SABCS17 Summary

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The San Antonio Breast Cancer Symposium (SABCS) is an annual conference designed to provide state-of-the-art information on the experimental biology, prevention, diagnosis, and therapy of breast cancer to an international audience of academic and private physicians and researchers. SABCS welcomes attendance by informed patient advocates representing patient advocacy, education & survivor support organizations.

I was a first-time attendee as a patient advocate for Living Beyond Breast Cancer. I plan to apply for the Alamo Breast Cancer Foundation scholarship to attend the symposium again next year. The scholarship program granted all patient advocates the opportunity to attend some of their sessions, but for those I was not able to attend, I am including notes from *Anne Loeser (noted in italics, with her permission)*. My notes are tailored to the metastatic community, but I think this summary will benefit all breast cancer survivors interested in learning more about the current research. **Promising drugs** are highlighted in bold red text throughout the document and I created a table of these drugs with corresponding clinical trials for each breast cancer subtype. All clinical trials accept metastatic patients, and the majority listed here are actively recruiting.

The overarching take home message from this meeting is that cancer treatments have become more tailored to the individual- sometimes we see a de-escalation of treatment, other times more aggressive treatments, but it depends on each individual case. The need for more integrative cancer care that takes into consideration patient-reported outcomes or PROs (i.e. outcomes important to the patient, such as reducing side effects & quality of life) was also highlighted throughout the conference. If you have any corrections, suggestions for improvement, etc. please feel free to email me at chodgdon513@gmail.com

Table of Contents

(click on an item to navigate to that section)

Challenges in Advanced/Metastatic Breast Cancer (ABC/MBC)

Evolutionary History & Genomic Landscape of MBC

Adrian V. Lee, PhD; University of Pittsburgh Cancer Institute; Pittsburgh, PA

- Primary and recurrent metastatic tumor tissue greatly differ; Metastatic tumors are genomically distinct & have significantly more coding mutations and copy-number alterations than their matched primary tumor of origin; Metastatic tumors have less genetic diversity between them than matched primary tumors
- Genomic alterations during tumor progression & treatment → 36% of patients switch at least one receptor (ER/PR/HER2) during tumor progression

Hormone Factors

Svasti Haricharan; Baylor College of Medicine; Houston, TX

- Both ESR1 mutations & fusions in ER+ MBC induce resistance to endocrine therapy
- Challenges to the field include the need for more large-scale studies of ER+ MBC to identify 1) association between specific ESR1 perturbations & clinical outcomes, 2) underlying mechanism by which ESR1 mutations/fusions can alter therapeutic response, 3) alternative strategies to target MBC patients with specific mutations/fusions, 4) causes underlying the increased incidence of ESR1 mutations/fusions in MBC
- A study looking at the frequency of ESR1 & progesterone (PGR) mutations in patients newly diagnosed with ER+ MBC revealed that PGR mutations are more common & the coincident mutations (mutations occurring at the same time) in ESR1 & PGR may be an important biomarker for worse outcomes. Read more here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4795822/
- ESR1 mutations confer novel metastatic functions in genome-edited breast cancer cell models, but more well-characterized ER+ cell line models are needed to study the effect of ESR1 mutations on growth & migration. Read more here: https://www.ncbi.nlm.nih.gov/pubmed/28535794
- In a Baylor study that looked at the gene fusion events in both early stage (ESR1-NOP2) and late stage (ESR1-YAP1 & ESR1-PCDH11x) breast cancers, researchers found that only specific ESR1 fusions (those found in late stage breast cancers) can drive endocrine therapy resistance & poorer outcomes, yet can be treated with CDK4/6 inhibition; Study provides pre-clinical rationale for targeting ESR1 mutant breast cancers

Luminal ABC: optimal use of all available options?

Angela M. DeMichele, MD, MSCE; University of Pennsylvania; Philadelphia, PA

- Luminal ABC has resistance mechanisms for CDK 4/6 inhibitors including retinoblastoma protein (Rb) mutations & endocrine therapy resistance
- Clinical trial approaches to overcoming resistance → 1) Add additional agents: PI3K, mTOR, 2) switch endocrine therapies, 3) provide CDK inhibitor-free period then re-challenge (reintroduce same therapy following relapse or progression)
- Combination of CDK/mTOR inhibition is consistent & comparable in prolonging progression-free survival (PFS) in combination with endocrine therapy in MBC
- New insights → CDK4/6 inhibitors have functions beyond the cell (e.g. metabolism, immune microenvironment) & have synergy with the stress survival mechanism for cancer cells (autophagy)

Local therapy of limited disease in ABC: what is the evidence?

