RECOMMENDED ER+ BREAST CANCER ABSTRACTS FROM ASCO 2019

RAS Lifescience Solution
Phase I trial of endoxifen gel versus placebo gel in women undergoing breast surgery

Abstract No: TPS1588

Background: Despite large Phase III clinical trials that have established the success of selective estrogen receptor modulators (SERMs) for breast cancer prevention and therapy of duct carcinoma in situ (DCIS), acceptance by women likely to benefit has been low, primarily because of toxicity related to systemic exposure. Local drug delivery to the breast in gel form is an attractive alternative since low systemic levels could minimize toxicity. Endoxifen (ENX) is an active metabolite of tamoxifen, that has unique activity compared with 4-hydroxytamoxifen (4-OHT). It is smaller and more polar than 4-OHT making it potentially more suitable for transdermal delivery. The NCI PREVENT program has developed ENX transdermal alcoholic gel products.

Methods: We are conducting a randomized, double-blind, placebo-controlled, Phase I trial to establish the dermal tolerability and safety of endoxifen (ENX) gel. 38 women planning unilateral or bilateral mastectomy will be enrolled across 3 institutions in 3 cohorts: (a) ENX gel 10mg (N = 8) vs. placebo gel (N = 4) daily; (b) ENX gel 20mg (N = 8) vs. placebo gel (N = 4) daily; (c) the maximum tolerated dose (N = 8) with last dose 72 hours prior to surgery. Treatment duration will be 4 ± 1 weeks. All participants will be evaluated for toxicity and skin tolerability. Secondary endpoints include TAM metabolite measurements in breast tissue and plasma; serum hormone concentrations, serum estrogenic response, changes in coagulation parameters, gene expression changes reflective of therapeutic effects, and experienced symptoms. 65 potential participants have been pre-screened for eligibility. 33 were ineligible prior to contact, most commonly due to the use of neoadjuvant chemotherapy. Of 32 potential participants who have been eligible to be contacted, 21 did not consent for screening, most commonly because they were too overwhelmed with their recent diagnosis. 7 have consented, 4 are pending consent, and 6 have started study intervention. No adverse events have been reported to date. This pre-surgical trial testing transdermal ENX for breast cancer prevention is accruing as projected. The results will establish the skin safety of this agent, provide data on skin permeability, and the duration of drug retention in the breast. Clinical trial information: NCT03317405

The CYP2C19 rs4917623 single nucleotide polymorphism to predict tamoxifen efficacy in ER+ breast cancer patients

Abstract No: e12001

Background: Tamoxifen is a selective estrogen receptor modulator that is widely used to treat estrogen receptor (ER)-positive breast cancer. However, not all patients benefit from the incorporation of tamoxifen into an adjuvant therapy. This is also the case when tamoxifen is used in chemoprevention, since only half of participants benefit from the drug. In order to improve treatment response, we attempted to identify single nucleotide polymorphisms (SNPs) that correlated with tamoxifen efficacy.

Methods: ER-positive breast cancer patients at our hospital were enrolled on this study between January 2007 and September 2010. The primary endpoint was ER-positive breast cancer-free survival. We examined 17 SNPs in these patients. The survival benefit associated with each genotype was determined with a log-rank test, and the hazard ratio was analyzed using a Cox proportional-hazards model.

Results: The median follow-up time of the 320 patients enrolled on the study was 3298 days. Of 240 patients who received any endocrine therapy, ER-positive breast cancer-free survival in patients with the 2q35 rs13387042 AA genotype was significantly shorter than in those who had the AG or GG genotype (p < 0.0001), and the hazard ratio was significantly higher (HR 8.83; 95% CI 2.09–25.53, p = 0.0064). Of the 145 patients who received tamoxifen therapy, there was a trend among ER-positive breast cancer patients with the CYP2C19 rs4917623 TT genotype to have a
shorter disease-free period (p = 0.0635) when compared to patients with TC or CC genotypes. Similarly, there was a trend for the TT genotype patients to exhibit a higher hazard ratio (HR 2.62; 95% CI 0.86–7.55, p = 0.0861).

Conclusions: The rs4917623 SNP in the CYP2C19 gene, which encodes a metabolic enzyme, predicts tamoxifen efficacy. This finding will facilitate selection of ER-positive breast cancer patients for tamoxifen treatment; it may also be useful for selection of patients most likely to benefit from tamoxifen-dependent chemoprevention.

Open label, phase II trial of neoadjuvant TAK-228 plus tamoxifen in patients with ER+HER2- breast cancer-ANETT

Abstract No: 584

Background: Neoadjuvant endocrine therapy is standard care for women with hormone receptor-positive breast cancer. However, both primary and acquired endocrine resistance is not uncommon, thereby limiting efficacy. [1] The PI3K-Akt-mTOR pathway is a major mediator of endocrine resistance. [2,3] Therefore, we determined the efficacy and safety of the mTORC1/2 inhibitor TAK-228 in combination with tamoxifen in neoadjuvant setting.

Methods: In this single-arm, open-label phase II trial, newly diagnosed patients with stage I–III ER-positive, HER2-negative breast cancer received TAK-228 (30 mg weekly) and tamoxifen (20 mg daily) for 16 weeks until 2-4 weeks prior to surgery. The primary endpoint was the change in Ki67 after 6 weeks. Secondary endpoints included pathological complete response rate (pCR), preoperative endocrine prognostic index (PEPI) score, and safety.

Results: Of the 28 patients enrolled in the study, 3 were excluded due to non-compliance. Mean patient age was 51.7 years. Most patients had stage I or II disease (12 [43%] each); 4 (14%) had stage III disease. Mean Ki67 was significantly lowered from baseline to Week 6 (17.2% vs. 15.2%, p = 0.0023). Interestingly, mean Ki67 increased to 20.1% from baseline to the time of surgery. This may have been due to a rebound effect, as TAK-228 was discontinued 2-4 weeks prior to surgery. Tumor size also significantly decreased from baseline to surgery, with a median decrease of 0.75 centimeters (p < 0.0001). PEPI score was intermediate risk (score 1–3) in 6 patients and high risk group (score ≥4) in 15 patients. No patients achieved a PEPI score of 0 and no pCR was achieved. Overall, the combination was well tolerated, the most common side effects were nausea (72%), vomiting (72%), fatigue (72%), mucositis (45%), and headache (45%). The any Grade 3 AE rate was 7.7%.

Conclusions: The TAK-228 and tamoxifen combination was found to be an effective neoadjuvant strategy with a favorable safety profile in newly diagnosed patients with hormone receptor-positive breast cancer. Further molecular analysis (PI3K-Akt-mTOR pathway) are pending and will be presented. Clinical trial information: NCT02988986

Randomized phase II study of eribulin mesylate (E) with or without pembrolizumab (P) for HR+ MBC.

Abstract No: 1004

Background: Studies of checkpoint inhibitor monotherapy show only modest activity in HR+ MBC. We report data from the first randomized study comparing E plus P versus E alone in HR+/HER2- MBC.

Methods: Eligible patients (pts) had HR+/HER2- MBC, ≥2 lines of hormonal therapies and 0-2 lines of chemotherapy for MBC. Pts were randomized 1:1 to E 1.4mg/m2 intravenously (IV) on d1 and d8 with P 200 mg/m2 IV on d1 of a 21-day cycle (Arm A) or E alone (Arm B). At time of progression, pts in arm B could crossover and receive P alone. Primary endpoint was progression-free survival (PFS). Key secondary endpoints were: objective response rate (ORR) and overall survival (OS). Exploratory analyses assessed the association between PFS and PD-L1 status, tumor-infiltrating
lymphocytes (TILs), neutrophil-lymphocyte ratio (NLR), tumor mutation burden (TMB), and genomic alterations by next generation sequencing on archival tissue.

