25th Annual UCSF Breast Oncology Program Scientific Retreat

Mission Bay Conference Center at UCSF

Poster Session

The full poster abstract handout was distributed by email to all retreat participants, and is available on line at http://cancer.ucsf.edu/bop2020.

Posters selected to give podium presentation are highlighted in bold font.

Detection and Biomarkers

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#7 Computational fluid dynamics validated with bioprinted vascular beds predicts metastatic colonization)
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#4 Catalyzing navigation for breast cancer survivors (CaNBCS)
#5 Breast Cancer Genetic Testing Station: A Model for Getting Genetic Test Results to Patients Before Surgery
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#8 OP-1250, an oral complete estrogen receptor antagonist (CERAN) that shrinks ER-positive breast tumors in xenograft models
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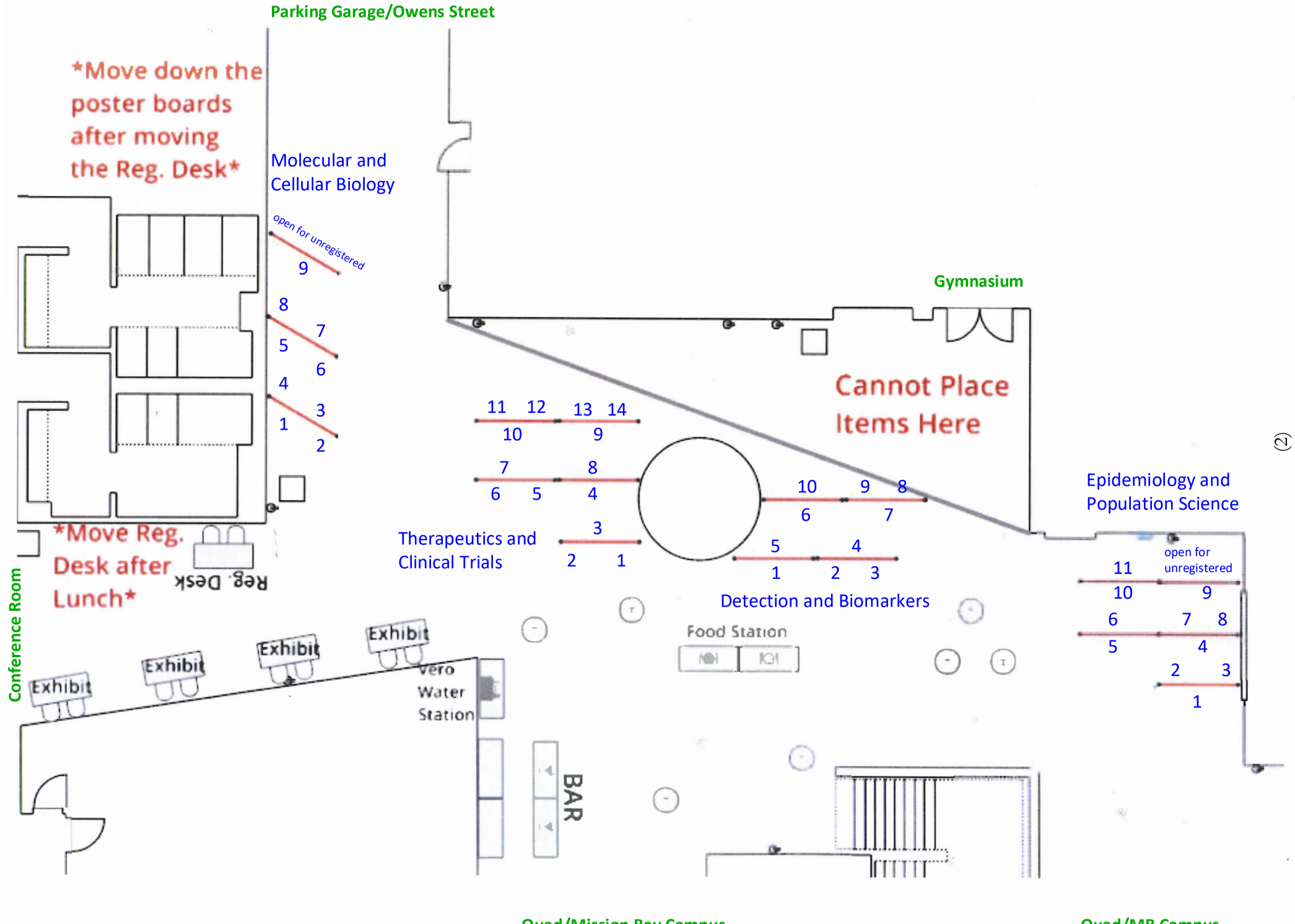
#13 A Characterization of the Clinical Outcomes of a Cohort of Women Undergoing Active Surveillance for Ductal Carcinoma In Situ
#14 Pazopanib (PZ) plus endocrine therapy as treatment for hormone resistant advanced breast cancer (ABC).

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.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Detection and Biomarkers #1

Breast cancer subtype specific association of pCR with MRI assessed tumor volume progression during NAC in the I-SPY 2 TRIAL

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Abstract
Background: In an adaptive randomized trial, when new treatment combinations are being tested, it is important to be able to identify patients who are progressing on treatment so that they can be changed to a different therapeutic regimen.

Methods: Four MRI exams were performed for each patient: pre-NAC (T0), after 3 weeks of NAC (T1), between regimens (T2), and post-NAC (T3). Functional tumor volume (FTV) was calculated at each exam by summing voxels meeting enhancement thresholds. Tumor progression at T1, T2 or T3 was identified by a positive FTV change relative to T0. Visual inspection was used to exclude false progression due to strong background parenchymal enhancement post-contrast, prominent vessels, motion, or insufficient image quality.

Results: 878 had pCR outcome data (pCR or non-pCR, pCR rate = 35%). Total and non-pCR numbers for each subtype, number of patients with tumor progression assessed by MRI at T1, T2, and T3, and NPVs, are shown in Table 1. In the full cohort, the NPV increased consistently over treatment, from T1 (NPV=83%) to T2 (93%), and to T3 (100%). The HER2+ cancer subtypes showed fewer MRI-assessed tumor progressions than HER2- subtypes: e.g. 10/209 (5%) vs. 108/669 (16%) at T1. NPV was 100% for HER2+ subtypes at T1 and T2 except for a single misclassification of a HR- tumor at T1. Only 6 tumor progressors, all HER2- were identified at T3, and all were confirmed at surgery as non-pCRs (NPV=100%). For HR+/HER2-, the NPV increased slightly from 89% at T1 to 91% at T2, while triple negative subtype had a more substantial increase, from 78% to 92%.

Conclusions: Our study showed strong association between tumor progressors assessed by MRI with true non-pCRs after NAC. For HER2+ tumors, although MRI progressors are rare, they strongly indicate non-pCR at all treatment time points, while HER2- subtypes show more accurate results later in treatment. We are evaluating MRI change at 6 weeks to determine if that time point is sufficient to predict progressors.

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Detection and Biomarkers #2

Dedicated Breast PET for Detection of Early Treatment Response in Breast Cancer Patients

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Abstract
Background: In the neoadjuvant chemotherapy (NAC) setting, imaging plays a critical role in non-invasively assessing the response of the intact primary tumor to targeted systemic therapies. Treatment-induced change in the primary tumor can serve as a surrogate marker for the effect of chemotherapy. Thus, imaging evaluation of the primary tumor during treatment can provide important prognostic and predictive information. While DCE-MRI depicts changes in tumor morphology and vascularity in response to NAC, PET provides molecular information about tumor biology that can predict treatment response early in the course of therapy. Whole-body PET (wbPET) with FDG has proven to be a powerful imaging technique for interrogation of breast lesions. However, its use for assessing primary breast tumors is hampered by poor spatial resolution and associated partial volume error in small lesions. Dedicated breast PET (dbPET) is an emerging PET technology specially designed for breast imaging. It has a high sensitivity to detect sub-centimeter lesions and high spatial resolution to depict molecular variations within the primary tumor. The incorporation of dbPET into breast cancer management, therefore, may provide critical molecular insights to guide treatment selection and to better assess early molecular changes in response to treatment.

Methods: In an IRB-approved protocol, patients with biopsy-confirmed stage II/III locally advanced breast cancers were imaged with breast MRI (1.5 T Signa LX, GE Healthcare, WI) and dbPET (MAMMI, General Equipment and Medical Imaging SA (OncoVision), Valencia, Spain) before and after three weekly cycles of treatment. Standard dynamic contrast-enhanced MRI was obtained using a dedicated breast coil. Patients also underwent dbPET imaging with 5 mCi of FDG at 45 min post-injection.

Results: Seven primary tumors from five breast cancer patients were analyzed. Patient age ranges from 29 to 63. Breast cancer subtype includes 2 HR+/HER2-; 1 HR-/HER2+; 1 HR+/HER2+ and 3 triple negatives (TN). Two patients had a complete resolution of FDG uptake by dbPET in the primary tumor after three weeks of neoadjuvant treatment, while MRI showed residual enhancement at the same visit. Tumors with over 70% SUVmax reduction after treatment were found to achieve pathologic complete response (pCR), but those with less than 40% SUVmax reduction at the same time point showed substantial residual disease that was confirmed by MRI and at surgery.

Conclusions: These examples illustrate that FDG-dbPET may capture the early response of primary breast cancer to NAC, revealing functional changes that precede anatomical changes at MRI. In breast cancer management, FDG-dbPET may be a promising predictor of pCR, differentiating patients from both ends of the response spectrum early in the course of treatment. While preliminary, the use of FDG-dbPET along with breast MRI may present an opportunity to guide earlier treatment redirection for excellent responders and to provide functional information to confirm chemo-resistance for non-responding patients. Further studies involving a larger cohort are needed to validate our initial findings.

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Detection and Biomarkers #3

Evaluation of primary breast cancers using dedicated breast PET and whole-body PET

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Abstract
Objective: Metabolic imaging of the primary breast tumor with 18F-fluorodeoxyglucose (FDG) whole-body PET (wbPET) may provide predictive information for stratifying treatment response in the neoadjuvant chemotherapy (NAC) setting. However, wbPET is limited in the quantitative and precise imaging of primary breast tumors due to significant partial volume effect caused by limited spatial resolution. Dedicated breast PET (dbPET) is a high-resolution modality that has demonstrated ability in highlighting intra-tumor heterogeneity and identifying small lesions in the breast volume. In this study, we characterized the uptake of 18F-FDG in both dbPET and wbPET to highlight the similarities and differences in distribution of PET signal in a cohort of breast cancer patients prior to treatment.

Methods: 13 patients with biopsy confirmed, locally advanced breast cancer were enrolled in this study and received bilateral dbPET following administration of 186 MBq 18F-FDG. 11 patients also received 307 MBq 18F-FDG wbPET on a separate day. Tumor volumes were segmented in the dbPET and wbPET images and converted to lean-body mass corrected standardized uptake values (SULs). Uptake metrics, tumor-background ratios, metabolic tumor volume, and total lesion glycolysis were compared between both modalities. 19 radiomic features based on morphology, tumor intensity, and texture were also calculated on dbPET and wbPET tumor volumes. Feature selection was performed using the least absolute shrinkage and selection operator (LASSO) regression model with three-fold cross-validation.

Results: 18F-FDG uptake metrics were significantly higher for dbPET compared to wbPET. DbPET exhibited a 4-fold increase in SULpeak and a 1.5-fold increase in tumor-background ratios relative to wbPET. The three highest weighted radiomic features (LASSO, r2 = 0.92) were the neighborhood grey-tone distance matrix strength ($p = 0.10$) and correlation ($p = 3.1e-5$) and grey-level co-occurrence matrix normalized inverse difference ($p = 0.002$).