Seema A. Khan, SM, MB; Northwestern University; Chicago, IL

- 6% of new breast cancers in the US are diagnosed metastatic, much of which is oligometastatic (i.e. limited number of mets, involving single or few organs); 50% of patients with newly diagnosed mets who go on clinical trials are oligometastatic

- Clinical data suggest patients with oligo mets are potentially curable, but rapid adoption of local therapy approaches to oligo mets has occurred in the absence of strong supporting clinical data- fundamental questions remain
- Biology and biomarkers that underpin an oligometastatic state remain unknown
- Implications for treatment of oligometastasis today: 1) lesions are few & small, 2) disease-free survival (DFS) is long, 3) complete removal of mets appears feasible, 4) toxicity is low
- Implications for treatment of asymptomatic intact primary tumor: 1) distant disease is well controlled, 2) breast conservation should be performed preferentially if feasible, 3) bilateral prophylactic surgery is strongly discouraged
- ECOG 2108 trial- women with stage IV oligo mets that have responded to or have stable disease after receiving systemic therapy will be randomized to receive early local therapy (i.e. surgery, radiation) vs. delayed local palliative therapy, if needed. The rationale for the study is that early surgery may have fewer side effects & improve recovery, but palliative surgery or radiation may help patients with advanced breast cancer live more comfortably
- More trials needed re: treatment of oligo mets & asymptomatic intact primary tumors

Novel approaches for selection & monitoring of treatment in MBC
Prof. Dr. Carsten Denkert; Charite Berlin; Berlin, GERMAN

- Re-testing of ER, PR, HER2 is recommended for recurrences
- Which markers are relevant for current clinical trials in ABC → ESR1, PIK3CA, & BRCA mutations, TILs, PD-L1, mutational load

Breast cancer PDXs as models for metastatic progression & therapeutic response
Alana L. Welm, PhD; University of Utah; Salt Lake City, UT

- Patient-derived xenografts **(**PDXs) are proving to be accurate models of human breast cancer, though not perfect
- Unmet need: Determine which patient-derived models best represent actual tumors which can have impact on pre-clinical models for drug development

What about neoadjuvant trials and pathological complete response?
Hope Rugo, MD; University of California; San Francisco, CA

- Immunotherapy more effective in MBC patients that are treatment naïve

Balancing active treatment and palliative care in ABC patients
Thomas J. Smith, MD; Johns Hopkins Sidney Kimmel Comp. Cancer Center; Baltimore, MD

- ASCO now strongly recommends concurrent palliative care (PC) with oncology care for every advanced cancer patient
- All evidence suggests better quality of life, fewer symptoms, equal or better survival, & less cost for patients that utilize PC
- Oncologists should start thinking of transition to best end of life care when patient has 6-12 months to live
- Oncologists should employ TEAM Concept: Time → an extra hour a month on PC, Education → symptom management, realistic options for txt, advanced care planning, Assessment → use communication prompts to talk to patients, Management → oncologists MUST start the conversations or bring in PC team (Note: those who HAVE end of life discussions are more likely to be satisfied)

Landscape of Mutations in MBC- Spotlight on Male & Lobular Breast Cancer

Spotlight on male breast cancer

Norah Lynn Henry, MD, PhD; Salt Lake City, UT

- 15-20% of men with breast cancer have an identifiable pathogenic/likely pathogenic variant (variant is inherited & development of symptoms is more likely, but not certain) using standard gene panels; BRCA2 is most common
- All men with breast cancer should be tested with a gene panel that contains a minimum of BRCA1, BRCA2, CHEK2, PALB2, & ATM
- For HR+ male breast cancer, Tamoxifen is standard of care & preferred option. If an aromatase inhibitor (AI) is used, it should combine AI + gonadotrophin-releasing hormone agonists (GnRHa) (ESO-ESMO 2015 Guidelines)
- Phase 2 Male-GBG54 trial (NCT01638247) is first trial to evaluate the efficacy & safety of different endocrine treatment options in male breast cancer. Trial compared 3 treatment arms: GnRHa + Tamoxifen vs. GnRHa + Exemestane (AI) vs. Tamoxifen alone; The GnRHa arms led to similar hormone profiles, but larger studies are needed to obtain efficacy data as well as quality of life difference measures in GnRHa + Tamoxifen vs. GnRHa + AI
- Molecular subtyping of male breast cancer using RNA sequencing of 152 samples, of which the first 73 samples were analyzed to reveal 2 distinct subgroups (M1 & M2); the M2 subgroup of male breast cancer associated with better relapse-free survival (RFS); Additional studies planned to provide thorough description of subgroups & analysis of markers associated with RFS

