar between age groups, greater serious adverse events and discontinuations occurred in patients ≥65. The inclusion of greater numbers of patients ≥70, in clinical trials will further inform clinicians about the safety and efficacy of CDK4/6 inhibitors in older adults.

2017 San Antonio Breast Cancer Symposium

Publication Number: GS5-07

Title: Weight change in postmenopausal women and breast cancer risk in the women's health initiative observational study

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Body: Purpose
While obesity is an established breast cancer risk factor, information about the influence of weight loss on breast cancer risk in postmenopausal women is mixed precluding generation of a strong public health message regarding potential benefits of weight loss with respect to cancer risk. Therefore, we evaluated associations between weight change and invasive breast cancer risk in postmenopausal women participating in the Women's Health Initiative (WHI) Observational Study.
Patients and Methods
Postmenopausal women (n=61,335) with no prior breast cancer and normal mammogram who were not underweight (body mass index [BMI] ≥ 18.5 kg/m^2), ages 50-79 years at WHI enrollment between 1993 and 1998 at 40 US clinical centers, had body weight and height measured and BMI calculated at the clinical centers at baseline and at year 3. Weight change over 3 years was categorized as: stable (no change ≤ 5%), loss (change ≥ 5%), or gain (change ≥ 5%) with weight lost intentionality determined by self-report response to direct query at year 3. Breast cancers were initially ascertained through annual survey and were centrally confirmed by medical record review. Multi-variable Cox proportional hazards regression models incorporating breast cancer risk factors and baseline BMI were used to evaluate relationships between weight change and breast cancer incidence.
Results
During 11.4 years (mean) of follow-up, 3,061 women developed invasive breast cancer. In multi-variable analyses, compared with women with stable weight (n=41,139), women with weight loss (≥ 5%) (n=8,175) had a significantly lower breast cancer risk (hazard ratio [HR] 0.88 95% confidence interval [CI] 0.78-0.98). Adjustment for mammography did not alter findings (HR 0.88 95% CI 0.78-0.99). There was no significant interaction for breast cancer effect by weight loss intentionality. Women with weight loss ≥ 15% had even lower breast cancer risk (HR 0.63 95% CI 0.45-0.90). While weight gain (≥ 5%) (n=12,021) was not associated with higher overall breast cancer risk, women with weight gain had a significantly higher risk of triple negative breast cancer (HR 1.54 95% CI 1.16-2.05). Weight change association with breast cancer incidence was examined in four subgroups: by tumor subtype (hormone receptor and HER2 status based), baseline BMI (normal, overweight, obese), race/ethnicity, and age group (50, -<70 years). Effects in all subgroups was similar with no evidence of heterogeneity as no interaction term test in these analyses was significant.
Conclusion
Weight loss in postmenopausal women is associated with lower breast cancer risk. These findings suggest that postmenopausal women who lose weight may reduce their breast cancer risk.

2017 San Antonio Breast Cancer Symposium

Publication Number: GS6-03

Title: Circulating tumor cells (CTCs) five years after diagnosis are prognostic for late recurrence in operable stage II-III breast cancer

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Body: **Background:** Late recurrence 5 or more years after diagnosis accounts for least one-half of all breast cancer recurrences, especially in hormone receptor (HR)+ disease. Biomarkers prognostic for late recurrence offer potential to more accurately identify subjects who might benefit from extended adjuvant endocrine therapy, or novel strategies to reduce late recurrence risk.
Methods: CTCs were assessed at a single time point using the CELL SEARCH® assay in patients without clinical evidence of recurrence between 4.5-7.5 years after an initial diagnosis of HER2- stage II-III breast cancer and enrolled in trial E5103; all patients received surgery plus adjuvant chemotherapy and endocrine therapy for at least 5 years if HR+ disease. Patients were followed for evidence of clinical recurrence in accordance with standard care, and the association between CTCs and clinical recurrence was evaluated.
Results: 546 patients without clinical evidence of recurrence enrolled between 2/25/13-7/29/16 and provided a blood sample that yielded a CTC result; 16 (2.9%) subsequently had a recurrence, of whom 15 had HR-positive disease. The median time between enrollment on E5103 and CTC assay was 5.2 years, and median/mean followup after the CTC assay was 1.6 years (range 0-3.9 years). The CTC assay was positive in 27 (4.9%) (median CTC count 1/7.5 ml blood, range 1-15). There were no significant differences in patient characteristics in the CTC+ vs. CTC- cases, including age < 50 years at initial diagnosis (52% vs. 44%), tumor size > 2 cm (63% vs. 59%), >/= 1 positive axillary node (81% vs. 72%), ER and/or PR+ (70% vs. 64%) or poor histologic grade (44% vs 55%). The recurrence rate per person-year in the CTC+ vs. CTC- groups was 19.6% vs. 1.1%, respectively (P<0.01). The median/mean time to recurrence after a positive CTC assay was 2.8 years. In multivariate analysis adjusted for clinical covariates (see table), a positive CTC assay was associated with an 18.3-fold increased risk of recurrence.