Conclusion: The higher 18F-FDG uptake metrics measured by dbPET highlighted the breast-specific modality's sensitivity. This characteristic, when combined with the higher spatial resolution, may enable dbPET to detect treatment response in the primary tumor during NAC. Results from this study support dbPET as a complementary method for assessing the primary tumor in breast cancers, and future studies with a larger cohort are warranted.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Detection and Biomarkers #4

Circulating tumor DNA in neoadjuvant treated breast cancer reflects response and survival

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Abstract
Pathologic complete response (pCR) to neoadjuvant chemotherapy (NAC) is strongly associated with favorable outcome. We examined the utility of serial circulating tumor DNA (ctDNA) testing for predicting pCR and risk of metastatic recurrence in 84 high-risk early breast cancer patients treated in the neoadjuvant I-SPY 2 TRIAL. Cell-free DNA (cfDNA) was isolated from 291 plasma samples collected at pretreatment (T0), 3 weeks after initiation of paclitaxel (T1), between paclitaxel and anthracycline regimens (T2), or prior to surgery (T3). A personalized ctDNA test was designed to detect 16 patient-specific mutations (from whole exome sequencing of pretreatment tumor) in cfDNA by ultra-deep sequencing. At T0, 61 of 84 (73%) patients were ctDNA-positive, which decreased over time (T1-35%; T2-14%; T3-9%). Patients who remained ctDNA-positive at T1 were significantly more likely to have residual disease after NAC (83% non-pCR) compared to those who cleared ctDNA (52% non-pCR; OR 4.33, P=0.012). After NAC, all patients who achieved pCR were ctDNA-negative (n=17, 100%). For those who did not achieve pCR (n=43), ctDNA-positive patients (14%) had significantly increased risk of metastatic recurrence (HR 10.4; 95% CI, 2.3–46.6); interestingly, patients who did not achieve pCR but were ctDNA-negative (86%) had excellent outcome, similar to those who achieved pCR (HR 1.4; 95% CI, 0.15–13.5). Lack of ctDNA clearance was a significant predictor of poor response and metastatic recurrence, while clearance was associated with improved survival regardless of pCR status. Personalized monitoring of ctDNA during NAC may aid in real-time assessment of treatment response and help fine-tune pCR as a surrogate endpoint of survival.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Detection and Biomarkers #5 – BEST DETECTION AND BIOMARKERS POSTER

Serial analysis of circulating tumor cells identifies four prognostic groups for novel risk-stratification in metastatic breast cancer (CALGB 40502/NCCTG N063H, Alliance)

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Abstract

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Purpose: We examined the prognostic significance of circulating tumor cell (CTC) dynamics during treatment in metastatic breast cancer (MBC) patients receiving first-line chemotherapy.

Methods: Serial CTC data (≥3 time points) from 469 patients (2,202 samples) were used to build a novel latent mixture model (adjusted for subtype) to identify groups with similar CTC trajectory (tCTC) patterns during the course of treatment. Cox regression was used to estimate hazard ratios for progression-free survival (PFS) and overall survival (OS) in groups based on baseline CTCs (bCTC), combined CTC status at baseline to the end of cycle 1 (cCTC), and tCTC. Akaike Information Criterion (AIC) was used to select the model that best predicted PFS and OS. Model validation studies were carried out in an independent cohort of 1,856 MBC patients.

Results: Latent mixture modeling revealed 4 distinct tCTC patterns: consistently undetectable CTCs (tCTCneg, 56%), low (tCTClo, 24%), intermediate (tCTCmid, 15%), or high (tCTChi, 5%). Patients with tCTClo, tCTCmid and tCTChi patterns had significantly shorter PFS and OS compared to those with tCTCneg. AIC values indicated that the tCTC model best predicted PFS and OS when compared to bCTC and cCTC models. Validation studies confirmed these findings. Further validation of the latent mixture model using only a single pretreatment CTC measurement confirmed prognostic performance of the tCTC model.

Conclusions: Our risk-stratification approach using the tCTC model yielded better discriminatory power to identify poor-prognosis patients receiving first-line chemotherapy (i.e., tCTCmid+tCTChi, 20% poor-prognosis) compared to the current model (CTC-positive, cutoff ≥5 CTC/7.5 ml, 50% poor-prognosis). This novel prognostic classification may be utilized for fine-tuning of CTC-based risk-stratification strategies to guide future prospective clinical trials in MBC.

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Detection and Biomarkers #6

Circulating tumor DNA (ctDNA) and magnetic resonance imaging (MRI) for monitoring and predicting response to neoadjuvant therapy (NAT) in high-risk early breast cancer patients in the I-SPY 2 TRIAL

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Abstract
Background: MRI measurements (Li et al, Magn Reson Imaging 2019; Hylton et al, Radiology 2016) and ctDNA (Magbanua et al, SABCS 2018) have both been independently shown to associate with response to NAT. We performed a retrospective study to examine correlation between ctDNA and MRI and to investigate whether information from these two measurements can be combined to improve early prediction of response.

Methods: We analyzed serial ctDNA and MRI data from 84 high-risk (stage II/III) breast cancer patients collected at baseline (T0), 3 weeks after initiation of paclitaxel-based NAT (T1), between paclitaxel and anthracycline regimens (T2), and after NAT prior to surgery (T3). The response variable was pathologic complete response (pCR), defined as the absence of invasive tumor in the breast and lymph nodes after NAT. We examined correlations between MR functional tumor volume (FTV) and ctDNA using Spearman's rho (r). Mean FTV between ctDNA+/- groups were compared using t-test. Monte Carlo simulation was used to assess correlation between FTV and ctDNA trajectories in individual patients. We investigated the impact of adding ctDNA information to MR FTV-based predictors using receiver operating characteristic curves to calculate area under the curve (AUC), logistic regressions, and decision trees using recursive partitioning.

Results: The mean levels of ctDNA (mutant molecules/mL plasma) were significantly correlated with FTV at all timepoints [T0 (r=0.49), T1 (r=0.42), T2 (r=0.42), T3 (r=0.43), all $p<0.05$]. The mean FTV in patients who had detectable ctDNA was significantly higher compared to those who were negative (all timepoints, all $p<0.05$). FTV and ctDNA trajectories in individual patients over the course of therapy were correlated (empirical 1-sided p=0.046).

Adding continuous ctDNA information (mutant molecules/mL plasma) to FTV at T1 improved AUC in the pCR-prediction model, but the increase was not statistically significant (FTV: 0.59, FTV+ctDNA: 0.69, p=0.25). No improvements in AUCs were observed at other timepoints.

Treated as a dichotomous variable, ctDNA positivity at T1 trended toward association with non-pCR in logistic regression models at T2 and T3 with MR-based prediction scores as a covariate ($0.05<p<0.1$). Adding ctDNA-positivity at T1 to (topleft) dichotomized MR-based predictors at T1-T3 resulted in a numerical increase in pCR

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prediction accuracy (from 0.57 to 0.68 at T1; 0.64 to 0.73 at T2; and 0.73 to 0.77 at T3). These models predict non-pCR if the MR-based probability of pCR is low or if ctDNA-status during treatment remains positive. Very similar logic was selected by the optimal decision tree model at T1, which included both FTV and ctDNA-positivity.

Conclusions: We demonstrate that ctDNA and FTV by MR were highly correlated measures of tumor burden. Moreover, our findings suggest that ctDNA information early in treatment may complement FTV as predictor of response to NAT. The study is, however, limited by the modest sample size, and thus validation in a larger cohort is warranted.

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Detection and Biomarkers #7

Prognostic Value of Residual Disease after Neoadjuvant Therapy in HER2-Positive Breast Cancer Evaluated by Residual Cancer Burden, Neoadjuvant Response Index, and Neo-Bioscore

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Abstract
Background: In breast cancer, pathologic complete response (pCR) to neoadjuvant systemic therapy (NST) is associated with favorable long-term outcome. Trastuzumab emtansine as additional adjuvant therapy improves recurrence-free survival of patients with HER2-positive breast cancer without pCR, but it is uncertain whether all patients without pCR need

additional therapy. We evaluated the prognostic value of residual disease after trastuzumab-based NST in patients with HER2-positive breast cancer using Residual Cancer Burden (RCB), Neoadjuvant Response Index (NRI), and Neo-Bioscore.

Methods: We included patients with stage II or III HER2-positive breast cancer treated with trastuzumab-based NST and surgery at The Netherlands Cancer Institute between 2004 and 2016. RCB, NRI, and Neo-Bioscore were determined. Primary endpoint was 5-year recurrence-free interval (RFI). A 3% difference compared with the pCR group was considered acceptable as noninferiority margin on the 5-year RFI estimate, based on a proportional hazards model, and its lower 95% confidence boundary.

Results: A total of 283 women were included. Median follow-up was 67 months (interquartile range 44–100). A total of 157 patients (56%) with pCR (breast and axilla) had a 5-year RFI of 92% (95% CI, 88–97); patients without pCR had a 5-year RFI of 80% (95% CI, 72–88). Patients with an RCB = 1 (N = 40, 15%), an NRI score between 0.75 and 0.99 (N = 30, 11%), or a Neo-Bioscore of 0 to 1 (without pCR; N = 28, 11%) have a 5-year RFI that falls within a predefined noninferiority margin of 3% compared with patients with pCR.

Conclusions: The RCB, NRI, and Neo-Bioscore can identify patients with HER2-positive breast cancer with minimal residual disease (i.e., RCB= 1, NRI >= 0.75, or Neo-Bioscore= 0–1) after NST who have similar 5-year RFI compared with patients with pCR. Validation in a large cohort with longer follow-up is required before implementation in clinical practice.

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Detection and Biomarkers #8

Decoding the Biology of High-Risk Ductal Carcinoma in Situ (DCIS) through Genomics and the Tumor Immune Microenvironment: the DEFENSE Study

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Abstract
Introduction: Ductal carcinoma in situ (DCIS) of the breast is a premalignant lesion representing a biological spectrum. While many patients with DCIS undergo surgical resection with no survival benefit given the indolent nature of their disease, others do possess DCIS that has the potential to evolve into invasive cancer if left untreated. Yet even among those patients with biologically aggressive DCIS, their risk of dying from metastatic breast cancer is only 3.3% versus 30-40% among patients with biologically aggressive invasive cancer. This study will identify molecular and tumor immune microenvironment factors that allow DCIS to develop high-risk features without ever becoming invasive breast cancer. Methods: This is a pilot study (DEFENSE) of 10 patients with invasive high-risk breast cancer enrolled on the I-SPY2 trial matched by age and tumor molecular profile to 10 patients with high-risk DCIS, defined as having at least two of the following characteristics: large (>5cm), high-grade, hormone receptor-negative, and/or HER2-positive. Tumors are divided into 22 sections with regions of pathologic interest identified prior to multi-modal analysis with whole exome DNA sequencing, SMART-3SEQ RNA sequencing, multiplex immunohistochemistry (mIHC), and stromal profiling. Each profiling modality is performed by a different institution included in the NIH Molecular Characterization of Screen-Detected Lesions (MCL) consortium. This pilot study will inform our decision to expand to a full-scale study of 200 patients (100 DCIS, 100 invasive cancer). Results: We have thus far demonstrated the feasibility of our pilot study with 10 blocks in total sent to and received by each institution. Pathologic annotation has also been completed. Whole exome DNA sequencing, SMART-3SEQ, mIHC, and stromal profiling work has begun, and we plan to make pathology, clinical and genomic data available through the MCL's collaborative partnership with the NASA Jet Propulsion Lab (JPL) cloud-based platform. Conclusions: We have successfully shown that a multi-institution collaborative can effectively share pathologic data and conduct data analyses using a variety of tumor profiling modalities. We anticipate that our data will allow us to differentiate the underlying biology of high-risk DCIS from invasive breast cancer, identifying mechanistic opportunities for future intervention.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Detection and Biomarkers #9

Effect of DWI sequence on geometric measurement errors: evaluation in a breast MRI phantom

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Abstract
Introduction: Diffusion weighted MRI (DWI) has shown promise for monitoring breast cancer treatment response and may provide complementary information to contrast-enhanced (CE)-MRI. One limitation of standard DWI techniques is spatial distortion that makes co-registration with T1w CE-MR images challenging. Previous work using the UCSF/NIST breast MRI phantom, demonstrated spatial distortion (stretching/compression) in single-shot echo planar imaging diffusion-weighted images (ss-EPI DWI) that was dependent on spatial location within the scanner (patient left or right) and was also present in patient breast DW-images. Experimental testing suggested the observed DWI distortion was not due to gradient nonlinearity or eddy currents. One hypothesized cause of the distortion was inhomogeneity effects in the main magnetic field (B0) of the MRI scanner

Advanced DWI techniques, such as multi-shot EPI DWI sequences, that may be less susceptible to potential causes of distortion, are becoming available for breast DWI. If distortion is due to B0 inhomogeneity, it would be expected to decrease when using multi-shot EPI techniques, which are less sensitive to off-resonance distortion. For this study, one UCSF/NIST breast MRI phantom was imaged to quantitatively measure the distortion of both standard single-shot and new multi-shot EPI DWI acquisitions.