Results: 88 pts initiated protocol therapy; the median age was 58, median prior lines of chemotherapy 1, prior lines of hormonal therapy 2. Median follow-up was 6.3 months. Median PFS and ORR were not different between Arms A and B (PFS 4.1 vs 4.2 months p = 0.38; ORR 25% and 34% respectively (p = 0.49). 14 patients initiated crossover treatment with pembrolizumab; 1 patient experienced a PR (ORR 7%). All-cause AEs occurred in 100% of pts (G3-4, 54.6%) including 2 treatment related deaths on Arm A, both from known AEs attributed to both drugs. PD-L1 assay was performed in 65 pts: 24 (36.9%) had PD-L1 positive (> 1% with 22C3, centrally tested) tumors. PD-L1 status, TILs, NLR, TMB, and genomic alterations were not associated with PFS (Table). Updated data, including OS and genomic results, will be presented.

Conclusions: Among pts with HR+/HER2- MBC, the combination of E and P was not associated with longer PFS than E alone in the ITT or PD-L1+ population, though the PD-L1+ subgroup had very limited power to assess P benefit. Clinical trial information: NCT03051659

A phase Ib/II trial of lenvatinib (len) and letrozole (let) incorporating pharmacodynamics studies in postmenopausal women with HR+ locally advanced/metastatic breast cancer (LABC/MBC)

Abstract No: 1045

Background: Endocrine blockade (EB) is standard of care for patients (pts) with HR+ LABC/MBC. RET over-expression (RET+) occurs in up to 75% of HR+ breast cancers and is a postulated mechanism of endocrine resistance. Preclinical studies show cross talk between RET and estrogen receptor, and at least additive treatment (Tx) effect of Len+EB.

Methods: We performed a phase Ib trial (3+3 dose escalation) to study safety, tolerability, pharmacodynamics and efficacy of Len+Let. Both drugs were given as continuous daily dosing with 2 weeks (wks) of Len alone, followed by Len+Let for 12 wks then surgery (LABC), or till disease progression (PD) (MBC). Serial tumor biopsies (n = 15) were done at baseline, after Len alone, 4 wks post Len+Let, and at surgery [LABC] / upon PD [MBC].

Results: 16 pts were treated (4 LABC, 12 MBC); Among MBC pts, median lines of prior Tx was 3 (range 0-10); 84.6%, 66.7%, and 58.3% had prior EB, EB+CDK4/6 inhibitor (i), and chemotherapy (CT) respectively. At dose level (DL) 1, 2/4 pts had dose-limiting toxicities (DLT). There was no DLT at DL-1, but 6/6 pts needed dose reductions (DR), with 4/6 DR within 6 wks of Len+Let (3 G3 hypertension [HTN], 1 G3 wound pain), deeming DL-1 intolerable. At DL-2, 0/6 pts had DLT; this was declared recommended phase 2 dose (RP2D). Most frequent G3 toxicities (tox) were HTN (6/16), proteinuria (2/16) and palmar-plantar erythrodysesthesia (PPE) (2/16), with no G4/5 tox. Len+Let was active with 93.8% overall disease control rate (DCR) (50.0% partial response [PR], 43.8% stable disease [SD]). Among MBCts (8/12 had prior EB+CDK4/6i), DCR ≥12 wks was 91.7%; 1 pt had sustained PR for 48 wks and 1 ongoing PR at 40 wks. 9/16 pts had RET+ tumors on immunohistochemistry at baseline, and 66.7% showed down-regulation with Tx (RECIST: 4 PR, 2 SD).

Everolimus and exemestane for the treatment of metastatic HR+ MBC patients previously treated with CDK4/6 inhibitor based therapies
Abstract No: 1058

Background: The combination of everolimus (EVE) and exemestane (EXE) is approved as second line endocrine therapy for metastatic hormone receptor positive breast cancer (mHRBC) patients who progressed on non-steroidal aromatase inhibitor (NSAI) therapy based on the BOLERO-2 trial. However, none of the patients in BOLERO-2 received prior CDK4/6 inhibitors, which have since become standard of care for metastatic HRBC. As such, the clinical benefit of EVE + EXE in mHRBC patients previously treated with CDK4/6 inhibitors remains unknown.

Methods: We reviewed patients ≥18yo with mHRBC treated with EVE + EXE following NSAI alone or NSAI + CDK 4/6 inhibitor at our institution between 2012-2018. Data collected included patient and tumor characteristics, therapies in the metastatic setting, special interest adverse events, and clinical outcomes. The primary objective was comparing PFS for EVE + EXE therapy between patients who received prior CDK4/6 inhibitor therapy and those who did not. Secondary endpoints included overall survival (OS). Patient features were summarized with descriptive statistics and time-to-event measures were estimated using the Kaplan-Meier method. Differences between groups were tested with Fisher’s exact, Kruskal-Wallis, or log-rank test.

Results: Thirty-three patients were included in the study; 17 had prior CDK4/6 inhibitor therapy and 16 did not. Subjects that took EVE + EXE for < 28 days were excluded. Patient characteristics, including prior therapies and sites of metastatic disease, were not significantly different. There was no significant difference in PFS (median 5.7 vs 4.7 months, p = 0.890) or OS (median 17.8 vs 11.4 months, p = 0.177) between patients who received prior CDK4/6 inhibitors and those who did not, respectively. Steroid mouthwash use was associated with a reduced incidence of stomatitis.

Capivasertib (AZD5363) plus fulvestrant versus placebo plus fulvestrant after relapse or progression on an aromatase inhibitor in metastatic ER+ breast cancer (FAKTION): A randomized, double-blind, placebo-controlled, phase II trial.

Abstract No: 1005

Background: The PI3K/AKT signaling pathway is frequently activated in patients (pts) with estrogen receptor (ER) positive breast cancer (ER+BC) and has been implicated in endocrine therapy resistance. Capivasertib (AZD5363) is a highly selective, oral, small molecule AKT inhibitor. The FAKTION trial investigated the addition of capivasertib to fulvestrant for postmenopausal women with ER+ and HER2 negative BC after relapse or disease progression on an aromatase inhibitor (AI).

Methods: FAKTION is an investigator-led, double-blind, placebo-controlled, randomised phase II trial. Patients were recruited from 21 UK sites and randomly assigned (1:1) to fulvestrant 500mg (day 1 and 15 of cycle 1 and day 1 only of subsequent 28 day cycles) with either capivasertib 400mg bd or placebo (4 days on/3 days off starting C1D15) until disease progression, unacceptable toxicity or withdrawal of consent. Allocation was balanced by minimisation according to PIK3CA mutation and PTEN expression status, measurable/non-measurable disease, and primary/secondary endocrine resistance. The primary endpoint was progression-free survival (PFS). The trial had 90% power to detect a hazard ratio of 0.65 at the one-sided 20% significance level. Secondary endpoints included overall survival (OS), objective response and clinical benefit rates, safety and the effect of PI3K/Akt pathway activation on PFS.

Results: Between Mar 2015 and Mar 2018, 140 pts were randomised to fulvestrant + capivasertib (n = 69) or fulvestrant + placebo (n = 71). In the Intention-to-treat analysis, after 112 events, median PFS was 10.3 months (m) for capivasertib compared to 4.8m for placebo (Hazard Ratio (HR) 0.57; 95% CI: 0.39 to 0.84; one-sided p = 0.0017; two-sided 0.0035). Fifty-two deaths were reported. Median OS was 26.0m for capivasertib compared to 20.0m for placebo, with a survival difference starting to emerge after 12m (HR = 0.59; 95% CI: 0.34 to 1.05; two-sided p = 0.071). Toxicity data and
subgroup analyses including relative capivasertib benefit by PI3K/Akt pathway alteration will be presented at the conference.

Conclusions: The trial met its primary endpoint. Addition of capivasertib to fulvestrant for patients with endocrine resistant advanced breast cancer resulted in significantly longer PFS and an improvement in OS. The FAKTION results warrant further investigation of capivasertib for the treatment of ER positive breast cancer. Clinical trial information: NCT01992952

Dose-escalation study of SAR439859, an oral selective estrogen receptor (ER) degrader (SERD), in postmenopausal women with ER+/HER2- mBC.

Abstract No: 1054

Background: SERDs result in ER competitive antagonism and degradation and can block signaling in ER-dependent tumors resistant to other endocrine therapies. This study investigates SAR439859, a potent oral SERD, +/- palbociclib in ER+/HER2- mBC. Here are preliminary results, as of 28 Nov 2018, for single-agent SAR439859 dose escalation.