Univariate and Multivariate Analysis - Association Between CTC Status and Recurrence

Covariate	Hazard Ratio for Recurrence - Univariate Analysis (95% CI)	Hazard Ratio for Recurrence - Multivariate Analysis (95% CI)
Age < 50 years	3.4 (0.95-11.8)	3.0 (0.8-10.9)
Tumor size > 2 cm	4.2 (0.98-19.2)	2.9 (0.6-13.2)
>/= 1+ node	2.6 (0.59-11.5)	0.7 (0.1-3.8)
ER and/or PR+	8.3 (1.1-63.5)	7.7 (0.7-79.9)
Poor grade	0.43 (0.14-1.2)	1.2 (0.4-3.8)
CTC -pos vs CTC-neg	20.9 (7.5-58.3)	18.3 (5.7-58.2)

Conclusions: A single positive CTC assay in patients without clinical evidence of recurrence 5 years after diagnosis of stage II-III HR+, HER2- breast cancer provides independent prognostic information for late recurrence, providing proof of concept for using liquid-based biomarkers for late relapse risk assessment. These findings provide a foundation for further evaluation of this new risk assessment paradigm using CTC and other blood-based assays in this setting, and designing clinical trials to tailor therapeutic risk interventions.
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2017 San Antonio Breast Cancer Symposium

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Title: EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline *BRCA* mutation

Background: Talazoparib (TALA) is a highly potent, dual-mechanism PARP inhibitor that inhibits the PARP enzyme and effectively traps PARP on single-stranded DNA breaks, preventing DNA damage repair and causing cell death in *BRCA1/2*-mutated cells.

Methods: EMBRACA is an open-label, randomized, 2-arm, phase 3 trial comparing the efficacy and safety of TALA (1 mg/day) with standard single-agent physician's choice of therapy (PCT) (capecitabine, eribulin, gemcitabine, or vinorelbine) in patients with advanced breast cancer (aBC) and a germline *BRCA1/2* mutation (gBRCA^{mut}). The primary objective was PFS assessed by blinded independent central review (BICR). Secondary objectives: OS, ORR, CBR at 24 weeks (CBR24), and safety. Exploratory objectives: patient-reported QoL and DOR. Eligibility criteria: age ≥ 18 years; HER2-negative aBC; deleterious or suspected deleterious gBRCA^{mut}; ≤ 3 prior cytotoxic regimens for aBC; and ECOG PS ≤ 2. Prior platinum was allowed. Patients were randomized 2:1 and stratified by receptor status, extent of prior therapy, and CNS metastases (NCT01945775).

Results: 431 patients were randomized (median age 46 years; 54% hormone-receptor [HR]+ BC; 45% *BRCA1*+ and 55% *BRCA2*+; 55% ECOG PS = 0; 38% chemo-naïve for aBC; 18% prior platinum; 15% CNS metastases); 287 were assigned to TALA and 144 to PCT (1 TALA, 18 PCT patients were not treated). Median duration of exposure was 6.1 and 3.9 months, respectively; TALA had a relative dose intensity of 87%. At 62% PFS data maturity:

	TALA	PCT	Hazard Ratio/ Odds Ratio (*P* value)
PFS by BICR, mo (95% CI)	8.6 (7.2-9.3); n = 287	5.6 (4.2-6.7); n = 144	0.542 (< 0.0001)
OS [interim], mo (95% CI)	22.3 (18.1-26.2); n = 287	19.5 (16.3-22.4); n = 144	0.761 (0.105)
ORR by INV, % (95% CI)	62.6% (55.8-69.0); n = 219	27.2% (19.3-36.3); n = 114	4.99 (< 0.0001)
DOR by INV, mo (IQR)	5.4 (2.8-11.2); n = 137	3.1 (2.4-6.7); n = 31	0.431 (0.0005)*
CBR24 by INV, % (95% CI)	68.6% (62.9-74.0); n = 287	36.1% (28.3-44.5); n = 144	4.28 (≤0.0001)

INV, investigator. *Not a randomized subset.