Methods: Using the UCSF/NIST quantitative breast MRI phantom, MRI data including: T1-weighted, standard ss-EPI DWI, and multi-shot EPI DWI, were acquired at two imaging sites: (Site 1: Siemens 3T scanner and Site 2: GE 3T scanner).

Image distortion was measured by automatically calculating 1) the width of the phantoms in both the right and left breast coils and 2) the center-to-center spacing across rows of the geometric distortion plate array.

Results: Standard ss-EPI DWI of the UCSF/NIST breast phantom at both sites demonstrated a stretching/compression distortion in the x-direction dependent on R/L spatial location within the magnet. The distortion decreased when using multi-shot DWI EPI techniques At both sites, the T1-weighted images were closest to the fabricated 15 mm spacing.

Discussion and Conclusion: This work found that multi-shot EPI DWI sequences had reduced distortion, suggesting a potential B0 dependence of the stretching/compression distortion, and showed that the UCSF/NIST breast MRI phantom is a useful tool for identifying and characterizing distortion artifacts.

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Detection and Biomarkers #10

Application of Machine Learning to elucidate the biology predicting response in the I SPY 2 neoadjuvant breast cancer trial

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Abstract
Background: Machine learning relies on algorithms that learn patterns in large, complex datasets to predict outcomes. The adaptive, neoadjuvant I-SPY 2 TRIAL evaluates novel agents added to standard therapy, and identifies their most responsive subtype. While previously proposed genes/signatures reflecting an agent's mechanism of action predicted pathologic complete response (pCR) in some treatment arms/subtypes, not all arms had strong predictive biomarkers. We leverage machine learning to explore the limitations of using only known mechanisms of action in predicting pCR, and the extent to which biology outside known drug action improves response prediction in the first 10 arms of the trial.

Methods: Our study involves 986 patients with pre treatment gene expression and pCR data across 10 treatment arms including inhibitors of HER2: neratinib (N), pertuzumab (P), TDM1/P; AKT (MK 2206; M); IGF1R (ganitumab); HSP90 (ganetespib); PARP/DNA repair (veliparib/carboplatin; VC); ANG1/2 (AMG386); immune checkpoints (pembrolizumab; Pembro); and a shared control arm (Ctr). Each arm/receptor subtype group was evaluated independently for groups with at least 20 patients (n=19), with 25% of data held out as independent test sets. We implemented a 3 fold cross validation technique with 10 repeats using Random Forest ensemble algorithm with recursive feature elimination. In combination with clinical data, a three pronged feature selection approach was employed: (1) restricted to mechanism of action genes: AKT/PI3K/HER (m=10 genes), IGF1 (m=11), HSP90 (m=88), DNA repair (m=79), TIE1/2 (m=11), and immune (m=61), as well as HER2 amplicon genes; (2) expanded to include targeted pathways for all 10 agents/combinations plus ESR1 and proliferation genes (m=339); (3) an unbiased whole genome approach (m=17,990). Models were considered predictive if AUROC ≥ 0.75, Sensitivity ≥ 0.6 and Specificity ≥ 0.6 in cross validation and independent test sets.

Results: Prediction of pCR using only genes reflecting the known mechanism of the drug succeeded in 5 subgroups, with DNA repair genes predicting VC response and immune genes predicting Pembro response in HR+HER2 and HR HER2 subsets, and AKT/PI3K/HER + HER2 amplicon genes predicting (P) response in HR+HER2+ patients. Expansion of the feature set to include genes associated with all mechanisms of action of all drugs proved sufficient to produce good predictive models in 8 of 19 subgroups. Examples include DNA repair + immune genes predicting response to ganitumab in HR+HER2 and to (N) in HR+HER2+. An unbiased approach using all data yielded predictive power in 8 of 19 subgroups, including 5 with no predictive models from the first two approaches. Examples include HR HER2 (N) predictors enriched for metabolic, cell division and membrane protein proteolytic processes; HR+HER2+ TDM1/P enriched for metabolic, stress response

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and cell cycle processes; and HR HER2 MK 2206 predictors containing Ser/Thr kinases. In total, we identify predictive biomarkers in 14 of 19 subgroups across the three feature selection approaches.

Conclusions: Our results suggests that hypothesis driven analysis restricted to assumed mechanisms of action of the experimental agents may be insufficient, and that exploration of possible off target effects may be needed to understand the underlying biology of response or resistance.

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Epidemiology and Population Science #1

Unlocking the vault: Can 2nd opinions by Comprehensive Cancer Center breast oncologists improve treatment quality for African Americans?

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Abstract
Research increasingly points to inadequate treatment as a factor in the excess breast cancer mortality among African Americans. Likely causes include lack of guideline-concordant care, underuse of medical advances, and limited opportunities to participate in clinical trials and genetic counseling. African Americans are disproportionately affected because they are more likely to receive care in low-resource settings. Research also shows that NCI-designated Comprehensive Cancer Centers (CCCs) have the best cancer outcomes compared with other clinical settings - yet African Americans and Latinx are under-represented in CCCs. It is as if the leading cancer clinicians are locked in a vault inaccessible to those with the greatest need.

We used ethnographic methods to explore the feasibility of and extent to which a CCC 2nd opinion can improve the quality of treatment offered to African American breast cancer patients receiving care elsewhere. Through community outreach, 14 patients were recruited and 17 CCC consultations were conducted free of charge. Each was observed and audio-taped. Patients were interviewed twice to document the impact of the consultation on their treatment. Consulting oncologists were also interviewed.

Our findings reveal numerous ways in which the CCC 2nd opinion improved quality of treatment from complete revision of a treatment plan to adding/changing medications, modifying the plan for monitoring, and/or improving management of side effects. Patients reported that all major recommendations were implemented by treating clinicians. In one dramatic case, chemotherapy failed to slow the growth a young public hospital patient's stage 3 tumor associated with a P53 mutation. The CCC clinician recommended an entirely different treatment. In remission two years later, the patient had another child.

We believe this is the first study to explore the CCC consultation as an intervention to reduce mortality disparities. It appears feasible to target CCC 2nd opinions to vulnerable patients at relatively low cost to the CCC. Many CCC clinicians were eager to see these patients, and to communicate directly with treating clinicians. Patients readily recognized the expertise of CCC clinicians and were deeply grateful for the opportunity.

Based on this pilot study, the 2nd opinion concept warrants further testing via a randomized trial.

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Epidemiology and Population Science #2

BRCA Exchange: Data Integration and Federated Analysis for BRCA Genetic Variant Interpretation

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Abstract
Genetic testing is improving patient care through early detection and improved management of heritable breast cancer risk, but its impact remains limited by Variants of Uncertain Significance (VUS). These VUS are rare variants for which no single institution may have enough observations for robust interpretation. The BRCA Exchange (https://brcaexchange.org) was launched by the Global Alliance for Genomics and Health to address this need, by developing data integration strategies to advance genetics with the BRCA genes as exemplars. The BRCA Exchange currently represents the single largest source of public BRCA variation data, integrating data from public resources including ClinVar, LOVD, gnomAD, and the Starita/Findlay functional assay. In our next steps, we are developing approaches for secure integration of case-level data through federated analysis. This involves “bringing the code to the data”, rather than sharing the data directly, and analyzing sensitive, PHI-containing data within its secure home environment to generate aggregated variant-level summaries that contain no PHI and can be shared more broadly. Working closely with the ENIGMA expert panel for BRCA variant interpretation, we are developing federated analysis strategies for generating statistical evidence of variant pathogenicity based on variant allele frequencies, summary family history, variant co-occurrences, and other information. We welcome new collaborations! This work is supported by the NCI Information Technology for Cancer Research (ITCR) program, Grant # 1U01CA242954-01. For more information, please contact Melissa Cline, mcline@ucsc.edu.

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Epidemiology and Population Science #3

Resources for HDFCCC Members

HDFCCC Administration

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Abstract
Explore the benefits of Cancer Center membership.

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Epidemiology and Population Science #4

Using a breast cancer risk model and risk thresholds as a predictor of chemoprevention uptake

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Abstract
Background: Large-scale chemoprevention trials validated endocrine risk reduction strategies to lower breast cancer risk. We sought to understand the risk at which women are likely to adopt chemoprevention. A 5-year Gail risk of 1.67% or above is considered elevated risk, and the FDA indication for prescribing chemoprevention. We examined chemoprevention use in the Athena Breast Health Network (Athena), which includes approximately 100,000 women who are screened by mammography at Sanford Health, UC Davis, UC Irvine, UC Los Angeles, UC San Diego, and UC San Francisco.

Methods: We calculated the Gail risk score for women who had completed an Athena online intake survey distributed before being seen at screening centers; this survey included questions about chemoprevention usage. First, we analyzed 16,518 surveys of 9,318 unique women without breast cancer or DCIS who received breast cancer screening at UCSF from 2011- 2018 and who consented to research. These women also self-reported use of chemoprevention. We stratified Gail risk scores by a threshold of 1.67%, and by percentiles to identify those women in the top 2.5% by age. We compared current chemoprevention use in these different breast cancer risk strata, and factors associated with its use. An analysis including all 100,000 women in the Athena Network will be presented at SABCS.

Results: Overall, at UCSF, 48 of 9,318 women (0.51%) reported current chemoprevention use. The 5-year Gail risk was greater than 1.66% in 3,675 of 9,318 women (39%), of whom 205 (2.2%) were in the top 2.5% of risk by age.

Chemoprevention use was reported by 13 of 205 (6.3%) women in the top 2.5% of risk by age (mean Gail risk 5.6%), as compared to 41 of 3,675 (1.1%) who were at Gail above 1.66% (mean Gail = 3.9%). Women in the top 2.5% and those with Gail risk >1.66% were significantly more likely to be using chemoprevention $p< 0.01$ for each respectively). Chemoprevention uptake was correlated with the joint effect of the top 2.5% of risk by age and increasing Gail score (OR = 10.25; P = 0.009). Preliminary results were consistent among the 100,000 women in the Athena registry (analysis ongoing).
In addition, chemoprevention use was more likely in older women (OR = 1.10; $P < 0.01$, for every year of age) and in those women with Ashkenazi ancestry on both sides of the family compared to none (OR = 2.32; P = 0.02). Race and education were not associated with use of chemoprevention.

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Discussion: Women with higher Gail scores in the top 2.5% of risk by age are positively associated with current chemoprevention use (6.34%). Importantly, this analysis presents a risk-stratified, population-level risk reduction strategy, using the top 2.5% risk threshold by age. It provides an opportunity to specifically target chemoprevention to women at highest need to reduce their breast cancer risk.

In the WISDOM Study (NCT02620852), we are prospectively testing active outreach based on breast cancer risk in the top 2.5% of risk by age, and have developed a breast health decisions aid to standardize communication of risk-reducing options.