Methods: Part A of this Phase 1/2 study (NCT03284957; TED14856) assessed SAR439859 dose escalation (dose range: 20–600 mg once daily [QD]; 3 + 3 design) in postmenopausal women with ER+/HER2- mBC treated for ≥ 6 months with prior endocrine therapy and ≤ 3 chemotherapies in the advanced setting. Endpoints: dose-limiting toxicities (DLTs); maximum tolerated dose (MTD); safety; pharmacokinetics (PK); tumor response (RECIST 1.1); pharmacodynamic (PD) inhibition of ER occupancy (18FES-PET scan).

Results: Patients (pts; n = 16) had a median age of 59.5 years (range 40–79), ECOG performance status of 0 (62.5%) or 1 (37.5%) and a median of three prior anticancer therapies (range 1–8) in the advanced setting (endocrine therapy n = 16; chemo/targeted therapy n = 13). All pts had ≥ 1 treatment emergent adverse event (mostly grade 1–2); most frequent were asthenia/fatigue (43.8%), hot flushes (37.5%), nausea (37.5%), diarrhea (31.3%), constipation (31.3%), and decreased appetite (31.3%). There were no DLTs at any of the five dose levels (maximum administered dose: 600 mg QD); MTD was not reached. In 18FES-PET scans, signal inhibition > 87% occurred with plasma concentrations > 100 ng/mL. There was a dose proportional increase of exposure up to 400 mg after repeated QD doses. Average C_trough was reached after repeated 400 mg QD allowing 90% of 18FES-PET signal inhibition. One pt (6.3%) had confirmed partial response (150 mg QD); eight (50%) had stable disease (SD) including three (18.8%) long-term SD (≥ 24 weeks); seven (43.8%) had progressive disease.

Conclusions: SAR439859 had a favorable safety profile, high ER occupancy and encouraging antitumor activity (to be confirmed in dose expansion) in pretreated pts with ER+/HER2- mBC. With no DLTs and MTD, 400 mg QD was selected for expansion cohorts based on safety, PD and PK data. Funding: Sanofi. Clinical trial information: NCT03284957

CDK4/6 inhibitors in advanced HR+/HER2- breast cancer: A network meta-analysis (NMA) of RCTs.

Abstract No: e12545

Background: Palbociclib(P), Ribociclib(R) and Abemaciclib(A) in combination with Endocrine therapy (ET) have demonstrated progression free survival (PFS) in patients with metastatic hormone receptor positive, HER2-negative breast cancer as compared to ET alone. In the absence of head to head clinical trials and to provide clinical guidance, we performed an indirect comparison for P, R and A using network Meta-Analysis (NMA).
Methods: MEDLINE, EMBASE and the Cochrane Library were searched to identify RCTs comparing P+ET, R+ET, A+ ET vs ET alone. NMA for PFS and toxicity endpoints was conducted using a multivariate random-effects meta-regression, using a consistency model, as described by White and colleagues. We used a frequentist approach and provided a point estimate from the network and a 95% CI from the frequency distribution of the estimate. We also estimated the relative ranking of the different treatments for each outcome using the distribution of the ranking probabilities and the surface under the cumulative ranking curves (SUCRA). Risk of bias was assessed using Cochrane Collaboration tool.

Results: 8 RCTs were identified including 4580 patients. Risk of bias was low. 5 RCTs tested CDK 4/6 inhibitors in endocrine naive and 2 in the refractory setting, while MONALESSA-3 included patients both with endocrine naive and endocrine resistant disease. In the endocrine naïve patients, PFS for P was similar when compared indirectly with R (HR, 0.95, 95% CI 0.67-1.35) or A (HR, 1.00, 95% CI 0.62-1.61). Similarly, indirect comparison between R vs A did not show any statistical significant (HR, 0.95, 95% CI 0.62-1.45). In endocrine refractory patients, P showed no difference when compared indirectly to A (HR 1.12, 95% CI 0.67-1.87) or R (HR 0.98, 95% CI 0.52-1.86). R vs A did not show any statistically significant PFS either (HR, 1.14, 95% CI 1.61-4.51). P was ranked first in terms of PFS in frontline setting (SUCRA of 70.5) while R ranked first in the refractory setting (SUCRA of 39.5). QT prolongation was reported for R only. P caused more neutropenia while A caused more fatigue, anemia and diarrhea, although the results were not statistically significant.

Conclusions: The efficacy of using either palbociclib, ribociclib or abemaciclib in combination with ET was similar in terms of PFS in either endocrine naïve or resistant disease. Palbociclib causes more neutropenia, abemaciclib causes more fatigue, anemia and diarrhea while ribociclib causes QT prolongation.

Assessing treatment benefits with CDK4/6i+ET for HR+ advBC: A network meta-analysis

Abstract No: e12543

Background: Previously, the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (aBC) has relied solely on endocrine therapy (ET). Unfortunately, almost all tumors developed resistance to ET. Although cyclin-dependent kinase inhibitors (CDKi)+ET clearly improve several clinical outcomes, many relevant questions remain unanswered: is there a benefit in (i) overall survival (OS) (ii) progression-free survival (PFS), and (iii) which CDKi is the best.

Methods: A systematic review was performed to identify trials that compared CDKi+ET versus ET alone for HR+/HER2-aBC. Pooled meta-estimates were generated to assess CDKi+ET OS benefit and PFS benefit. Bayesian network meta-analysis was performed to compare each CDKi in terms of PFS, clinical benefit rate (CBR), response rate (RR) and toxicity.

Results: 2,523 studies were screened, and 8 studies satisfied the inclusion criteria. There was a trend for OS benefit with CDKi+ET compared to ET alone with 97% posterior probability that CDKi+ET is better than ET alone and HR 0.81 (95% CrI 0.66-1.00). CDKi+ET also showed > 99% probability of better than ET alone in both first and second-line settings in terms of PFS, RR, and CBR with PFS HR 0.56 (0.47-0.66) first line, 0.49 (0.39-0.60) second-line; RR OR 1.61 (1.29-1.97) first-line, 2.58 (1.71-3.80) second-line; CBR OR 1.75 (1.38-2.25) first-line, 2.38 (1.65-3.37) second-line. Ribociclib and abemaciclib showed weak-moderate evidence of better PFS and RR compared to palbociclib (64% to 81% posterior probability of superiority). There was no evidence of differences between ribociclib and abemaciclib. Palbociclib achieved better CBR compared to ribociclib and abemaciclib, although this difference may be related to the poor performance of placebo arm in studies that used palbociclib. In terms of safety, abemaciclib caused less neutropenia, but more diarrhea than ribociclib and palbociclib. Deep vein thrombosis was less frequent with ribociclib.
Conclusions: CDKi+ET was 97% superior in terms of OS and > 99% superior in terms of PFS, RR, and CBR compared to ET alone. Further studies are necessary in order to find the best agent and the best sequencing of CDKi for HR+/HER2- aBC treatment.

Conclusions: EVE + EXE is well tolerated and shows similar efficacy in metastatic HRBC patients who received CDK4/6 inhibitor therapy and those who did not. There was a non-significant trend towards improved OS in the CDK4/6 inhibitor group that needs to be further evaluated in larger patient cohorts.

Endocrine-based targeted combination versus endocrine therapy alone as first-line treatment in elderly patients with HR+ advanced BC: Meta-analysis of phase II and III randomized clinical trials.

Abstract No: 1046

Background: Combined endocrine approaches have been widely investigated as first-line treatment in hormone receptors positive metastatic breast cancer. In particular, multiple randomized trials showed that the addiction of CDK4/6 inhibitors to endocrine therapy (ET) increase progression free survival (PFS). Elderly patients (aged ≥65 years) are under-represented in most of the clinical studies. Moreover, due to the multi-morbidity and the major toxicity associated with the targeted agents, the combination strategy in that subgroup is widely discussed. The present meta-analysis aimed to understand the role of the new endocrine approaches in women aged ≥65 years.