Improved clinical benefit was seen in all subsets including those with HR+ BC (HR 0.47; 95% CI 0.32-0.71) and CNS metastasis (HR 0.32; 95% CI 0.15-0.88). There was a significant delay in the time to deterioration in global health status (GHS)/QoL for TALA vs PCT (HR 0.38; 95% CI 0.26-0.55; $P < 0.0001$]. Grade 3-4 hematologic adverse events (AEs) occurred in 55% TALA (mainly anemia)/39% PCT (mainly neutropenia). Grade 3-4 non-hematologic AEs were seen in 32% TALA/38% PCT; TALA was associated with fewer gastrointestinal disorders (5.6% vs 11.9%) and skin/subcutaneous tissue disorders (0.7% vs 5.6%) than PCT. Grade 3-4 serious AEs were observed in 26% TALA/25% PCT. AEs associated with permanent study drug discontinuation occurred in 8% TALA/10% PCT. AE resulting in death occurred in 2.1% TALA/3.2% PCT.

Conclusions: Single-agent TALA significantly prolonged PFS by BICR in HER2-negative aBC patients with a gBRCA^{mut} compared to PCT; all key secondary efficacy endpoints demonstrated benefit with TALA, with a significant delay in time to deterioration in GHS/QoL. TALA was generally well tolerated with minimal non-hematologic toxicity and few AEs associated with treatment discontinuations.

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2017 San Antonio Breast Cancer Symposium

Publication Number: GS5-03

Title: Risk of arm morbidity after local therapy in young breast cancer survivors

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Body: BACKGROUND: Arm morbidity, the most reported comorbidity following axillary surgery for breast cancer, is of particular importance in young patients given the longer survivorship period and detrimental effects of arm-morbidity on body image and social-, home- and personal care functions. We assessed the incidence of arm-morbidity stratified by local therapy strategies in young women enrolled in the Young Women's Breast Cancer Study (YWS).
PATIENTS AND METHODS: The YWS, a multicenter prospective cohort study, established to explore biological, medical and psychosocial issues in young breast cancer patients, enrolled 1302 women with stage 0-4 breast cancer ≤40 years of age from October 2006 to June 2016. For this analysis, we examined incidence of patient reported arm-swelling or decreased range of motion (ROM) 1-year after diagnosis using relevant items of the CARES-SF. Patients with stage 4 disease (n = 60), those for whom no information on arm-morbidity was available (n=198) and those with bilateral cancer with different local therapy strategies on each side (n=7), were excluded. We performed logistic regression analyses to identify risk factors for arm morbidity.
RESULTS: Among 1037 patients (median age 37 years), 13% and 40% reported arm-swelling or decreased ROM, respectively, in the ipsilateral arm at 1-year. 52% (n=539) of patients underwent SLNB and 39% (n=407) ALND. The incidence of arm-swelling was 4% (11/280) in patients who underwent SLNB without RT, 8% (21/252) in patients who underwent SLNB with RT, 20% (13/66) in patients who underwent ALND without RT and 24% (84/337) in patients who received ALND with RT. The incidence of decreased ROM was 21% (59) in patients who underwent SLNB without RT, 34% (86) in patients who underwent SLNB with RT, 33% (22) in patients who underwent ALND without RT and 44% (148) in patients who received ALND with RT. Being overweight, uncomfortable financial status, T4 tumors, ALND and RT were independently associated with an increased risk of arm-swelling. Overweight, mastectomy and RT were independently associated with an increased risk of a decreased ROM

Table 1). Results of the logistic regression analyses.

	Arm swelling at 1 year (n=137)		**Decreased ROM at 1 year (n=335)**	
	OR	p	OR	p
BMI				
<18.5	0.7	0.62	0.7	0.40
18.5-24.9	ref		ref	
25-29.9	1.7	0.03	1.5	0.05
≥30	1.1	0.79	1.1	0.70
Financial comfort				
Comfortable	ref		ref	
Uncomfortable	0.6	0.02	0.9	0.67
pT stage				
pT1	ref		ref	
pT2	1.2	0.62	1.5	0.13
pT3	1.2	0.70	1.3	0.63
pT4	4.4	0.03	2.2	0.29
pN stage				

pN0	ref		ref	
pN1	1.1	0.85	1.7	0.08
pN2	3.0	0.11	1.9	0.27
pN3	3.2	0.11	2.7	0.16
Surgery				
BCS	ref		ref	
Mastectomy	1.2	0.61	1.8	0.02
Bilateral mastectomy	1.1	0.84	1.6	0.06
Axillary surgery				
SLNB	ref		ref	
SLNB + ALND	3	<0.01	1.3	0.33
ALND	3.6	<0.01	1.0	0.90
RT				
No	ref		ref	
Yes	1.8	0.05	2.4	<0.01

Note. In these analysis we also corrected for age, incidence year, employment status, stage of disease, reconstructive surgery, and chemotherapy treatment.

CONCLUSION: Patient reported outcomes reveal high rates of arm-swelling and decreased ROM 1 year after breast cancer diagnosis in a large prospective cohort of young breast cancer survivors. These findings suggest an opportunity for pre-operative education and early intervention for arm impairment in this population.