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Epidemiology and Population Science #5

Personalized breast cancer screening in a population-based study: Women Informed to Screen Depending On Measures of Risk (WISDOM)

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Abstract
Background: The WISDOM Study is a preference-tolerant, pragmatic study seeking to determine if personalized screening, compared to traditional annual screening, is as safe, less morbid, enables prevention, and is more accepted by women. WISDOM personalized screening integrates previously validated genetic and clinical risk factors (age, family history, breast biopsies, race/ethnicity, mammographic density) into a single risk assessment model to direct screening. The study is registered on ClinicalTrials.gov, NCT02620852.

Methods: Women aged 40-74 years with no personal history of breast cancer, DCIS, or double mastectomy can join the study online at wisdomstudy.org. Participants can randomize or self-select a study arm. For all participants, risk of developing breast cancer is calculated according to the Breast Cancer Surveillance Consortium (BCSC) model. Participants in the personalized arm undergo panel-based mutation testing, and their 5-year risk is calculated using the BCSC score combined with a Polygenic Risk Score (BCSC-PRS) that includes 229 single nucleotide polymorphisms (SNPs) known to increase breast cancer risk. 5-year risk level thresholds are used to stratify for low-, moderate- and high risk to determine age to start, stop, and frequency of screening.

Accrual: The study is currently open for accrual nationwide. To date, 33,931 women have registered, and 25,099 have consented to participate. The median age is 56 years old. 85% of participants are Caucasian, 2% African-American, and 5% Asian. 6% self-reported Hispanic ethnicity. WISDOM is actively partnering with self-insured companies, health insurers, and Blue Cross Blue Shield Association for national coverage using a coverage with evidence progression approach.

Expansion and diversity: To strengthen generalizability, WISDOM is enhancing the diversity of our potential participant population by expanding to other states and partnering with other health insurers and self-insured companies. Additionally, the study is available in Spanish to engage Spanish-speaking communities. With the involvement of patient advocates and community partnerships, diversifying out recruitment will strengthen our scientific knowledge of breast cancer risk and increase the accessibility to personalized breast cancer screening recommendations for all women.

Conclusions: We have established a robust online enrollment portal which allows women across the US to participate. Results at 5 years will enable us to demonstrate that personalized screening improves healthcare value by reducing screening volumes and costs without jeopardizing outcomes.

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Epidemiology and Population Science #6

Triaging breast care center patients to supportive care services based on the Athena Breast Health Network online intake form and the Patient-Reported Outcomes Measurement Information System (PROMIS)

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Abstract
Background: At the UCSF Breast Care Center (BCC), an Athena Breast Health Network electronic Health Questionnaire System (eHQS) is distributed to new patients. This questionnaire includes self-reported Patient-Reported Outcome Measurement and Information System (PROMIS) quality of life domains and proactively triages patients to genetic counseling, psycho-oncology, onco-fertility, smoking cessation, peer support, nutritional counseling, behavioral sleep, and social work. This analysis aims to assess the eHQS as a means to effectively refer patients to supportive care services.

Patients and Methods: Over 6,000 patients have completed the questionnaire since 2013. 4,984 patients consented to research and 3,627 completed all relevant data for analysis. The number of referrals pended after eHQS completion was reviewed. PROMIS T-Scores in 8 domains (depression, anxiety, fatigue, sleep-related impairment and disturbance, cognitive function, applied cognition and physical function) were calculated with the Health Measures system and compared to the US general population and between patient age and cancer type.

Results: Compared to the US general population, UCSF BCC patients have impaired quality of life in every assessed PROMIS domain except for depression. As age increases, scores indicate lower symptom burden in depression, anxiety, sleep disturbance, and cognitive function. Importantly, high symptom burden in the anxiety PROMIS domain was suggestive of lower quality of life scores in 6 of the other 7 assessed PROMIS domains. 39% of analyzed BCC patients received at least one referral to a supportive care service. 50% of patients with an Invasive Breast Cancer (IBC) diagnosis and 43% of patients with a DCIS diagnosis triggered at least one referral. 31% of patients received a genetic counseling referral, 16.3% psycho-oncology, 11% behavioral sleep, 8% nutritional counseling, 7.6% social work, 2.4% smoking cessation, and 1.6% onco-fertility. Patients with IBC were more likely than those with DCIS or no cancer diagnosis to receive a genetic counseling or psychosocial service referral. Referral count decreases as age increases.

Conclusion: The Athena intake form at the UCSF BCC effectively triages patients to supportive care services. Preliminary results regarding the correlation between anxiety and overall poor quality of life suggest that referrals to psycho-oncology may be most efficacious in decreasing symptom burden.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Epidemiology and Population Science #7

Breast Cancer Risk and Prevention Education: Implications from the WISDOM Study's Breast Health Decisions Tool Pilot

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Abstract
Introduction: From May 2019 to February 2020, the Breast Health Decisions (BHD) Tool Pilot Study was rolled out to Women Informed to Screen Depending on Measures of Risk (WISDOM) Study participants. The tool addresses AIM 4 of the WISDOM Study: to determine whether knowledge of personal risk improves uptake of preventative interventions. The BHD Tool utilizes engaging visuals and distilled language to communicate to women their personalized risk and risk reduction methods. The goal is to not only provide the risk but also actively educate women in the top 2.5% breast cancer risk in their age group.

Methods: After developing the BHD tool, we conducted a pilot with 20 women in the target risk group to test its usability and utility. A breast health specialist contacted each participant for an online consultation of the tool. Next we asked participants to complete a feedback survey and follow-up interview.

Results: 20 participants completed a breast health specialist consultation. Of those, 14 completed the quantitative feedback survey and 11 participated in a follow-up interview. From the feedback survey, 14 of the 14 (100%) participants indicated that they had a better understanding of their chance of developing breast cancer. 13 (93%) thought the aid was either "extremely helpful" or "very helpful" in helping them understand their breast cancer risk. 10 (71%) indicated that they were either "extremely motivated" or "very motivated" to reduce their risk. 10 (71%) noted they would consider lifestyle changes (exercise, reducing alcohol intake, and/or reducing BMI). 6 (43%) indicated they would consider chemoprevention medication. From the qualitative interviews, we learned that some women were not previously aware of chemoprevention medications. A majority of women found the visuals helpful in understanding and remembering their breast cancer risk compared to the average woman. And many women felt empowered to take control of their health.

Conclusions: A health decisions tool can be pivotal in not only educating women about their breast cancer risk but also motivating them to take preventative action. We plan to launch the BHD Tool to WISDOM Study participants in February 2020 to further assess prevention uptake in risk-based screening.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Epidemiology and Population Science #8

Restructuring Nurse Navigation to Enhance Patient Experience: Patient-Centered Survey Findings

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Abstract
Introduction: A nurse navigator is a registered nurse who can serve as a patient advocate, educator and coordinator. At the UCSF Breast Care Center, nurse navigators assist with care coordination for new patients. In some centers, they are also the point-person throughout a patient's entire treatment process. The effect of nurse navigation on patients has not been adequately assessed. Our study attempts to elucidate the efficacy of nurse navigation in patient care.

Methods: We provided a 9-question survey to 50 patients at the UCSF Breast Care Center before their breast oncology appointment. After survey completion, patients had the chance to talk about their patient experience.

Results: 28 (56%) patients surveyed did not have nurse contact before their appointment and 22 (44%) patients surveyed did. 16 out of 28 (57%) of no-nurse contact patients felt informed before their appointment compared to 16 out of 22 (73%) of patients with nurse contact. 4 out of 28 (14.3%) of no-nurse contact patients strongly agreed that their initial questions were answered compared to 11 out of 22 (50%) of patients with contact. 12 out of 28 (43%) of no-nurse contact patients strongly agreed that their care was coordinated effectively compared to 15 out of 22 (68%) of patients with nurse contact. Our last set of questions asked no-nurse contact patients whether nurse contact would 1) improve their patient experience and 2) better deal with stressful emotions. Patients with nurse contact were asked whether a nurse did improve statements 1 and 2. 14 out of 28 (50%) of no-nurse patients strongly agreed to both statements. 16 out of 22 (73%) of patients with nurse contact strongly agreed to statement 1 and 20 out of 22 (91%) agreed with statement 2.

Conclusions: A greater proportion of patients with nurse contact felt informed before their appointment and believed their care was effectively coordinated than those without nurse contact. And the majority of patients with nurse contact believed their nurses improved their patient experience and relieved anxiety/stress. Thus, nurse navigators can play vital roles in streamlining workflow and improving patient well-being at the cancer center.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Epidemiology and Population Science #9

Adjuvant chemotherapy in small node-negative triple-negative breast cancer

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Abstract
Background: Recommendations on adjuvant chemotherapy in pT1N0M0 triple-negative breast cancer (TNBC) differ between international guidelines due to lack of randomized trial data. We evaluated associations of adjuvant chemotherapy with long-term outcome in a population-based cohort of pT1N0M0 TNBC.

Methods: All patients diagnosed with pT1N0M0 TNBC in the Netherlands between 2005 and 2016 were identified from the Netherlands Cancer Registry. Patient, tumor, and treatment characteristics were recorded. Date and cause of death were obtained from Statistics Netherlands. We used multivariable Cox-regression models to evaluate associations of adjuvant chemotherapy with breast-cancer specific survival (BCSS) and overall survival (OS), adjusted for baseline characteristics and performed sensitivity analyses using propensity-score (PS) weighting.

Results: We identified 4,366 patients: 284 with pT1a, 923 with pT1b, and 3,159 with pT1c tumors. Adjuvant chemotherapy was administered in 53% of patients. Patients receiving chemotherapy had more unfavorable baseline characteristics including younger age, larger tumors, and higher tumor grade. At 8.2 years median follow-up (IQR=5.8-10.9), 671 patients had died, of whom 311 due to breast cancer. After adjustment for baseline characteristics, chemotherapy was associated with improved BCSS (adjusted HR [aHR]=0.65; 95%CI=0.48–0.89). The effect of chemotherapy differed by tumor size (pT1a: aHR=4.28, 95%CI [1.12-16.44]; pT1b: aHR=1.12, 95%CI [0.51-2.49]; pT1c: aHR=0.60, 95%CI [0.43-0.82]; pinteraction=0.02). Findings for OS were in line with BCSS results. PS-weighting analysis confirmed the results of the primary analysis.

Conclusions: Adjuvant chemotherapy is associated with better BCSS and OS in pT1N0M0 TNBC. Benefit is most evident in pT1c tumors and may not outweigh harms in pT1a/pT1b tumors.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Epidemiology and Population Science #10 – BEST EPIDEMIOLOGY AND POPULATION SCIENCE POSTER

Prediction of long-term survival in oligo-metastatic breast cancer (MBC)

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Abstract
Background: MBC is generally considered incurable. Nevertheless, ~5% of patients with MBC are alive 10 years with no evidence of disease. Observational studies show that long-term survivors (LTS) tend to have a limited number of metastases, often referred to as oligo-MBC. Oligo-MBC may indicate a state of limited metastatic potential with a role for local ablative treatment of metastatic lesions. However, oligo-MBC can also represent the tip of a metastatic iceberg. In a large cohort of long-term MBC survivors, we investigated the optimal definition of oligo-MBC and factors associated with a favorable outcome in patients with oligo-MBC.

Methods: All patients < 80 years diagnosed with de novo MBC between 1/2000 and 12/2007 and alive ≥10 years were selected from the Netherlands Cancer Registry. For each LTS we selected 3 patients who survived <10 years, matched on ER-status, age, and year of diagnosis. Detailed data on clinical presentation and therapy was collected from medical records. Vital status was updated via linkage with the Dutch Personal Records Database until 2/2019. We assessed 10-year overall survival (OS) according to the number of metastatic lesions to determine the optimal oligo-MBC definition. Next, we used weighted Cox regression models with inverse sampling probability weighting to study prognostic factors in oligo-MBC. Factors associated with OS at p-value ≤0.10 were included in multivariable models; 95% confidence intervals (CI) were estimated using robust standard-errors.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Results: We identified 3,328 eligible patients with de novo MBC, of whom 207 (6%) were alive ≥10 years. Three or less distant metastases showed statistically significant better OS compared to multiple (>5) metastases whereas 4-5 metastases showed similar HR to > 5 metastases (table). Therefore, we used ≤ 3 metastases to define oligo-MBC. In multivariate analyses, local therapy of oligo metastases (HR 0.56, 95% CI 0.34-0.92), premenopausal status (HR 0.39, 95% CI 0.19-0.80), and absence of lung metastases (HR 0.26, 95% CI 0.11-0.64) were significantly associated with better OS while single organ metastases, bone metastases, central nervous system metastases, surgery of the primary tumor were not.