Methods: This meta-analysis included first line phase II/III randomized published trials comparing (ET) to the experimental strategy. Trials with no data about hazard ratios (HR) for PFS in the subgroup of patients aged ≥65 years were excluded. The heterogeneity of the data was evaluated by Chi-square Q test and I² statistic.

Results: 8 studies were included in the analysis. 4 trials (Paloma1/TRIO-18, Paloma2, Monaleesa2, Monarch3) investigated the role of CDK 4/6 inhibitors, 2 trials (SWOG and FACT) analyzed the combination of Fulvestrant plus Aromatase Inhibitors, while other two trials explored the association of ET with Bevacizumab (LEA) and Temsirolimus (HORIZON), respectively. Overall, the meta-analysis showed a PFS advantage for the experimental arms [HR 0.77, p 0.016] with a significant high/moderate heterogeneity [I² 65.46%, p 0.005]. The 4 studies adding CDK4/6 inhibitors to ET showed a significant improvement in PFS compared to ET alone. No significant advantages for the addition of anti-angiogenic agents or Fulvestrant to ET have been found in elderly population subgroup.

Conclusions: The novel experimental combo-strategies in the first line setting showed an improvement in PFS in the subgroup of elderly patients. Adding CDK4/6 inhibitors to ET significantly prolongs PFS as compared to ET alone. The magnitude of PFS benefit due to addition of CDK4/6 inhibitors to ET is age-independent.

GeparOLA: A Phase II RCT to assess the efficacy of paclitaxel + olaparib versus paclitaxel/carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients (pts) with HER2-negative early breast cancer (BC) and homologous recombination deficiency (HRD).

Abstract No: 506
Background: The efficacy and toxicity of olaparib in early BC pts with homologous DNA repair deficiency (here defined as HRD score high tumors +/- germline (g) or tumor (t) BRCA mutation) is not well described. GeparOLA investigates olaparib in HER2 negative early BC with HRD.

Methods: GeparOLA (NCT02789332) randomized 102 pts to either paclitaxel 80 mg/m² weekly (Pw) plus olaparib 100 mg twice daily for 12 weeks (PwO n = 65) or Pw plus carboplatin (Cb) AUC2 weekly for 12 weeks (PwCb n = 37), both followed by EC. Randomization was stratified by hormone receptor status (HR+ vs HR-) and age (< 40 vs ≥40 years). Pts with untreated primary cT2 - cT4a-d or cT1c with either cN+ or pNSLN+ or triple negative or Ki-67 > 20% were included, with either g/tBRCA mutation and/or high HRD score. The primary endpoint is pathological complete response (pCR; ypT0/is ypN0). A one group χ²-test was planned to exclude the pCR rate of ≤55% in PwO → EC arm. Secondary endpoints are other pCR definitions, breast conservation rate, clinical and imaging response, tolerability and safety.

Results: A total of 107 pts were randomized between 9/2016 and 7/2018; 106 started treatment. Median age was 47.0 years [range 25.0-71.0]; 36.2% of pts had cT1, 61.0% cT2, 2.9% cT3, and 31.8% cN-positive tumors; G3: 86.8%; Ki-67 > 20%: 89.6%; TNBC 72.6%; confirmed g/tBRCA 1/2 mutation: 60.4%. pCR rate with PwO was 55.1% (90%CI 44.5% - 65.3%) vs PwCb 48.6% (90%CI 34.3% - 63.2%). Analysis for the stratified subgroups showed higher pCR rates with PwO in the cohorts of pts < 40 years and HR+ pts.

Conclusions: GeparOla could not exclude a pCR rate of ≤55% in the PwO arm. Subgroup analysis is hypothesis generating and need further confirmation.

Phase II randomized study of neoadjuvant metformin plus letrozole versus placebo plus letrozole for ER-positive postmenopausal breast cancer [METEOR Study]

Abstract No: 576

Background: Neoadjuvant endocrine therapy with an aromatase inhibitor has shown efficacy comparable to that of neoadjuvant chemotherapy in postmenopausal breast cancer. Pre-/Clinical data have shown that metformin, a widely used anti-diabetic drug also one of mTOR inhibitor have shown anti-tumor activity. We report the result of prospective, multicenter, phase II randomized, placebo-controlled trial aiming to evaluate the direct anti-tumor effect of metformin in non-diabetic postmenopausal women with hormone-receptor (HR) positive breast cancer.

Methods: 203 postmenopausal women diagnosed with hormone receptor positive, T1-3/N0-2 invasive breast cancer were randomized to 24 weeks of neoadjuvant letrozole (2.5 mg/day) and either metformin (2000 mg/day) or placebo. Women with history of diabetes were excluded. Primary endpoint was clinical response rate (complete, partial response by caliper). Secondary endpoint was pathologic complete response rate, breast conservation rate, percent mammographic density change. PEPI score and toxicity profile were compared between two groups.

Results: 153 intention-to-treat population were analyzed (72 metformin, 75 placebo group). Overall clinical response rate was 61.4% (94/153) by caliper and did not reach statistical significance between metformin versus placebo groups (66.7% versus 56.4%, p = 0.193). Breast conservation rate was 68.0% (100/147) (66.7% versus 69.3%). Overall, 87.3% (183/207) displayed Ki67 < 10% at surgical specimen and 16.7% (35/216) had zero PEPI score. Neither Ki67 nor PEPI score was different between two groups. However, among the 20 patients with core-needle biopsy after 4 weeks of medication, greater number of patients displayed Ki67 < 10% in metformin group than in placebo group (87.5% versus 83.3%, p = 0.017). Patients with 4week Ki67 < 10% had higher clinical response rate (100% versus 57.1%, p = 0.038). Grade 3 side effects were reported in three patients (vomiting, high blood pressure, weight loss) and no hypoglycemia event was observed.

Conclusions: 61.7% overall clinical response was achieved with 24-weeks of neoadjuvant letrozole, with numerically > 10% higher response rate in letrozole+metformin group (66.7% versus 56.4%). 4-weeks Ki67 < 10% level was
predictive of clinical response. With < 2% grade 3 side effects, preoperative letrozole (with/without metformin) followed by 4-week Ki67 evaluation may indeed serve as primary choice to postmenopausal hormone receptor positive breast cancers. Clinical trial information: NCT01589367

Event-free survival analysis of the prospectively randomized phase III ETNA study with neoadjuvant nab-paclitaxel (nab-P) versus paclitaxel (P) followed by anthracycline regimens in women with HER2-negative high-risk breast cancer

Abstract No: 515

Background: The ETNA study showed that substituting P with nab-P did not significantly increase the overall rate of pathological complete response (pCR) (P 18.6%, nab-P 22.5%, p = 0.19). The multivariate analysis revealed that tumor subtype (triple negative vs luminal B-like) was the most significant factor (OR 4.85) influencing treatment outcome (Gianni L et al, JAMA Oncol 2018).

Methods: This multicenter open label study (NCT01822314) in collaboration with GEICAM and BCRC-WA randomized 695 patients with centrally-confirmed HER2-negative breast cancer to nab-P 125 mg/m² (346 patients) or P 90 mg/m² (349 patients). The two drugs were given on weeks 1, 2 and 3 followed by 1-week rest for 4 cycles before 4 cycles of an anthracycline regimen as per investigator choice. The primary endpoint was pCR (absence of invasive cells in breast and nodes). A secondary endpoint is event-free survival (EFS) defined as the time from randomization to the first date of disease progression while on primary therapy or disease recurrence (local, regional, distant, invasive contralateral breast cancer) after surgery or death due to any cause.

Results: The ITT analysis of the secondary endpoint EFS at 5 years is reported below: Clinical trial information: NCT01822314 Overall 5-year survival was 84.8% after P and 87.3% for nab-P. No serious adverse events were documented during the follow-up.

Conclusions: The improved 5-year EFS after nab-P failed to reach statistical significance (unadjusted P = 0.245). In the analysis by subgroup the numerical improvement was almost exclusively observed in luminal B and not in TN tumors. So far the data do not support substitution of P with nab-P in the schedule and doses adopted in the ETNA trial. Additional analyses will be based on ongoing molecular studies

Sequential versus concurrent use of chemotherapy and endocrine therapy in the adjuvant treatment of ER-positive breast cancer: A systematic review and Bayesian network meta-analysis.