Invasive lobular breast cancer- pathology, genomics, & biology

Jorge S. Reis-Filho, MD, PhD; Memorial Sloan Kettering Cancer Center; New York, NY

- Variants of invasive lobular cancer (ILC) include classic, alveolar, trabecular, solid, mixed, pleomorphic, histiocytoid, signet ring
- ILC makes up 8-14% of all invasive cancers & the vast majority are ER+, PR+, HER2-negative and have the Luminal A phenotype
- As compared to invasive ductal carcinoma (IDC), ILCs are often larger at diagnosis, have lower responses to chemo, potential greater benefit from aromatase inhibition, & have more frequent mutations affecting CDH1, FOXA1, TBX3, PTEN, HER2, & HER3
- Inactivation of E-cadherin encoded by the CDH1 gene causes the phenotype of lobular carcinomas

Adrian V. Lee, PhD; University of Pittsburgh Cancer Institute; Pittsburgh, PA

- Genomic alterations are largely unchanged between metastatic sites of invasive lobular cancer (ILC), but metastatic invasive ductal carcinoma (IDC) and ILC are largely distinct.
- ILCs exhibit a unique metastatic pattern whereby cells grow single file through the stroma with little disturbance of normal tissue making detection difficult
- Many unique alterations in metastatic ILC may be targetable; Frequently altered genes include mammary transcription factors (e.g. RUNX1, CBFB, TBX3) & AKT pathway genes (63% in metastatic ILC); ESR1 & NF1 variants are common in metastatic ILC
- Check out the new website from Lobular Breast Cancer Alliance: https://lobularbreastcancer.org

Steffi Oesterreich, PhD; University of Pittsburgh; Pittsburgh, PA

- Unique features of ILC include discohesive cells that grow linearly which allows more interaction with the tumor microenvironment, increased multifocality & bilaterality, extreme hormone sensitivity, & more late distant recurrences- less to liver & lung, but more to unique sites (e.g. ovary, peritoneum)

- Endocrine resistant ILC models show an increase in fatty acid synthase (FASN) & cholesterol metabolism (SREBP1) as well as overexpression of Fibroblast Growth Factor Receptor (FGFR4); FGFR4 is a new potentially druggable target in endocrine resistant metastatic ILC

Tackling breast cancer diversity
Nicholas C. Turner, PhD, FRCP; Institute of Cancer Research & Royal Marsden; London, UK

- Dying tumor cells release small pieces of DNA into bloodstream aka circulating tumor DNA (ctDNA); Liquid biopsies can be obtained while undergoing treatment to monitor tumor progression- may provide warning when tumors develop resistance & may guide next best therapy
- Longitudinal liquid biopsies are required to monitor adaptive evolution in tumors

Biological Targets for Breast Cancer- Androgen, Progesterone & Glucocorticoid Receptors

Per A. Loeser: It was noted that in clinical trials that leverage or study biomarkers, a common problem is that the cutoff for positivity for the specific biomarker is not clearly defined, and hence future studies should endeavor to quantify cutoff points where feasible. Furthermore, it is important that these studies include a group of patients without the biomarker as well as a group of patients with the biomarker for comparison.