Conclusions: In a nationwide cohort of patients with MBC, a maximum of 3 metastases appeared the optimal cut-off to define oligo-MBC. In patients with oligo-MBC, local therapy of metastases, was associated with better OS as were premenopausal status and absence of lung metastases.

Table

# metastases	HR	95% CI	P-value	10-year OS
1	0.68	0.51-0.91	0.010	15%
2-3	0.72	0.54-0.96	0.023	13%
4-5	0.80	0.52-1.24	0.313	7%
>5	ref			3%

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Epidemiology and Population Science #11

Teens for Screens: Implementation of a Breast Cancer Awareness Education Program Among High School Students from Minority Communities in San Francisco

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Abstract

Introduction: National racial/ethnic and socioeconomic (SES) disparities in breast cancer (BC) risk and survival are well documented. In a study of the BC population in San Francisco (SF), we identified neighborhood and racial/ethnic differences in stage of diagnosis, molecular subtype, and survival. Specifically, women that resided in low SES areas were diagnosed with more advanced BC stage and had lowest screening rates. With the goal of eliminating observed disparities, the SF Cancer Initiative (SFCAN) created Teens for Screens (T4S). T4S is a high school student (HS) based education program aimed to educate and empower HS to promote BC screening and health behavior changes in their families and communities.

Methods: T4S was developed using a continuous-stakeholder-engagement approach, including HS partners and the SFCAN BC task force members. The program was advertised via dissemination of flyers among public schools of SF. Applications were completed online and applicants were selected to represent a diverse group of HS based on self-reported race/ethnicity, different public high schools, and teens who reside within neighborhoods with lowest screening rates. Selection was limited to current 10th or 11th graders and priority was given to teens reporting a close experience with BC. During phase 1 (P1), participants attended 4 weekly half-day educational sessions focused on: introduction to BC, risk factors, health disparities, and local community resources. P1 sessions integrated the participation of healthcare professionals, survivors, and community partners, as well as interactive exercises focused on communication, and leadership skills. Participants were provided with an online educational video created by HS and the SFCAN website as resources for dissemination during phase 2 (P2). Participants completed a P1 evaluation survey and are currently completing weekly dissemination reports as part of P2.

Results: After 3-weeks of advertisement, T4S received 76 applications. We accepted 39 sophomore and junior HS from 10 different SF public high schools based on the program's selection criteria. Among 39 recruited HS, 64% self-identified as Asian/Asian American, 20% Hispanic/Latino, 8% African American, and 5% non-Hispanic White. The majority of participants were female (74%), identified as bilingual (64%; 15% trilingual), and resided in neighborhoods of northeastern and southern SF, consistent with areas of lowest BC screening rates. Thirty-five (90%) participants completed P1 of the pilot. Most participants were satisfied or very satisfied with T4S (95.5%). Ninety two percent of HS reported their understanding of BC increased, and 83% expressed confidence in their ability to discuss the importance of BC screening with others. Preliminary results of P2, show that 83% of HS remain engaged reporting their dissemination efforts.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Conclusions: Implementing a BC educational program for HS from diverse targeted communities is feasible and acceptable. The T4S program increased HS knowledge on BC and empowered them to disseminate their knowledge to peers and other community members. Our ongoing efforts during P2 of this pilot include evaluating the dissemination, adaptation, and impact of T4S.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Molecular and Cellular Biology #1

HDFCCC Shared Resources

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Abstract
Explore the shared resources of the Cancer Center

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Molecular and Cellular Biology #2

Association of breast cancer risk factors with epithelial cell proportions and hormone signaling state in the premenopausal human breast

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Abstract
Reproductive history and body weight are two major breast cancer risk factors. Prior pregnancy (parity) reduces lifetime risk by up to 50%, and obesity reduces premenopausal risk by up to 45%. Here, we use single-cell RNA sequencing to directly link these risk factors with tumor-protective changes in epithelial proportions and hormone signaling in the premenopausal breast. We show that parity reduces the proportion of transformation-susceptible luminal cells and increases the proportion of tumor-suppressive myoepithelial cells in the epithelium. Additionally, we identify two distinct mechanisms by which parity and obesity could contribute to reduced hormone signaling. First, parity reduces the per-cell transcriptional response to ovarian hormones in hormone-responsive cells. Second, parity and obesity reduce the overall proportion of hormone-responsive cells, leading to a decreased paracrine signaling response in myoepithelial cells. Together these findings provide mechanistic insight into how these risk factors affect the mammary epithelial microenvironment to modify breast cancer susceptibility.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Molecular and Cellular Biology #3

The Yap oncogene: a promising candidate that may be involved in early breast cancer progression

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Abstract
Yap misregulation has been implicated in many cancers yet its precise role in breast cancer is only beginning to be understood. Yap is reported to be associated with both the basal/triple negative and luminal breast cancer subtypes, as well as higher tumor grade and decreased survival. However, there are many seemingly conflicting studies about Yap association with different subtypes. Our laboratory has found that Yap misregulation is associated with increased age in luminal progenitor cells (putative breast cancer cells of origin). As increased age is one of the most significant risk factors associated with breast cancer, our laboratory has previously proposed that molecular changes associated with age (such as Yap) may act early in breast cancer precursor cells to make them susceptible to breast cancer progression. Our laboratory is in a unique position to test this hypothesis because we have previously developed a cell culture system that accurately models the early steps of breast cancer progression starting with normal finite-lifespan epithelial cells from women who have undergone breast reduction surgery. Overall, we have found that Yap overexpression in early progression (i.e., prior to immortalization) causes increased telomerase activity, decreased levels of the long non-coding RNA MORT, and an increased propensity to continue proliferation past the replicative senescence barrier. Together, these data suggest Yap may be associated with an increased susceptibility to become immortal, a significant transition that is first seen in vivo in pre-malignant high-grade DCIS cells and is needed for them to become malignant. In addition, immunofluorescence and anchorage independent growth assays suggest Yap may cause increased cancer stem cell and malignancy phenotypes in breast cancer cells when it is mis-expressed in cancer precursor cells. Continued research in our laboratory aims to identify targets of Yap and immortalization that can be inhibited early in progression to prevent breast cancer before it is able to form.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Molecular and Cellular Biology #4 – BEST MOLECULAR AND CELLULAR BIOLOGY POSTER

MYC deregulates mitosis and induces chromosomal instability in breast cancer

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Abstract
Tumors that overexpress the MYC oncogene frequently demonstrate aneuploidy, which is associated with highly aggressive cancers and tumor evolution. However, how MYC causes aneuploidy is not well understood. Here, we show that MYC overexpression induces mitotic spindle assembly defects and chromosomal instability (CIN) through effects on microtubule nucleation and organization. Depleting MYC reverses mitotic defects, even in established tumor cell lines, implicating an ongoing role for MYC in CIN emergence. MYC reprograms mitotic gene expression and we identified TPX2 to be permissive for spindle assembly in high MYC cells. TPX2 depletion blocks mitotic progression, induces cell death and prevents tumor growth. Further elevating TPX2 expression reduces mitotic defects in MYC-high cells. MYC and TPX2 expression might be useful biomarkers to stratify patients for new anti-mitotic therapies. Our studies implicate MYC as a regulator of mitosis and suggest blocking MYC activity can attenuate the emergence of CIN and tumor evolution.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Molecular and Cellular Biology #5

Environmental chemicals cause extensive branching in human mammary gland organoids and a carcinogenic proteome

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Abstract
Bisphenol A (BPA) is a chemical compound used as a plasticizer in a variety of plastic goods and has been detected in the blood of women and girls. It was shown to interact with the endocrine system, thereby having carcinogenic effects. Hence, BPA has been removed from many commercial products and replaced by other chemicals such as bisphenol S (BPS) and bisphenol F (BPF). However, little is known about the biological effects of these compounds. We investigated the effects of different environmental chemicals on human mammary gland organoid morphology and on the proteome.

We established organoid cultures from non-malignant primary human mammary gland tissue as an advanced disease model. The organoids were treated with physiological levels of various environmental chemicals, including BPA, BPF, BPS, and 17-β-estradiol (E2). We studied effects on organoid morphology using brightfield and confocal microscopy and analyzed relative protein abundance by quantitative mass spectrometry to determine proteome changes between the different treatments.

The exposure to the environmental chemicals and E2 resulted in altered branching morphology, while organoid size was not affected. Although BPA has known oncogenic potential, in our study, BPA had the least severe effects on branching morphology when compared to the other bisphenols. BPF or BPS treatment led to more extensive branching and altered organoid morphology.

On protein level, each environmental chemical resulted in distinct protein profiles, which show alterations predominately independent of endocrine signaling. The exposure to the different bisphenols resulted in the upregulation of proteins, which are involved in carcinogenesis, tumor progression and metastasis in various cancer types including breast cancer and thus may support tumor initiation and development.

Our study suggests that BPS and BPF may be potential carcinogens. Not only BPA but also BPF and in particular BPS alter branching morphology of human mammary organoids and influence various biological processes that are distinct from endocrine signaling. Our study highlights the desperate need for a thorough characterization of environmental chemicals to prevent the development of breast cancer caused by the exposure to potentially harmful and carcinogenic substances.

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Molecular and Cellular Biology #6

Paclitaxel Causes Transcriptional and Structural Changes in Human Induced Pluripotent Stem Cell-Derived Sensory Neurons

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Abstract
Background: Paclitaxel (PTX) is a taxane used in first- or second-line treatment of breast cancer. Despite its therapeutic efficacy, this may cause dose-limiting sensory peripheral neuropathy (PIPN). Severe PIPN may result in treatment interruption, and significantly impact patients' quality of life. Understanding the neurotoxic mechanisms of PTX may lead to the identification of molecular targets for prevention or treatment of PIPN.

Methods: A human-induced pluripotent stem cell (iPSC) line was differentiated into sensory neurons (iPS-SNs), and subsequently exposed to PTX. Transcriptional changes with PTX treatment were investigated with RNA-seq and validated by RT-qPCR. Differentially expressed genes were identified with DEseq2 and STRING was used to identify connections among proteins encoded by the genes affected by PTX. iPS-SNs exposed to PTX were stained with Phalloidin (F-actin) and Tuj1 (β-tubulin III) antibody for examination of neurite networks, growth cones and retraction bulbs. High content imaging was performed to study the concentration- and time-dependent effect of PTX on neurites.

Results: PTX treatment increased the expression of 84 genes and decreased the expression of 38 genes. Many genes that were down-regulated are controlled by MRTF/SRF, YAP/TEAD-dependent TGF-β signaling or both. SRF luciferase assays and MRTF localization showed no direct effect of PTX on MRTF/SRF-mediated transcription. STRING analysis identified a network of proteins involved in structure and function of the actin cytoskeleton and extracellular matrix that were significantly downregulated by PTX. Phalloidin staining showed a disruption of actin filaments after 48h PTX exposure and retraction bulb-like swellings in the axons after 6h PTX exposure. Neurite density decreased in a dose- and time-dependent manner with PTX treatment.

Conclusions: PTX decreases expression of actin cytoskeleton genes involved in structure and function of neurites and the extracellular matrix genes. Neurite extension is critical for epidermal innervation as it turns over, and morphological changes may be in part implicated in the clinical phenotype of PIPN. Effects of PTX on growth cones and actin filaments are consistent with PTX-dependent axon degeneration observed in vivo. These findings support ongoing studies to further define the mechanisms underlying PIPN.