Abstract No: e12040

Background: Chemotherapy followed by endocrine therapy is the standard adjuvant treatment strategy for estrogen receptor-positive breast cancer patients. However, no direct evidence so far demonstrated better efficacy of sequential use of chemotherapy and endocrine therapy over concurrent. Objective: To evaluate the efficacy between sequential and concurrent use of chemotherapy and endocrine therapy in the adjuvant treatment of ER positive breast cancer.
Methods: Randomized clinical trials comparing chemotherapy and/or endocrine therapy in the adjuvant treatment of ER positive breast cancer were included. Hazard ratios (HRs) of disease-free survival (DFS) and overall survival (OS) were extracted and analyzed in Bayesian analysis. Patients were stratified by menopause status for subgroup analysis.

Results: 37 trials were identified with 37225 patients enrolled in total, 37 trials with DFS results and 24 with OS. 3 comparisons were done between sequential and concurrent arms. In DFS analysis, no statistical significance was found in all 3 comparisons [CHE seq/con TAM (HR 1.01, 95%CI 0.8497 - 1.199); CHE seq/con OFS+TAM (HR 0.9119, 95%CI 0.5666 - 1.49); CHE seq/con OFS+AI (HR 1.032, 95%CI 0.6291 - 1.776)]. The same were seen in OS analysis [CHE seq/con TAM (HR 0.9512, 95%CI 0.8053 - 1.125); CHE seq/con OFS+TAM (HR 1.065, 95%CI 0.6344 - 1.789); CHE seq/con OFS+AI (HR 1.069, 95%CI 0.665 - 1.717)]. Rankings were done for preferable treatment recommendations. In DFS analyses, sequential arms ranked higher than concurrent arms [CHE seq/con OFS+AI (1 vs. 3); CHE seq/con OFS+TAM (6 vs. 7); CHE seq/con TAM (8 vs. 8)]. The same tendency was seen in OS analyses [CHE seq/con OFS+AI (1 vs. 2); CHE seq/con TAM (4 vs. 5)] except for CHE seq/con OFS+TAM (11 vs. 6-9). In subgroup ranking results, CHE seq/con OFS+AI and CHE seq/con OFS+TAM showed consistency among comparisons with concurrent arms ranked higher than sequential arms. However, CHE seq TAM ranked higher than CHE con TAM in all comparisons.

Conclusions: The combination of chemotherapy and endocrine therapy in the adjuvant treatment of ER positive breast cancer demonstrated equal efficacy either used sequentially or concurrently. However, concurrent arms were recommended over sequential arms in premenopausal patients for better DFS and OS, except for the combination of chemotherapy and tamoxifen which was recommended to be used sequentially. Others: This study has been registered in PROSPERO (CRD42018104889).

In-depth gene expression analysis of premenopausal patients with HR+/HER2− advanced breast cancer (ABC) treated with ribociclib-containing therapy in the Phase III MONALEESA-7 trial.

Abstract No: 1018

Background: The Phase III MONALEESA-7 study (NCT02278120) is the first dedicated trial of endocrine therapy (ET) ± a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in premenopausal patients (pts) with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2−) ABC. The study demonstrated that the addition of ribociclib (RIB) to a nonsteroidal aromatase inhibitor (NSAI) or tamoxifen (TAM) + goserelin (GOS) significantly extended progression-free survival (PFS; hazard ratio [HR] 0.55; Tripathy D, et al. Lancet Oncol. 2018). Here we present a gene expression analysis of baseline tumor mRNA from MONALEESA-7.

Methods: Premenopausal pts with HR+/HER2− ABC were treated with RIB or placebo (PBO) + GOS with either an NSAI (letrozole or anastrozole) or TAM. Baseline archival tumor samples from 360 of 672 intent-to-treat (ITT) pts were evaluated for gene expression (RIB n = 185; PBO n = 175) using a customized NanoString nCounter® GX 800-gene panel containing relevant breast cancer, CDK, and proliferation pathway–related genes. Pt subgroups were classified as having low or high mRNA expression using median expression as the cutoff.

Results: PFS benefit in the biomarker-assessed group was similar to that in the ITT population. A trend toward a more pronounced PFS benefit with RIB was observed in pts with high vs low expression of CCND1 (HR 0.38 vs 0.67, respectively), IGF1R (HR 0.33 vs 0.77), and ERBB3 (HR 0.33 vs 0.76). The PFS benefit seen with RIB also tended to be greater in pts with low vs high expression of CCNE1 (HR 0.38 vs 0.65, respectively) and MYC (HR 0.37 vs 0.69). The PFS benefit with RIB was similar in pts with high vs low expression of FGFR1 (HR 0.45 vs 0.61, respectively), ESR1 (HR 0.57 vs 0.57), and tumor proliferation genes, such as MKI67 (HR 0.50 vs 0.51).

Conclusions: This is the first gene expression analysis of a large set of premenopausal pts with ABC. The benefit with RIB was generally consistent across gene expression subgroups, although the magnitude varied in certain subsets.
This analysis suggests that there may be unique resistance mechanisms to ET ± CDK4/6 inhibitors in premenopausal pts with ABC. Clinical trial information: NCT0278120

Adjuvant endocrine monotherapy (ET) versus adjuvant breast radiation (RT) alone in healthy older women with stage Stage I ER+ BC: An analysis of the National Cancer Database (NCDB).

Abstract No: 519

Background: The NCCN guidelines state that breast RT may be omitted in patients > 70 years of age with ER+, clinically node-negative, T1 breast cancer (BC) who receive adjuvant ET. Available data on older patients notes that local relapses are the most frequent site of failure, and distant relapse rates are low. The side effects of ET are not inconsequential and negatively affect QOL. The objectives of this study are to examine clinical outcomes including overall survival (OS) in women ≥70 years of age treated by lumpectomy(L)+ET and L+RT in the NCDB.

Methods: The 2004-2013 NCDB includes 76,431 women ≥70 years with ER+ stage I BC who underwent L, and had a minimum one year follow up. Women who received no adjuvant therapy, both ET+RT, or any chemotherapy were excluded. To limit the analysis to healthy women, we excluded subjects with a Charlson comorbidity index > 0. We identified 24,572 patients who received either adjuvant ET monotherapy or adjuvant RT alone. Among these, 46% (11,313) received ET and 54% (13,259) breast RT. Overall median follow up was 57 months (range: 12-143 months).

Analysis of OS between the 2 treatment groups was performed using Kaplan-Meier statistics and Cox proportional hazards regression; propensity weighting was used to balance covariates across the 2 treatment groups.

Results: After propensity weighting, demographic covariates including age, race, insurance, and facility type were balanced between the 2 treatment groups. The median OS for ET was 125.9 months (95% CI 120.1-131.8), and 127.2 months for RT (95% CI 124.5-131.7) (p < 0.0001). The weighted hazard of death was 11.7% less in women receiving RT alone compared to ET (HR 0.883, 95% CI 0.834-0.936, p < 0.0001).

Conclusions: To our knowledge, this is the first large study comparing RT and ET monotherapy in healthy older women with stage I, ER+ BC. The OS with RT alone is not inferior to ET alone, and in this study population is noted to be better. While this analysis has various limitations not dissimilar from other NCDB database studies, our observations are encouraging and warrant further research with prospective studies.

Comparative efficacy of neoadjuvant to adjuvant chemotherapy for the treatment of early-stage HER2 negative breast cancer: A population-based analysis.