Androgen, Progesterone & Glucocorticoid Receptors: Drivers of Tumor Progression
Moderator: Suzanne A.W. Fuqua, PhD; Baylor College of Medicine; Houston, TX

- Estrogen receptors (ER) couple with androgen (AR), progesterone (PR) and glucocorticoid receptors (GR) to gain resistance to estrogen inhibition

Androgen receptor in breast cancer; When might it serve as a suitable target?
Jennifer K. Richer, PhD; University of Colorado; Aurora, CO

- 77% of 2,171 invasive breast cancers were androgen receptor positive (AR+) by ImmunoHistoChemistry (IHC)
- Many triple negative breast cancer (TNBC) tumors are androgen receptor (AR+) or glucocorticoid receptor (GR+)
- AR overexpression leads to Tamoxifen/AI resistance
- High AR:ER ratio predicts poor outcome & is often increased in resistant disease; 3x more likely to recur while on Tamoxifen
- When ER signaling is blocked, tumors can switch from dependence on ER to AR
- Hypothesis: AR inhibition may improve response to HER2/PI3K/mTOR inhibition
- See table in the TNBC section for clinical trials for AR+ breast cancer patients

Tracking progesterone receptor actions in breast cancer progression: Jekyll & Hyde
Carol A. Lange, PhD; University of Minnesota; Minneapolis, MN

- Early events in breast cancer development impact hormone signaling
- 80% of breast cancers are positive for estrogen or progesterone
    - Luminal A breast cancers
        - 50-60% of all BCs (high ER+ & PR+)
        - High ER & markers of ER function (PR, FOXA1, GATA3)
        - Low mitotic activity (Ki67)
        - Good response to endocrine therapy
    - Luminal B breast cancers
        - 15-20% of all BCs (low ER+, PR-low/null)
        - Increased expression of proliferative genes (Ki67 high)
        - HER2+/-

        - Insensitive to endocrine therapy; Good response to neoadjuvant chemo
- Frequent early events in luminal breast cancer
    - C-Src co-overexpression with EFGR family members (~70%)
    - Increased ERK1/2 MAPKs (~50%)
    - PIK3CA gain of function mutations (~45%)
    - PTEN loss (30%) or PIK3CA amplification (10%)
    - Mutant p53 (17% luminal A; 41% luminal B)
    - Upregulation of cyclin D1 (29% luminal A; 58% luminal B)
    - Gain of CDK4 (14% luminal A; 25% luminal B)

* This was my first time hearing about molecular subtypes of breast cancer, to learn more click HERE. The molecular subtype of your tumor is not part of your pathology report and is not used to guide your treatment.

Modulating glucocorticoid receptor function in breast cancer
Suzanne D. Conzen, MD; University of Chicago; Chicago, IL

- In TNBC, high glucocorticoid receptor (GR) expression (~30% of primary tumor) is associated with higher relapse & drives tumor cell survival gene activation
- Novel GR modulators (GR antagonists) can block GR activity, increasing sensitivity to chemotherapy
- In ER+ breast cancers, it is hypothesized that GRs modulate ER transcriptional activity whereby GR antagonists can slow proliferation

Drugging protein synthesis in cancer therapy
Robert J. Schneider, PhD; New York University; New York, NY

- 50-80% of cancer cell energy goes into protein synthesis; The signal for cancer cell division is the doubling of protein mass
- Cancer mets & drug resistance all depend on selective mRNA translation
- Oncogenic mRNA translation provides ability to target multiple pathways
- mTORC 1/2 inhibitors are strong protein synthesis inhibitors (~70% have upregulation of mTORC)
- Most studies dose to toxicity of mTOR inhibitors which results in increased toxicity, but not specificity; one can dose an mTOR inhibitor by only 20% to reduce toxicity

Progress, paradigms, and pathways of long non-coding RNAs in cancer
Liuqing Yang, PhD; UT MD Anderson Cancer Center; Houston, TX

- LncRNA (long non coding) are emerging as breast cancer risk genes as well as markers of drug resistance
- Deregulation of LncRNAs lead to hyper- or hypo-activation of cancer signaling, leading to resistance to current targeted therapies
- Targeting LncRNA alone or a co-targeting strategy may improve the efficacy of current targeted cancer therapy

Circulating complexes of stromal and tumor cells in breast cancer metastasis
Dorraya El-Ashry, PhD; University of Minnesota; Minneapolis, MN

- Metastasis is facilitated by circulating cancer-associated fibroblasts (cCAFs) in the tumor microenvironment through mechanisms yet to be determined
- Presence of cCAFs in 30/34 (88%) patients with metastatic disease and in 3/13 (23%) patients with localized breast cancer with long-term disease-free survival; No cCAFs as defined were detected in healthy donors
- cCAFs are found in all stages of breast cancer & increase in incidence & number with stage