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Molecular and Cellular Biology #7

Computational fluid dynamics validated with bioprinted vascular beds predicts metastatic colonization)

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Abstract
Background: Metastatic colonization of distant organs is responsible for 90% of cancer deaths. It is widely believed that forces and flows can govern where circulating tumor cells deposit in vascular beds but predicting site of circulating tumor cell (CTCs) deposition remains impossible. Computational fluid dynamics models have been developed to address this problem but testing fluid dynamics predictions remains impossible without controllable systems.

Methods: To address these issues, we bioprinted endothelialized vascular beds and compared the behavior of circulating metastatic mammary gland carcinoma cells in these physical models to computational predictions.

Results: We found that endothelial cells aligned with flow direction and remodeled the vascular beds, depositing basement membrane proteins and increasing resistance to deformation, resulting in much higher wall shear stress in vascularized constructs. We seeded these vascular models with tumor cells under physiological flow rates and observed that malignant cells were deformable and excluded from boundary zones and computational modeling excluding these features showed significant error. Tumor cells flowed through these vascular mimics deposited preferentially into incoming vasculature, with large clusters of CTCs seen at vascular forks. In endothelialized vascular beds compared to acellular beds, we found that tumor cell clusters were more likely to be multicellular (average size of 600um2 vs. 81um2, $p<1e-8$) and more likely to be found at fork regions ($p<1e-6$), whereas single cells deposited throughout the vascular tree in acellular geometries, resulting in a higher tumor area and burden.

Conclusions: This integration of two technologies, bioprinting and computational fluid dynamics affords new ability to decouple physical and biological factors affecting metastasis and builds towards predicting metastasis sites and early and effective treatment for cancer.

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Molecular and Cellular Biology #8

Mapping cellular interactions between cancer and normal cells via synthetic Notch ligand/receptor pairs

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Abstract
Understanding how cells move within an organism and what other cells they come into contact with is critical for elucidating fundamental mechanisms of development, organogenesis as well as pathologic processes such as metastasis. Here we show, in vitro, a synthetic-Notch ligand/receptor pair (synNotch - Morsut et al. Cell 2016) based approach can be used to detect physical interactions between immortalized human retinal pigment epithelial (hTERT RPE-1) cells and patient derived Adenoid Cystic Carcinoma (ACC) cells. hTERT RPE-1 or ACC cells, expressing synthetic ligand (outer plasma membrane localized GFP), were co-cultured with hTERT RPE-1 cells, expressing transgenic (i) LoxP-tagBFP-STOP-LoxP-DsRed, (ii) synthetic Notch receptor/transcriptional activator (outer plasma membrane anti-GFP nanobody combined with internal Gal4 transcription factor through a transmembrane domain) and (iii) CRE-recombinase fused to Estrogen receptor (ER-T2). By combining FACS and fluorescence microscopy facilitated scratch assays, we find that cells carrying the receptor component of synNotch system can switch their fluorescent reporter expression from tagBFP to DsRed more than 10 times when co-cultured with ligand carrying cells in the presence of estrogen receptor modulator, 4-hydroxy-tamoxifen (4-OHT) in comparison to mock control. We also find that it takes about one cell division to switch the fluorescent reporter color of a single, receptor carrying cell after its attachment with a ligand carrying one is achieved. Surprisingly, we observed that ligands are not fixed in position between two interacting cells but also are internalized by the receptor presenting cells via a transendocytosis-like process. Our findings suggest that dynamic physical interactions between cells can be mapped using cell surface localized synthetic Notch ligand/receptor pairs in a highly specific manner. Ultimately, we seek to integrate our system into mice to study how an individual cancer cell metastasizes and identify all of the non-tumor host cells with which it comes into contact during the metastatic process. We envision the same sensor mice will be valuable to study other processes, such as neurogenesis or development of the immune system.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Molecular and Cellular Biology #9

Understanding the role of Nuclear β-Actin (N-Actin) localization in growth and quiescence in normal and malignant breast

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Abstract
Actin is an essential and well-established component of the cytoskeleton, however, it is also present in the nucleus where it has been associated with a variety of processes that control gene expression. Cofilin-1 (CFL1) and Importin-9 (IPO9) have been linked to the nuclear import of actin, however, the mechanism by which actin enters the nucleus has yet to be elucidated. We have shown that myoepithelial-derived laminin-111 (LN-1) controls tissue quiescence by regulating N-Actin concentration. In order for cells to become quiescent, N-Actin must exit the nucleus and, if N-Actin remains within the nucleus, cell division continues unabated. Preliminary studies in our lab using 3D phenotypic reversion models have shown that there is elevated nuclear IPO9 in malignant cells, and, upon reversion, the nuclear IPO9 is diminished. Using genomic data from TCGA, we examined IPO9 and CFL1 expression in primary breast tumors and found that both IPO9 and CFL1 expression was significantly higher in all primary breast tumors compared to normal adjacent tissues. Although, many studies to date have highlighted the importance of myoepithelial derived LN-1, studies characterizing LN-1 and N-Actin import dynamics is lacking. Together, these findings provide critical insight into better understanding the role of N-Actin in breast cancer progression.

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Therapeutics and Clinical Trials #1

Modulation of the immune microenvironment in high risk DCIS

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Abstract
Background. Ductal carcinoma in situ (DCIS) is a risk factor for the subsequent development of invasive breast cancer. Features of DCIS that are associated with a high risk of a subsequent event include large size (> 5 cm), high grade, comedo necrosis, palpable mass, hormone receptor negativity, and HER2 positivity. Immune infiltrates in DCIS are positively associated with these high-risk features, suggesting that manipulating the immune microenvironment in high risk DCIS could potentially alter disease progression.

The study objectives were to 1) define dose limiting toxicities, tolerability, and feasibility of intralesional injection of an immune checkpoint inhibitor (pembrolizumab) into DCIS; and 2) determine response rate as measured by an increase in total T cells or CD8+ T cells from baseline to post treatment.

Methods. Study participants received 2 (dose escalation cohort) or 4 (dose expansion cohort) intralesional injections of pembrolizumab, 3 weeks apart, with surgery approximately 3 weeks after the last dose. Multiplex immunofluorescence analyses were used to compare immune cell populations in pre-treatment biopsies to post-treatment surgical specimens.

Results. The intralesional injections were well tolerated and there were no systemic toxicities observed. Multiplex immunofluorescence analyses demonstrated significant increases in total T cells, as well as cytotoxic CD8+ T cells and CD20+ B cells following therapy. Changes in macrophage and Treg numbers were not significant. Despite an increase in T cell infiltrates, there were no measurable indicators of an anti-tumor response: no reduction in lesion size by MRI, no reduction in proliferation of DCIS cells (Ki67 staining), and no increase in cell death (cleaved caspase 3 staining). Tissue segmentation indicated that there were significant increases in the total T cell and CD8+ T cell populations in the stroma, but not in the ducts themselves.

Conclusions. We have demonstrated the safety and feasibility of intralesional injection of pembrolizumab in high risk DCIS. Local immunotherapy resulted in the local proliferation/expansion of T cells. However, there was no significant change in lesion size or evidence for T cell killing at the cellular level. This suggests that there may be other factors involved, such as immune exclusion or immunosuppression of effector T cell activity.

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Therapeutics and Clinical Trials #2

The Impact of Axillary Surgery on Recurrence-Free Survival in Invasive Lobular Carcinoma (ILC) of the Breast

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Abstract
Background: Clinical trials demonstrate that axillary lymph node dissection (ALND) is unnecessary for most breast cancer patients with 1-3 involved nodes, but whether this is true for those with ILC is unknown. We evaluate the impact of ALND on recurrence-free survival (RFS) in ILC and 1-3 positive nodes.

Methods: We performed a retrospective cross-sectional analysis of patients with ILC treated between 1992-2019 at our institution. All patients received either sentinel lymph node biopsy (SLNB) or ALND and underwent either breast conservation surgery (BCS) or mastectomy. The primary outcome was RFS, defined as the absence of locoregional or distant recurrence.

Results: Of 496 cases, 250 (50.4%) underwent BCS, and 246 (49.6%) underwent mastectomy. A total of 93% of patients were hormone receptor positive, and 89% had low or intermediate grade disease. Among patients with 1-3 positive nodes, there was no significant difference in 5- and 10-year RFS based on receipt of ALND for both BCS and mastectomy cohorts. Using a multivariate model, we found no association between ALND and RFS overall (HR = 0.98, 95% CI 0.36-2.7, p>0.20) and among those with 1-3 positive nodes (HR = 0.60, 95% CI 0.12-3.4, p>0.20).

Discussion: These findings support the safety of omitting ALND in patients with ILC and 1-3 positive nodes, regardless of whether they receive BCS or mastectomy. Further studies of axillary management in ILC, including imaging tools to predict nodal involvement and response to therapy, are warranted.

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Therapeutics and Clinical Trials #3

Lack of background parenchymal enhancement suppression in breast MRI during neoadjuvant chemotherapy may be associated with inferior treatment response in hormone receptor positive breast cancer

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Abstract

Purpose: In breast MRI, contrast enhancement of normal fibroglandular tissue is referred to as background parenchymal enhancement (BPE). Hormonal status significantly affects the degree of BPE, potentially due to the association with mammary vascularity and activity. In most patients undergoing NAC, BPE is suppressed by the nonspecific anti-proliferative effects of chemotherapy on normal breast and/or ovary. However, some patients exhibit equivalent or even stronger BPE post-NAC compared to pre-NAC. We hypothesized that non-suppressed BPE in post-NAC MRI may be associated with inferior treatment response, especially in hormone receptor positive (HR+) cancers. This study aimed to investigate the association between BPE suppression and treatment response as defined by pathologic complete response (pCR).

Methods: Patients with stage II/III breast cancer enrolled in the I-SPY 2 neoadjuvant trial were included (HR+, n= 536; HR-, n=452). Patients underwent dynamic contrast enhanced MRIs at four time points during NAC: baseline (T0), after 3 weeks of the first regimen (T1), inter-regimen (T2), and pre-surgery (T3). Using in-house software, the contralateral breast parenchyma was automatically segmented for the entire breast volume. Quantitative BPE (qBPE) was calculated as the mean early (~150s post-contrast injection) percent enhancement of the central 50% of the axial slices. A breast radiologist reviewed all exams and excluded those where automated segmentation failed to accurately define tissue. For T1, T2 and T3, BPE was categorized based on the change from T0 as suppressed (qBPE < qBPE[T0]) or non-suppressed (qBPE ≥ qBPE[T0]). Chi-squared test was used to examine the association between BPE suppression and pCR, with $p<0.05$ considered statistically significant.

Results: HR+ cohort: pCR rates were lower for patients with non-suppressed BPE than those with suppressed BPE at every visit (T1–T3). The difference was statistically significant at T2 ($p=0.04$) and T3 ($p=0.01$).
HR- cohort: pCR rates were slightly lower for the non-suppressed BPE group, but no statistically significant association was found.

Conclusion: In HR+ breast cancer, lack of BPE suppression may indicate inferior treatment response. The contrasting results in HR+ and HR- cohorts are noteworthy in terms of the possible relationship between suppression of normal mammary and ovarian activity and treatment response in HR+ cancer.