Abstract No: e12100

Background: The use of neoadjuvant treatment has increased over the past decade due to its ability to assess tumour sensitivity to systemic treatment in vivo, and to downstage women for increased breast conserving surgery. Recent studies have stratified patients with residual disease to receive additional treatment, which has resulted in meaningful improvements in survival. However, meta-analysis data suggest similar long-term outcomes for patients treated with neoadjuvant chemotherapy (NACT) compared to adjuvant chemotherapy (ACT) in historical randomized trials. The comparative efficacy in a real-world setting utilizing modern chemotherapy regimens is unknown.
Methods: A retrospective review of the BC Cancer Breast Cancer Outcomes Unit (BCOU) was performed to identify patients with stage I-III HER-2 negative breast cancer treated with chemotherapy at the BC Cancer Agency from 2005-2010. Patients were then divided into 2 groups: those who received neoadjuvant chemotherapy (NACT) and those who received adjuvant chemotherapy (ACT). A matched analysis (age, stage, subtype) for patients treated with NACT vs ACT (matched 1:3) was then performed using a propensity scoring method to compare distant disease-free survival (DDFS), breast cancer specific survival (BCSS) and overall survival (OS). No patients received adjuvant chemotherapy for residual disease after NACT.

Results: A total of 656 patients met the inclusion criteria, consisting of 164 NACT and 492 ACT cases. Median age was 49 years (37-68) in the NACT group vs 49 (37-65) in the ACT group (p = 0.71). The majority had stage 3 disease, 64% in both groups (p = 1.0). Most were hormone receptor positive (HR+), 67.1% vs 70.7% in the NACT vs ACT groups, respectively (p = 0.41). 5-year DDFS was 75% with NACT (95%CI 67, 82) and 77% with ACT (95%CI 72, 81), p = 0.87. 5-year OS for patients treated with NACT was 77% (95%CI 71, 84) and 80% (95%CI 75, 85) for patients treated with ACT, p = 0.33. 5-year BCSS was 80% with NACT (95% CI 70, 86) and 82% (95%CI 77, 86) with ACT, p = 0.75. Multivariate analysis for tumor size, nodal involvement and subtype are ongoing.

Conclusions: The use of NACT compared to ACT in a population-based setting did not result in significant differences in DDFS, OS or BCSS. Acknowledging the comparative efficacy of these approaches will be informative to determine if the addition of subsequent adjuvant treatment for patients with residual disease after NACT will lead to differential benefits in a population-based setting.

Does the time to initiate adjuvant chemotherapy effect outcome in BC patients? A National Cancer Database-based retrospective analysis

Abstract No: e12054

Background: The Early Breast Cancer Trialists Collaborative Group showed that adjuvant therapy for breast cancer (BC) significantly reduces the 5-year recurrence and 15-year mortality rates. After surgery, it usually takes around 4-6 weeks to begin adjuvant chemotherapy and delay in initiating the same is believed to lead to poorer outcomes. A number of studies have sought to evaluate the role of delayed initiation of chemotherapy on survival but results have remained controversial and an optimal time has not been defined.

Methods: Our aim was to determine the effect of delay in starting chemotherapy from the date of surgery on survival of patients with early BC using the National Cancer Database (NCDB) data. From the database, we selected patients aged >18 years with stage 1-3 BC who received adjuvant chemotherapy. We included all ER/PR statuses. A total of 544,005 patients were divided into 3 groups based on the time of initiating chemotherapy from the date of surgery i.e., 0-60 days, 60-90 days and >90 days and had a distribution of 38.07%, 35.90% and 26.03 % respectively.

Results: Estimates from cox models showed the following adjusted Hazard Ratios(HR): 0-60 days vs >90 days (HR 0.976, CI 0.955-0.998), 60-90 days vs >90 days (HR 0.899, CI 0.879-0.920). Kaplan Meier Survival estimates revealed that the 0-60 days and the 60-90 days groups had a better 10 year survival estimate than the > 90 days group with a p<0.0001. The factors that correlate with delay in initiating adjuvant chemotherapy are African American race, poor Charlson Deyo Score, uninsured or government insurance holders, well differentiated tumors and ER/PR positive status.

Conclusions: Based on our analysis from a large national database, we hypothesize that delaying adjuvant therapy for more than 90 days may have worse outcomes due to reasons like rapid growth of micro metastasis following removal of the primary tumor. Thus for stage 1-3 BC, the ideal time to start adjuvant chemotherapy from the date of surgery is before 90 days. Survival estimates from Kaplan-Meier analysis.
Biomarker analysis of PALLET: A neoadjuvant trial of letrozole (L) ± palbociclib (P).

Abstract No: 570

Background: PALLET randomized 307 postmenopausal women with ER+ primary breast cancer to one of 4 treatment groups (3:2:2:2 ratio): A: L for 14wks; B: L for 2wks then L+P to 14wks; C: P for 2wks then L+P to 14wks; D: L+P for 14wks. This allowed a randomized 1:2 comparison of L (Group A) vs L+P (Groups B+C+D) at 14wks. P was given 125mg/d PO (21 days on, 7 days off). Adding P to L markedly enhanced Ki67 suppression and Complete Cell Cycle Arrest (CCCA, Ki67 < 2.7%) by 14wks but did not substantially increase clinical response. We now report exploratory analysis of the association of baseline expression of 6 pre-specified biomarkers involved in estrogen and CDK4/6 signaling with CCCA at 14wks and changes in their expression during therapy.

Methods: Estrogen receptor (ER), progesterone receptor (PgR), RB and CCNE1 were measured by IHC and CCND1 by IHC and FISH (CCND1/CEP11 ratio≥2.0 amplified). Baseline biomarker values were available with 14wk Ki67 values in up to 64 patients for L alone and up to 124 patients for L+P. Of these 59% and 90%, respectively, achieved CCCA.

Results: With L alone CCCA was significantly less frequent (indicating relative resistance) with low baseline PgR (odds ratio [OR] 0.22, 95%CI 0.05-0.96, p = 0.04) or high CCNE1 levels (OR 10.39, 95%CI 1.19-90.48, p = 0.03). With L+P CCCA was also significantly less frequent with high CCNE1 (OR 50.34 95%CI 5.12-495.34, p = 0.001) or with low baseline ER (OR 0.21 95%CI 0.08-0.60, p = 0.004). CCCA was not significantly different with either treatment according to CCND1 amplification status or expression overall. However, CCCA showed a tendency to be less frequent in non-amplified cases with low baseline cyclin-D1 expression when treated with L+P (p = 0.10). There were no significant changes in ER levels or CCND1 amplification over 14wks. By 14 wks PgR, RB, CCND1 and CCNE1 levels were significantly suppressed by L or L+P (geomeans PgR: -96.4% vs -94.9%; CCND1: -79.9% vs -70.7%; CCNE1: -68.2% vs -74.7%; RB: -23.5% vs 26.1%, respectively) and there was no significant difference between the treatments.

Conclusions: These data support low ER, possibly indicating limited luminal status, and high CCNE1 as markers of poor Ki67 response to L+P in primary disease and are consistent with findings in studies in advanced disease. Clinical trial information: NCT02296801

A randomized phase II study of palbociclib plus exemestane with GNRH agonist versus capecitabine in premenopausal women with HR+ MBC (KCSG-BR 15-10, NCT02592746).

Abstract No: 1007

Background: Endocrine treatment is preferred recommendation by clinical guidelines in premenopausal as well as postmenopausal women with hormone receptor HR+, HER2-negative metastatic breast cancer (MBC). In real-world clinical practice, however, substantial numbers of patients are treated with chemotherapy in earlier lines based on endocrine resistance and/or on physician's concern of worse prognosis associated with aggressive tumor behavior and younger age. In terms of the chemotherapy regimens, capecitabine seems one of the most popular options. The purpose of this phase II study is to assess the safety and the clinical anti-tumor activity of exemestane plus GNRH agonist in combination with palbociclib versus capecitabine in premenopausal HR-positive MBC patients.

Methods: This is a prospective, two-arm, randomized, multi-center open-label phase II study of the Korean Cancer Study Group. Patients were allowed with previous 1 line of chemotherapy for MBC. De Novo metastatic patients should have been treated with tamoxifen before enrollment. Patients were randomized to chemotherapy (capecitabine 1250 mg/m² twice a day from day 1 to 14 every 3 weeks) or endocrine therapy combination ( exemestane 25 mg for 28 days
and palbociclib 125 mg for 21 days every 4 weeks with GNRH agonist). Primary endpoint was Progression-Free Survival (PFS).