- Both cCAF and circulating tumor cells (CTC) were significantly greater in the metastatic group compared with the localized group, suggesting cCAF may complement CTC as a clinically relevant biomarker in metastatic breast cancer

HER2+ Breast Cancers

Adjuvant therapy for HER2-positive breast cancers: Is less more?
Ruth M. O'Regan, MD; University of Wisconsin; Madison, WI

- In the ExteNET Phase III clinical trial (more details in "Noteworthy Clinical Trial" section), extended HER2-blockade with Neratinib (Nerlynx) & reduced recurrence in HR+/HER2+ higher risk breast cancers
- In the APHINITY phase III clinical trial, the addition of Pertuzumab (Perjeta) to adjuvant regimens improves disease free survival (DFS), but this is restricted to node-positive breast cancers
- Cross-talk between ER & HER2 → Inhibition of HER2 increases signaling through ER; ER signaling is increased in HER2+ cell lines that are resistant to HER2-directed agents
- Inhibition of HER2 without inhibition of ER may increase ER signaling allowing ER to act as an escape mechanism
- There may be a subset of ER+ HER2+ breast cancers where ER inhibition is critical, perhaps more important than chemotherapy
- Dual HER2-blockade with endocrine therapy may be optimal in triple positive breast cancers
- A subset of HR+ HER2+ cancers have luminal A phenotype and appear driven by ER

Can we improve treatment tailoring in advanced HER2+ breast cancer?
Martine J. Piccart, MD, PhD; Institut Jules Bordet; Brussels, BELGIUM

- Liquid biopsies & molecular imaging studies deserve more interest in advanced HER2+ breast cancers & should be pursued
- New Drugs (see table below): Anti-HER Tyrosine Kinase Inhibitors (TKIs), Antibody-drug Conjugates (ADCs), Anti-HER antibodies, Bi-specific antibodies
- New Combos: Anti-HER2 (Trastuzumab or Pertuzumab or TDM1) + mTOR or + PI3K or + CDK 4/6 Inhibitors or + Anti PD-1/Anti PD-L1
- Resistance to anti-HER2 therapy was reversed by CDK 4/6 inhibitors in cell lines; CDK 4/6 inhibitors may push the field forward

2017 guidelines for HER2 testing
Robert B. Jenkins, MD, PhD; Mayo Clinic; Rochester, MN

- Revision of 2013 guidelines for IHC & ISH testing will be released soon to improve accuracy of HER2 testing
- Definition of IHC 2+ equivocal cases (low expressing-HER2+ breast cancer) remains unclear
- Mayo Clinic began following up equivocal IHC 2+ cases with a 17p arm probe; Resulted in converting equivocal (ambiguous) cases to being HER2+
- The National Surgical Adjuvant Breast & Bowel Project (NSABP) B-47 clinical trial showed no benefit for adjuvant trastuzumab to chemo in low expressing-HER2+ early breast cancer

Spotlight on Novel Drugs / Predicting Response for HER2+ Breast Cancer
Aleix Prat, MD, PhD; IDIBAPS Hospital Clinic; Barcelona, SPAIN

- **Trastuzumab deruxtecan (DS-8201a)** is a highly potent antibody-drug conjugate (ADC) composed of anti-HER2 antibody (trastuzumab) & a cytotoxic agent (exatecan); DS-8201a binds to HER2 receptors & is internalized by the cancer cell where the exatecan is released which can stop tumor cell growth & induce tumor cell death; Designated as breakthrough therapy in Aug 2017 for Herceptin/Perjeta/Kadcyla-resistant HER2+ breast cancer