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Therapeutics and Clinical Trials #4

Catalyzing navigation for breast cancer survivors (CaNBCS)

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Abstract
Background; Survivorship care plans (SCPs) are personalized documents, provided at the end of the treatment by patients' oncology clinicians that summarize the diagnosis and treatment, late and long-term adverse effects, ongoing surveillance for recurrence, screening for new cancers, and health maintenance of cancer survivors. Considered as a tool for cancer survivors, experts in cancer survivorship and accrediting organizations such as Commission on Cancer (CoC) have endorsed the use of SCPs even in the absence of firm evidence of their efficacy. Safety net hospitals are at the forefront of providing care for vulnerable low-income cancer survivors who may also have low educational attainment, low health literacy, and limited English proficiency. Cancer survivors who are racial and ethnic minorities and low income may experience higher symptom burden and limitation of function. Prior work has shown that patients who in safety net health setting, do not benefit from SCPs and only 25% share them with their primary care providers. Methods This study is a pilot randomized clinical trial to assess the role of patient navigation in cancer survivors. Breast cancer survivors were randomized to SCPs with or without patient navigation. In the intervention, arm navigators discussed the survivorship care planning and issues with patients at the time of delivery, 6 weeks by phone, at 3 months and then at 6 months. The primary outcome was breast cancer-related quality of life (QOL) was assessed by FACT B questionnaire. The secondary outcome was self-efficacy. In addition, we conducted focus groups for cancer survivors, patient navigators, and oncology providers to understand their perspective. Cancer survivors who had completed the treatment for breast cancer within 1-5 years were eligible to participate in the study. Participants spoke English(N=20), Chinese (n =10) or Spanish (n=10). Results: There were 20 participants in each arm, 10 English speaking and 5 each Spanish and Chinese speaking. At 6 months and final follow up, 32 patients were available for analysis. One patient developed metastatic cancer, two patients had changes in their insurance status and five were not available for final analysis. We performed Wilcoxon non-parametric analysis to assess changes in all five domains of FACT B. There were trends towards improvement in the change in emotional well-being score, functional well-being score and overall QOL in the intervention arm, but it was not statistically significant. Physical well-being score change was similar. There was no difference in the mean self-efficacy scores for both arms. At baseline, 57.7% breast cancer survivors reported being not all/a little bit satisfied with their sex life and 53.9% reported not all/a little bit feeling sexually attractive. 87.5 % of survivors reported having accepted their illness quite a bit/ very much. Conclusions Our study successfully recruited patient from a diverse patient population in safety net settings. Patient navigation combined with survivorship care showed encouraging trends in improvement in emotional well-being, physical well-being, and QOL, although it was not statistically significant. There was no difference in mean self-efficacy score. We are currently analyzing the qualitative data to assess the implementation of the intervention.

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Therapeutics and Clinical Trials #5

Breast Cancer Genetic Testing Station: A Model for Getting Genetic Test Results to Patients Before Surgery

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Abstract
In order to ensure timely access to genetic testing for patients with breast cancer at UCSF, we have implemented a Genetic Testing Station (GTS) model, in which clinicians are able to request same-day genetic testing for patients with active-diagnosis breast cancer. Last year, our research found that this model significantly decreased turnaround time in getting genetic test results to patients. However, a primary aim of this model, which was not addressed in last year's research, is to disclose genetic test results to breast GTS patients before their scheduled surgery. Therefore, this year, we explore whether the breast GTS model has been successful in getting results to patients with active-diagnosis breast cancer before undergoing surgery.

We compiled data for patients seen at the breast GTS from its inception (11/2018) through the end of 2019, including surgery dates, the date they were referred to Cancer Genetics, the date their results were released from the laboratory, and the date they received their genetic test result. We excluded patients who did not undergo surgery, had their surgery outside of UCSF, or had their surgery before being referred to Cancer Genetics.

We found that of the 112 patients who met inclusion criteria, 87% (97 patients) received their genetic test results before their operation. We report how many days it took genetics providers to disclose results and how long patients had their genetic test results before surgery. Of the 15 patients who did not receive results before surgery, 6 patients had results reported from the laboratory after their operation. The remaining 9 patients had results reported out before surgery, but did not receive them until after their operation.

The breast GTS model has been largely successful in getting results to patients with active-diagnosis breast cancer before they undergo surgery; however, there is still room for improvement. In our poster, we plan to identify why patients did not receive results before surgery, such as insurance issues, patient preference, or errors in workflow. In doing so, we hope to identify areas of improvement and next steps as we work toward continually improving the breast GTS model.

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Therapeutics and Clinical Trials #6 – BEST THERAPEUTICS AND CLINICAL TRIALS POSTER

Computational drug repositioning for the identification of new agents to sensitize drug-resistant breast tumors across treatment arms and molecular subtypes

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Abstract
Introduction: Drug repositioning is the application of FDA-approved drug compounds for novel indications beyond the scope of the drug's original intended use. This approach can greatly reduce development costs and provide shorter paths to approval. One approach for computational drug repositioning involves generating a disease gene expression signature and then identifying a drug that can reverse this disease signature. In this study, we extracted drug resistance signatures from the I-SPY 2 TRIAL by comparing gene expression profiles of responder and non-responder patients stratified by treatment and molecular subtype. We then applied our drug repositioning pipeline to predict compounds that can reverse these signatures. Our aim is to improve the outcomes of breast cancer patients who did not respond to their predicted best-in-class compound by providing an additional opportunity for therapeutic response before surgery. We hypothesize that reversing these drug resistance signatures will resensitize tumors to treatment and prolong survival.

Methods: We extracted drug resistance signatures by identifying differentially expressed genes between responders (RCB 0/I) and non-responders (RCB III) within treatment arms, molecular subtypes, treatment arms and molecular subtypes, and all tumor samples. We selected the log fold-change cutoff for each signature by identifying the cutoff that best separates the responder and non-responder samples in principal component space. We then applied our drug repositioning pipeline to identify compounds that significantly reverse these signatures using the drug perturbation profiles in the Connectivity Map v2 dataset. Briefly, the pipeline uses a non- parametric, rank-based pattern-matching strategy based on the Kolmogorov-Smirnov (KS) statistic to assess the enrichment of resistance genes in a ranked drug gene expression list. Significance of each prediction is estimated from a null distribution of scores generated from random gene signatures.

Results: We found that few individual genes are shared among the resistance signatures across the treatment arms and molecular subtypes. At the pathway-level, however, we found that immune-related pathways are generally enriched among the responders and estrogen-response pathways are generally enriched among the non-responders. Although most of our drug predictions are unique to treatment arms and molecular subtypes, our drug repositioning pipeline identified the estrogen receptor antagonist fulvestrant as a compound that can potentially reverse resistance across a majority of the treatment arms and molecular subtypes. This includes, interestingly, many of the hormone receptor-negative groups.

Conclusion: We applied our drug repositioning pipeline to identify novel agents to sensitize drug-resistant tumors in the I-SPY 2+ clinical trial and identified fulvestrant as a potential candidate for multiple molecular subtypes and treatment arms.

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Therapeutics and Clinical Trials #7

Extending the reach of genetic counseling to the safety net: Study design and recruitment challenges of a randomized trial

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Abstract
Genetic counseling (GC) for hereditary breast and ovarian cancer is available mainly in academic settings. Despite equal risk, most low-income public hospital patients remain unaware and untested. Remote counseling may be a solution, but research has been limited to phone counseling. Our study compares in-person, phone, and video conference GC among high-risk patients in three public hospitals to determine the comparative effectiveness of GC across these modes with regard to patients' knowledge, cancer distress, decisional conflict, perceived stress, risk perception, satisfaction, and recall. We also assessed how patient counseling mode preference affects outcomes.

We conducted a multicenter partially randomized preference noninferiority trial with English-, Spanish-, and Cantonese-speaking patients assigned by randomization or patient preference to one of the modes. High-risk patients were identified using a screener in clinics or physician referral. Study staff verified risk by phone, conducted informed consent, and administered a baseline survey. After patients were assigned a mode, they were given a GC appointment and called again within two weeks for a follow-up survey. Power calculations required 270 randomized patients.

A total of 23,633 screener forms yielded 1,574 likely to be high-risk; 681 completed baseline surveys. Race/ethnic composition was 40% Latinx, 26% White, 22% African American, and 9% Asian.

Of these, 571 were counseled, and 551 completed final surveys. The majority (64%) of non-randomized patients chose counseling by phone, 33% in-person, 3% by video.

- Participation exceeded projections, showing that diverse low-income patients were interested in participating in research they deemed relevant.
- Our greatest recruitment challenges were due mostly to settings. Collection of screeners varied by month and/or clinic. Oncologists appreciated the risk services offered, but intensive engagement was necessary with front-line staff/supervisors because of their job demands.
- Partial randomization functioned well. Prior studies showed that many high-risk women refuse randomization for GC. Adding a preference arm created greater inclusiveness and yielded more generalizable findings.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Practice-based safety net research presents numerous challenges that require close partnerships, extensive planning, and highly skilled staff capable of sensitive personnel engagement. The work is rewarded by real-world findings, the sine qua non in efforts to eliminate cancer disparities.

This retreat is supported in part by: an educational grant from the UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103), Genentech, an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Celgene, Merck & Co., and TerSera therapeutics.

Therapeutics and Clinical Trials #8

OP-1250, an oral complete estrogen receptor antagonist (CERAN) that shrinks ER-positive breast tumors in xenograft models

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Abstract
Fulvestrant (FASLODEX) is the most effective endocrine therapy for estrogen receptor positive (ER+) metastatic breast cancer (MBC). Despite this superiority, fulvestrant must be delivered by intramuscular injection and its efficacy appears limited by poor drug exposure. Thus, an oral compound that shares fulvestrant's pharmacodynamic virtues with improved drug exposure might be both more convenient and more effective than fulvestrant. Fulvestrant development was aimed at creating a Complete Estrogen Receptor ANtagonist (CERAN) using the rodent uterine weight gain assay. It is now understood that the ability of fulvestrant to shut off both the AF1 and AF2 transcriptional activation functions of the ER underlies this activity. In contrast to CERANs, selective estrogen receptor modulators (SERMs) such as tamoxifen efficiently shut off AF2 signaling (turned on by estradiol), but incompletely antagonize AF1, a function that is turned on by multiple cell signaling pathways and shown to play a role in the development of endocrine resistance. We have developed a sensitive cell culture assay that distinguish between CERANs and SERMs. Fulvestrant is also a Selective Estrogen Receptor Degrader (SERD), and it has become widely but mistakenly assumed that such ability makes a compound a CERAN. In our assay several SERDs under clinical investigation, including AZD9496 and GDC-0810, were identified as SERMs that exhibited ER-mediated agonism on genes dependent on AF1 activity. Further, these SERM/SERDs stimulate cell proliferation of CAMA-1 and HCC-1500 breast cancer cells even in the absence of estrogen. These proliferation assays may model clinical breast cancer progression in which tumors become less dependent on estrogen and more sensitive to AF1 signaling mediated by SRC family kinases, IGFs, and FGFs. We thus predict that SERM/SERDs will be inferior in preventing and treating resistance compared to CERAN/SERDs.

Guided by our cell culture assay, we have developed the CERAN/SERD OP-1250. OP-1250 completely blocks both AF2 and AF1 activity as seen in cell culture and the ovex mouse uterine weight gain assay. Unlike SERM/SERDs, OP-1250 is a potent inhibitor of CAMA1 and HCC-1500 breast cancer cell proliferation. OP-1250 also is a SERD in a large variety of cell lines including those in which some SERM/SERDs have little activity. OP-1250 achieves high and stable drug exposure in multiple animal species unlike fulvestrant and many SERMs. As might be expected for a compound with this spectrum of activities, OP-1250 shrinks tumors in xenograft models in which fulvestrant (because of limited drug exposure) and SERM/SERDs (because of residual estrogen-like action) fail to shrink the tumors. These models include HCC-1500 xenografts with a wild type ER and HCI-013 patient-derived xenografts with ESR1Y537S. These results suggest that OP-1250 has potential to be a superior compound to treat ER+ MBC, especially in patients whose tumors allow high activity of AF1 and including those with activating mutations ins ESR1. We expect to bring OP-1250 into the clinic shortly.

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Therapeutics and Clinical Trials #9

Radiological complete remission in HER2-positive metastatic breast cancer patients: what to do with trastuzumab?

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Abstract
Background: Patients with HER2-positive metastatic breast cancer (MBC) treated with trastuzumab may experience durable tumor response for many years. It is unknown if patients with durable radiological complete remission (rCR) can discontinue trastuzumab. We analyzed clinical characteristics associated with rCR and overall survival (OS) in a historic cohort of patients with HER2-positive MBC and studied the effect of stopping trastuzumab in case of rCR.