**Results:** Among 189 patients enrolled between 2016 and 2018 from 14 centers, 184 patients were randomly assigned to chemotherapy (n = 92) or endocrine therapy with palbociclib (n = 92). Median age was 44 (range 28-58). De Novo MBC was found equally in both arm (30%). During median 14 months of follow-up, median PFS was superior in endocrine with palbociclib than in capecitabine arm [19.0 vs. 11.3 months, p = 0.0493 by log-rank test; Hazard Ratio (HR) 0.643 (0.415-0.999), p = 0.0493]. Approximately half of the patients (51%) were treatment naïve in the advanced setting (49% for palbociclib vs. 51% for capecitabine). Grade III or more hematologic toxicities were more common in palbociclib than in capecitabine with statistical significance (60.9% vs. 19.2%, p < 0.0001). Diarrhea (11% vs. 38%) and Hand-Foot syndromes (1% vs. 76%) were more common in capecitabine arm.

**Conclusions:** Exemestane plus palbociclib with ovarian suppression showed clinical benefit in terms of PFS compared with capecitabine in patients with premenopausal ER-positive MBC. Clinical trial information: NCT02592746

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**Abemaciclib with or without fulvestrant for the treatment of HR+/HER2-MBC with disease progression following prior treatment with palbociclib.**

**Abstract No:** e12533

**Background:** Abemaciclib is a selective inhibitor of CDK4 and CDK6 kinase activity. It is approved for patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, advanced or metastatic breast cancer (MBC) previously treated: in combination with fulvestrant for patients with disease progression following endocrine therapy (MONARCH 2) and as monotherapy for patients with disease progression after endocrine therapy and chemotherapy for MBC (MONARCH 1). The patients in these trials were CDK 4/6 inhibitor-naïve. It has not yet been studied in patients who previously received a CDK 4/6 inhibitor.

**Methods:** We performed a chart review of patients with HR positive, HER2-negative MBC treated at Rush University Medical Center who progressed on palbociclib, either with an aromatase inhibitor (AI) or fulvestrant, and were subsequently treated with abemaciclib with or without fulvestrant. We documented patient demographics, prior treatment, and response to abemaciclib therapy.

**Results:** 21 female patients, mean age 57.8 (+/- 13.2y), were included. Patients had received 1-5 prior lines of endocrine therapy and 0 – 4 prior lines of chemotherapy for MBC. All patients received prior palbociclib: 14 patients with an AI, 6 patients with fulvestrant, and 1 patient received palbociclib with an AI and then with fulvestrant. Of the 21 patients, 17 were treated with abemaciclib monotherapy and 4 received abemaciclib with fulvestrant. SD was seen in 19% of patients (4/21) and 62% had PD (13/21). The CBR was 29% (6/21) and all of these patients received abemaciclib monotherapy. Due to expected toxicities of the drug (diarrhea, neutropenia, and thrombocytopenia), 19% (4/21) of patients discontinued treatment. 4 patients continued abemaciclib monotherapy for greater than 8.3M. 3 patients were on treatment for less than 35 days; 2 stopped due to expected toxicities and one had progression of disease on physical exam. Median treatment duration was 3.1M.

**Conclusions:** This retrospective chart review of 21 patients demonstrates that abemaciclib has limited activity as a single agent in patients previously treated with palbociclib.

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**Lasofoxifene as a potential treatment for ER+ MBC.**
Abstract No: 1056

Background: Estrogen receptor positive (ER+) metastatic breast cancers (MBC) that express constitutively active somatic ESR1 mutations at Y537S and D538G allow tumors to progress in the presence of approved endocrine therapies. For patients with ER+ MBC, fulvestrant is the first line of treatment. Palbociclib or other CDK4/6 inhibitors are now being included. Preliminary studies show that lasofoxifene, a selective ERα modulator (SERM), was effective in reducing tumor growth in an endocrine resistant xenograph model expressing ERα mutations Y537S or D538G. Additionally, lasofoxifene more effectively inhibited the development of liver and lung metastases than fulvestrant. Lasofoxifene is currently under evaluation in a phase 2 study. Because certain combinations of hormonal agents like fulvestrant improved efficacy, we investigated the combination of palbociclib and lasofoxifene as a potential therapeutic for mutant ESR1 MBC. We hypothesized that this combination should improve outcome and compared it to a combination with fulvestrant.

Methods: We first determined the optimal dose of lasofoxifene in an intraductal (MIND) xenograph model of MCF-7 cells that express active ERα Y537S and D538G. Subsequently, we performed combination studies with lasofoxifene (10mg/kg 5/week SQ) +/- palbociclib (100mg/kg gavage, 5/week) or fulvestrant (5mg/mouse/week, SQ) +/- palbociclib.

Results: Lasofoxifene alone was significantly more effective than fulvestrant at inhibiting the metastasis of both MCF7 Y537S and D538G tumors to the lungs and liver. Lasofoxifene + palbociclib was more effective than fulvestrant + palbociclib at reducing primary tumor growth; both combinations demonstrated an increased response. Lasofoxifene + palbociclib was more effective at inhibiting liver metastasis than either drug alone and was more effective than fulvestrant + palbociclib at reducing metastasis to the liver and lung. Structural studies showed that lasofoxifene effectively disrupts the active conformation of the ERα Y537S ligand-binding domain.

Conclusions: These results demonstrate that lasofoxifene, in combination with CDK4/6 inhibitors like palbociclib, has promise for treating endocrine therapy resistant ER+ MBC patients whose tumors express activating ESR1 mutations, more effectively than either drug alone.

Real-world evidence evaluating continuation of CDK4/6 inhibitors beyond first progression in HR+ MBC.

Abstract No: e12538

Background: CDK inhibitors (CDKi), in combination with aromatase inhibitors (AI), are approved for the treatment of hormone receptor positive (HR+) Her2 negative metastatic breast cancer (MBC). The effectiveness of continuing CDKi beyond first disease progression is not known. This study evaluated real world evidence and assessed the impact of continuation of CDKi beyond first disease progression in combination with endocrine therapy.

Methods: This is a retrospective, single institution review of HR+ MBC patients treated with CDKi from 2015-2018 who continued CDKi after initial progression. The primary outcome was progression-free survival (PFS) beyond first disease progression, as assessed by the clinician based on radiological and/or clinical criteria. Overall survival (OS) – defined as date of initial CDKi treatment to date of death or last follow up – was a secondary outcome.

Results: 30 women with HR+/HER2- MBC, median age 47.5 years (range: 31 – 81), sequentially continued on CDKi beyond first progression were identified from a database of patients treated with Palbociclib. Median and average follow up times on CDKi were 27.18 and 24.53 months, respectively. Initial endocrine/CDKi regimen received included: palbociclib (PA)/letrozole (LTZ) [67%], PA/fulvestrant (FULV) [23%], and PA/other AI [10%]. Prescribed combinations beyond 1st progression were: PA/FULV [56.7%], PA/LTZ [16.7%], and PA/other AI [20%], abemaciclib plus LTZ or FULV [6%]. As of 1/31/2019, 25 patients (83.3%) were still alive, and 19 (63%) had undergone a second progression on CDKi. The estimated median PFS for the entire duration while on CDKi was 23.5 months (95% CI 12.8 – 27.8), of
which 11.8 months (95% CI 5.34 – 13.13) was the median PFS beyond first progression. The estimated median OS was 45.4 months.

Conclusions: Among a small cohort of HR+ MBC patients, in a non-clinical trial setting, continuation of palbociclib plus endocrine therapy beyond first progression was associated with a median PFS of approximately 11 months. Formal clinical evaluation of continuation of CDK inhibitor plus endocrine therapy beyond first progression is warranted.

Interim results from the full population of the phase 3b CompLEEEment-1 study of ribociclib (RIBO) plus letrozole (LET) in the treatment of HR+/HER2– advanced BC.

Abstract No: 1041

Background: RIBO, an oral, selective inhibitor of CDK4/6 (CDK4/6i), is approved for use in combination with endocrine therapy (ET) in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) ABC in multiple countries worldwide. Here we report interim safety and efficacy results from CompLEEEment-1, a phase 3b trial evaluating RIBO+LET in an expanded patient (pt) population and the largest CDK4/6i trial in ABC to date.

Methods: Pts with HR+, HER2– ABC, ≤1 line of prior chemotherapy (CT), and no prior ET for ABC received RIBO+LET. Treatment regimens and study endpoints have been reported previously (De Laurentiis, et al. ASCO 2018. Poster 1056).

Results: Overall, 3,246 pts, who received ≥1 dose of study treatment, were evaluated (cut-off date, August 8, 2018). Median duration of RIBO exposure was 8.1 months (min, 0.0; max, 22.4). Demographic and baseline characteristics indicated a diverse population including men (1.2%), premenopausal women (22.2%), and patients aged ≥70 years (19.5%). Pts were well represented in terms of age, race, and disease history; 5.9% of pts received prior CT for ABC. The only non-hematologic any-cause grade ≥3 AEs ≥5% were increased alanine (7.3%) and aspartate (5.3%) aminotransferase. Treatment-related AEs (any grade) led to discontinuation in 11.4% of pts. Of the 51 (1.6%) on-treatment deaths, 26 were due to study indication and 25 to other reasons. The median time to progression was not estimable (NE) (95% confidence interval [CI], 17.1-NE). Overall response rate was 20.5% (95% CI, 19.1%-21.9%) and clinical benefit rate was 66.1% (95% CI, 64.4%-67.7%). Consistent mean change from baseline in Functional Assessment of Cancer Therapy – Breast Cancer questionnaire scores indicated that pts maintained their quality of life throughout treatment.

Conclusions: This interim analysis demonstrates the safety, tolerability, and efficacy of RIBO+LET in a large, diverse cohort of pts with HR+, HER2– ABC who had not previously received ET for ABC. Safety results were consistent with those observed in RIBO pivotal studies and no new safety signals were observed. Clinical trial information: NCT02941926

A phase II study of pembrolizumab in combination with palliative radiotherapy (RT) for HR+ MBC.

Abstract No: 1047
Background: RT is frequently used for palliation in MBC. In animal models its use has been reported to induce distant (abscopal) tumor responses when combined with immune checkpoint inhibitors. Here, we report the safety and efficacy of palliative RT plus pembrolizumab in a phase II single-arm study in patients (pts) with HR+/HER2- MBC.

Methods: Eligible pts had HR+/HER2- MBC, ECOG PS ≤2, indication for palliative RT, and ≥1 measurable lesion outside of the RT field; there was no limit on prior lines of therapy. A total RT dose of 20 Gray was delivered over 5 daily fractions. Pembrolizumab was given at 200 mg IV 2-7 days before day 1 of RT, then every 3 weeks until disease progression. The primary endpoint was objective response rate (ORR) outside the field of radiation by RECIST v1.1. Using the Simons "optimal" method, if ≥ 1/8 pts responded during the first stage, 19 more would be enrolled. If ≥ 3/27 responded, the null hypothesis (ORR=3%) would be rejected in favor of a 20% ORR. Predefined secondary endpoints included progression free survival (PFS) and toxicity. Analyses associating PD-L1 expression, tumor-infiltrating lymphocytes (TIL), and neutrophil/lymphocyte ratio (NLR) with outcomes were exploratory.

Results: Eight women were enrolled into the first stage of the trial; no objective responses were seen, and the study was closed to further accrual. The median age was 59y (37-68y), 6 (75%) had ECOG PS 1, all had bone and 5 (63%) had liver metastases. The median number of prior cytotoxic therapies for MBC was 2 (range 0 to 8). While one patient had a PR by RECIST criteria, this patient experienced concurrent clinical progression. Two pts had SD < 16 weeks and 5 had PD as best response. The median PFS was 1.4 months (95% CI 0.4–2.1). All-cause adverse events occurred in 87.5% of pts (G3-4, 12.5%). TIL were available for 6 pts: 4 had ≤10%, and 2 > 10%. Among 5 pts with PD-L1 status available, 2 were positive. Six pts had NLR > 4.

Conclusions: Pembrolizumab combined with RT was well-tolerated, and no unexpected adverse events were observed; however, clinical benefit of the combination was not demonstrated in this heavily pretreated HR+ population. Clinical trial information: NCT03051672

Real-world effectiveness of ribociclib + aromatase inhibitor, or endocrine monotherapy, or chemotherapy as 1L treatment in postmenopausal women with HR+, HER2- locally adv./met. breast cancer: Baseline data from the RIBANNA study.

Abstract No: e12520

Background: Ribociclib, a selective CDK4/6 inhibitor, in combination with an aromatase inhibitor (AI) is approved for the treatment of HR+/HER2- advanced breast cancer (aBC) (locally advanced or metastatic). Real-world evidence for the effectiveness, safety and tolerability of ribociclib + AI in routine clinical practice is needed to support its use.

Methods: RIBANNA (CLEE011ADE03) is a non-interventional study running in Germany since October 2017 involving up to 3020 postmenopausal patients receiving ribociclib + AI, endocrine monotherapy (ET), or chemotherapy (CT) as first-line treatment for HR+/HER2- aBC, prescribed in line with German guidelines. Data are collected from clinical practice in all three cohorts. Further lines of treatment are documented to examine outcomes of sequential therapy.

Results: 461 patients enrolled to October 9, 2018 (Table). First-line mean daily ribociclib dose was 382 mg including and 540 mg excluding dose interruptions; mean duration of exposure to ribociclib: 128 days. Ribociclib was given in combination with anastrozole (8%), exemestane (7%), and letrozole (83%); ET comprised a selective estrogen receptor degrader (25%), nonsteroidal AI (64%), steroidal AI (5%), and a selective estrogen receptor modulator (7%); CT included taxane-based monotherapy (30%) or combination therapy (27%), anthracycline-based combination therapy (5%), other monotherapy (23%) or other combination therapy (13%).

Conclusions: Population characteristics from the RIBANNA study show a diverse group of patients from a real-world setting of ribociclib treatment. Baseline demographics and characteristics. Clinical trial information: CLEE011ADE03
Different maintenance strategies versus observation in patients with HR+ mBC after 1L chemotherapy: A real-world study and meta-analysis.

Abstract No: e12529

Background: Current guidelines lack definitive evidence regarding the clinical outcomes associated with different maintenance strategies for hormone-receptor HR+ MBC. We aimed to evaluate different maintenance modalities after first-line chemotherapy in this setting.

Methods: We conducted a multicenter real-world study to compare maintenance chemotherapy, endocrine therapy and observation in patients with HR positive MBC who achieved disease control after first-line chemotherapy. The primary endpoint was overall survival (OS), secondary endpoint was progression-free survival (PFS). We further examined the results from fourteen multicenter prospective studies in a meta-analysis.

Results: A total of 928 patients were enrolled in the real-world study. The median age was 48 years (range, 18 to 76 years). Of these patients, 269 received chemotherapy, 330 received endocrine therapy and 329 received observation as their maintenance treatment. OS was significantly longer in the chemotherapy group and endocrine therapy group than in the observation group (median 33.0 vs 36.0 vs 19.0 months, respectively, P < 0.001), as was PFS (median 12.0 vs 14.0 vs 8.0 months, respectively, P < 0.001). However, there was no significant difference of OS between chemotherapy group and endocrine therapy group (HR, 0.947, 95% CI: 0.743-1.207, P = 0.656), so did PFS (HR, 0.969, 95% CI: 0.787-1.194, P = 0.765). In the meta-analysis of all cohorts (2706 participants), maintenance endocrine therapy provide similar PFS and OS compare with chemotherapy, but with lower odds of G1-G2 adverse events.

Conclusions: Our study provided strong evidence for OS and PFS benefits of maintenance therapy over observation after first-line chemotherapy in HR+ MBC patients. Maintenance endocrine therapy was noninferior to chemotherapy with less treatment-related toxicity, which was worthy of a clinical recommendation.

Conclusions: Len+Let showed significant anti-tumor activity, even in pts who failed prior CT or EB+CDK4/6i. RP2D of 14mg Len and 2.5mg Let is tolerated with efficacy; dose expansion is currently underway. Clinical trial information: NCT02562118