Methods: We included patients with HER2-positive MBC treated with first or second-line trastuzumab-based therapy in eight Dutch hospitals between 2000 and 2014. Data were collected from medical records. We used multivariable regression models to identify independent prognostic factors for rCR and OS. Time-to-progression after achieving rCR for patients who continued and stopped trastuzumab, and breast cancer-specific survival were also evaluated.

Results: We identified 717 patients with a median age of 53 years at MBC diagnosis. The median follow-up was 109 months (IQR 72-148). The strongest factor associated with OS was achievement of rCR, adjusted hazard ratio 0.27 (95% CI 0.18–0.40). RCR was observed in 72 patients (10%). The ten-year OS estimate for patients who achieved rCR was 52 versus 7% for patients who did not achieve rCR. Thirty patients with rCR discontinued trastuzumab, of whom 20 (67%) are alive in ongoing remission after 78 months of median follow-up since rCR. Of forty patients (58%) who continued trastuzumab since rCR, 13 (33%) are in ongoing remission after 68 months of median follow-up. Median time-to-progression in the latter group was 14 months.

Conclusions: Achieving rCR is the strongest predictor for improved survival in patients with HER2-positive MBC. Trastuzumab may be discontinued in selected patients with ongoing rCR. Further research is required to identify patients who have achieved rCR and in whom trastuzumab may safely be discontinued.

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Therapeutics and Clinical Trials #10

OneSource: A Framework for Integrating Clinical Care and Research

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Abstract
Today's electronic health record (EHR) systems consist largely of information stored in an unstructured narrative format that lacks consistency in organization, content and terminology. As data are not standardized, there are significant barriers for healthcare providers and researchers to utilize EHRs for secondary uses, such as clinical research and registries. As much as 29% of the operational costs of a large Phase 3 clinical trial are associated with verifying source data and cleaning poor quality EHR-abstracted data. Additionally, manual source data capture and verification can compromise data quality. A comparison of data elements between case report forms for the I-SPY 2 TRIAL and the EHR revealed discordance rates of 3.25% to 14.77% over a 6-month period. These outcomes are the result of a fractured system where care and research are separate.

The goal of the OneSource project is to integrate clinical care and research via developing methods and tools to automate the flow of structured EHR data into external systems, thereby reduce operating costs, save time, and improve data quality for clinical trials. Phase One of the OneSource Project developed a framework for collecting data for clinical trials that populates an Electronic Data Capture (EDC) system directly from an EHR system using consensus-based clinical data standards (e.g., Health Level Seven (HL7), Clinical Data Interchange Standards Consortium (CDISC)).

To achieve the aim of integrating clinical care and research, standardized checklists of clinician-vetted data elements have been developed to enable the collection of high quality data at the point of care- once- and to use many times. Technology platforms will be leveraged that allow for seamless integration of these discrete data elements with the UCSF EPIC EHR as well as data visualization tools that support clinical decision-making.

Phase II of the project, beginning December 2019, aims to apply these solutions to three areas in the setting of breast cancer care: development of an electronic patient reported outcomes platform, creation of an integrated Residual Cancer Burden calculator tool (I-SPY TRIAL primary endpoint), and standardization of the collection of ongoing treatment adverse events. These tools will be tested throughout the UCSF Breast Care Center and the 20 site I-SPY 2 TRIAL to demonstrate feasibility and scalability.

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Therapeutics and Clinical Trials #11

Single-institution Evaluation of Local Recurrence Rates Following Intraoperative Radiation Therapy for Breast Cancer

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Abstract
Intraoperative radiation therapy (IORT) offers a simplified delivery of radiation treatment to breast cancer patients during surgery and has been shown to be non-inferior to traditional external beam radiation therapy (EBRT) for select patients. Utilizing post-surgery follow-up data collected from patients who underwent IORT at UCSF, we seek to evaluate risk of local recurrence and association with demographics, disease characteristics, and receipt of EBRT.

Patients received IORT either as part of a randomized or a single-arm trial. Eligibility was restricted to patients aged 45 or older with small (<3.5cm) ER+, HER2- tumors undergoing partial mastectomy. This cohort included a total of 101 patients with at least 3 years of follow-up data. All accrued patients received a single dose of IORT (20 Gy) by the Ziess Intrabeam® device immediately following tumor excision. The median age at consent was 62.57 years. Following IORT, 25 (24.75%) patients were referred for EBRT. Fisher's exact test was used for analysis of statistically significant differences between the local recurrence and non-recurrence groups.

The median follow-up for the cohort was 60 months following surgery. A total of 6 (5.94%) instances of local recurrence in the index quadrant were reported. The cumulative hazard risk estimate at 5 years following surgery was 2.45%. Mean tumor size at surgery was significantly ($p \leq 0.05$) larger in the group with local recurrence (24.00 mm) than in the group with no recurrence (15.45 mm).There was no other significant correlation between any clinical characteristic and local recurrence.

These further characteristics include tumor grade, cancer subtype, lymph node involvement, and hormone receptor status. Of the 6 local recurrences reported, 2 occurred in the EBRT referral group. There was no significant difference in local recurrence between the group receiving EBRT following IORT versus IORT alone.

The limited correlation between clinical characteristics and local recurrence indicates the accurate accrual of the appropriate population for treatment.The 5-year local recurrence cumulative hazard reported here supports the findings of the original randomized TARGiT-A trial. Our results support that for select patients, IORT is non-inferior for treating early-staged breast cancer.

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Therapeutics and Clinical Trials #12

Comparison of segmentation methods in assessing background parenchymal enhancement as a biomarker for response to neoadjuvant therapy

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Abstract
Breast parenchymal enhancement (BPE) has shown an association with breast cancer risk and response to neoadjuvant treatment. However, BPE quantification is challenging, and there is no standardized segmentation method for measurement. This study investigated the use of a fully automated breast fibroglandular tissue segmentation method to calculate BPE from dynamic contrast-enhanced MRI (DCE-MRI) for use as a predictor of pathologic complete response (pCR) following neoadjuvant treatment in the I-SPY 2 TRIAL. In this trial, patients had DCE-MRI at baseline (T0), after 3 weeks of treatment (T1), after 12 weeks of treatment and between drug regimens (T2), and after completion of treatment (T3). A retrospective analysis of two cohorts was performed: one with 735 patients and another with a final cohort of 340 patients meeting a high-quality benchmark for segmentation. We evaluated three different sub-volumes of interest segmented from bilateral T1-weighted axial breast DCE-MRI: full stack (all axial slices), half stack (center 50% of slices), and center 5 slices. The differences between methods were assessed, and a single-predictor logistic regression model was implemented to determine the predictive performance of each segmentation method. The results showed that the half stack method provided the best compromise between sampling error from too little tissue and inclusion of incorrectly segmented tissues from extreme superior and inferior regions. Our results indicate that BPE calculated using the half stack segmentation approach has potential as an early biomarker for response to treatment in the hormone receptor negative and human epidermal growth factor receptor 2 positive subtype.

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Therapeutics and Clinical Trials #13

A Characterization of the Clinical Outcomes of a Cohort of Women Undergoing Active Surveillance for Ductal Carcinoma In Situ

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Abstract
Introduction: Standard treatment for ductal carcinoma in situ (DCIS) includes surgery, often with radiation and endocrine therapy. However, surgery may sometimes constitute overtreatment, as the rate of progression from DCIS to invasive ductal carcinoma (IDC) is suspected to be < 50%. This study seeks to characterize the clinical outcomes of a cohort of women who elected active surveillance (AS) for DCIS.

Methods: We identified 63 women with DCIS seen at UCSF between 2002 and 2019 who elected AS without pre-planned surgery and with at least two breast MRIs. Patient demographics, clinicopathological variables, decisions, and outcomes were collected and analyzed. Differences in survival were assessed using a log rank test.

Results: Median age at diagnosis was 52.1 +/- 9.5 years, and median follow-up was 4.3 +/- 3.7 years. At presentation, 57 patients had a new diagnosis of DCIS (90.4%), 3 had recurrent DCIS (4.8%), and 3 had positive margins following prior resection of DCIS (4.8%). Of 62 cases with pathologic data, 20 were high grade (32.3%), 31 were intermediate grade (50.0%), and 11 were low grade (17.7%). Of 58 cases with receptor data, 57 were ER positive (97.8%). A total of 57 of the 63 patients received endocrine therapy (90.5%) for a median duration of 2.0 +/- 1.9 years. Of the cohort, 30 patients eventually had surgery (47.6%), 16 of whom had local progression to IDC (25.4%). For 14 of the 16 cases of local progression (87.5%), physicians recommended surgery due to changes on imaging. For 10 of those 14 surgical recommendations (71.4%), the patient delayed surgery for further AS. Patients continuing AS against surgical recommendation were significantly more likely to locally progress to IDC (p=.009). There were no indications of local progression in the 33 patients that did not have surgery (52.4%). There were no significant differences in the clinicopathological variables of patients who progressed to IDC compared to those who did not. No patients died while on AS.

Conclusion: A period of AS with endocrine therapy allows for identification of women at high-risk for local progression and allows a substantial proportion of women with ER positive DCIS to avoid surgery with no evidence of worse outcomes.

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Therapeutics and Clinical Trials #14

Pazopanib (PZ) plus endocrine therapy as treatment for hormone resistant advanced breast cancer (ABC).

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Abstract
Background: A major limitation of endocrine therapy in hormone receptor positive (HR+) ABC is the development of resistance. Preclinical data suggests that higher levels of vascular endothelial growth factor (VEGF) are associated with endocrine therapy resistance. We conducted a phase II trial to evaluate the clinical benefit (CB) of PZ, a VEGF receptor tyrosine kinase inhibitor (TKI) combined with nonsteroidal aromatase inhibitors (NSAIs) in pts with ABC resistant to NSAIs.

Methods: Eligibility included postmenopausal women with HR+ ABC and progressive disease (PD) after at least one month of NSAIs. Treatment was PZ 800 mg/day plus either letrozole or anastrozole. The primary endpoint was clinical benefit rate at 12 weeks (CBR12, wks). Secondary endpoints were PFS and safety. A CBR of 20% was considered a clinically meaningful comparison to the expected CBR of < 5% with continued NSAIs after PD. Using a 2-stage design, stable disease in at least 1 of the first 13 pts allowed continued enrollment to a planned 28.

Results: 32 pts were enrolled; 28 are evaluable for study endpoints and all patients completed the study. The median age was 58 years (range: 41-77). Pts were heavily pre-treated, with a median 2 prior hormone therapies (range 1-6) and 1 prior chemotherapy (range 0-8). 8 pts (28.6%) stopped treatment due to adverse events (AE) including hypertension (HTN), fever, transaminitis, nausea, vomiting, rash, hand foot syndrome and pulmonary embolism (PE); 6 pts progressed before wk 12. CBR12 was 46.4% (12 SD, 1 PR); CBR24 was 25% (5 SD, 2 PR). Median PFS for pts with CBR12 was 24 wks. 7 pts had PFS > 6 months (24, 32, 36, 36, 48, 184 and 274 wks). Two pts had PFS > 3 years (184 and 274 weeks). The most common grade 1/2 AE were nausea (48.2%), fatigue (33.3%), diarrhea (29.6%), back pain (22.2%), and arthralgias (22.2%). Grade 3/4 AEs included HTN (3/28; 11.1%), transaminitis (3/28; 11.1%), headache (2/28; 7.4%), heart failure, vertigo, nausea, oral pain, vomiting, fever, fatigue, and hypokalemia (one patient each: 3.7%).

Conclusions: The addition of PZ to NSAIs resulted in a CBR12 of 46.4%, and a CBR24 of 25% in pts with heavily pre-treated ABC resistant to NSAIs. These results support clinical efficacy of antiangiogenic TKI in HR+ ABC, and suggest benefit in hormone resistant disease. Expected toxicities resulted in early discontinuation in 28.6%, which limited drug exposure.

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