- Phase 1 study of DS-8201a shows overall response rate (ORR) of 35/57 (61%) in HER2+ patients & 6/19 (31.6%) in HER2+low patients
- **U3-1402** is an ADC composed of an anti-HER3 antibody (Patritumab) & cytotoxic agent (DX 8951); U3-1402 binds to HER3 receptors & is internalized by the cancer cell where DX 8951 is released which can inhibit DNA replication & induce cell death of HER3-overexpressing tumor cells
- **Pyrotinib (HTI-1001)** binds to both EGFR & HER2 receptors which may result in inhibition of tumor growth & formation of blood vessels (angiogenesis) in EGFR/HER2 expressing tumor cells
- Phase 1 study of Pyrotinib shows ORR = 50% in 38 patients & of those, a significantly higher ORR (83%) for patients that are trastuzumab naïve
- Phase 2 comparing Pyrotinib + chemo vs. Lapatinib + chemo; Study shows progression free survival (PFS) of 18 mo. (pyro+chemo) vs. 7 mo. (lap+chemo) irrespective of prior trastuzumab
- **Tucatinib (ONT-380)** binds to HER2 receptors & inhibits tumor cell proliferation & induces tumor cell death in HER2-expressing tumor cells; Can cross the blood-brain barrier (BBB); HER2 Climb & other trials with Tucatinib are listed in table below
- **Neratinib (HKI-272)** binds to the cysteine residue in the ATP-binding pockets of both HER2 & EGFR which can inhibit tumor cell proliferation & vascularization & induces tumor cell cycle arrest & death; Can cross the BBB; FDA approved in July 2017 for early stage HER2+ BC

Table 1: Novel Drugs & Corresponding Clinical Trials for HER2+ Breast Cancer

KEY: STK = Serine-Threonine Kinase Inhibitor; TKI = Tyrosine-Kinase Inhibitor; ADC= Antibody-drug conjugate; AR= Androgen Receptor

Drug Category	Generic Name	Code Name	Brand Name	Specific Target	Clinical Trial
STK	Abemaciclib	LY2835219	Verzenio	CDK4/6	NCT02308020 NCT02675231
TKI	Afatinib	BIBW 2992 MA2	Gilotrif	EGFR/ HER1/2/4	NCT01125566
Misc Inhibitor	Alpelisib	BYL719	N/A	PI3K	NCT02167854
Therapeutic Antibody	Atezolizumab	MPDL3280A	Tecentriq	PD-L1	NCT02924883 NCT03125928
Misc Inhibitor	Buparlisib	BKM120	N/A	Pan-PI3K	NCT01470209 NCT01570296 NCT02439489
Therapeutic Antibody	Durvalumab	MEDI4736	Imfinzi	PD-L1, CD80	NCT02318277 NCT02499328 NCT02586987 NCT02725489
STK	Everolimus	RAD001	Afinitor	mTOR	NCT02152943
Hormone Therapy	Enzalutamide	ASP9785/ MDV3100	Xtandi	AR	NCT02091960
Therapeutic Antibody	Margetuximab	MGAH22	N/A	HER2	NCT02492711 NCT03133988
TKI	Neratinib	HKI-272	Nerlynx	HER1/2/4	NCT01670877 NCT01953926 NCT02236000 NCT02673398

					NCT03101748 NCT03289039
Therapeutic Antibody	Nivolumab	MDX-1106	Opdivo	PD-L1	NCT02099058
STK	Palbociclib	PD0332991	Ibrance	CDK4/6	NCT03054363
Therapeutic Antibody	Patritumab	AMG 888/ U3-1287	N/A	HER3	NCT01042379
Therapeutic Antibody	Pembrolizumab	MK-3475	Keytruda	PD-L1	NCT03032107 NCT03199885
Misc Inhibitor	Pilaralisib	SAR245408/ XL147	N/A	PI3K	NCT01082068
TKI	Poziotinib	HM781-36B	N/A	HER1/2/4	NCT02544997 NCT02659514
TKI	Pyrotinib	HTI-1001	N/A	EGFR/ HER1/2/4	NCT02361112 NCT02500199 NCT02973737 NCT03080805
STK	Ribociclib	LEE011	Kisqali	CDK4/6	NCT02657343
Misc Inhibitor	Taselisib	GDC-0032	N/A	P13K	NCT02390427
ADC	Trastuzumab deruxtecan	DS-8201a	N/A	HER2	NCT03248492
TKI	Tucatinib	ONT/ARRY-380	N/A	HER2	NCT02614794 NCT03054363
Therapeutic Antibody	N/A	GBR 1302-101	N/A	CD3/ HER2	NCT02829372
Therapeutic Antibody	N/A	LJM716	N/A	HER3	NCT02167854
Therapeutic Antibody	N/A	MCLA-128	N/A	HER2/3	NCT02912949
ADC	N/A	MEDI4276	N/A	HER2	NCT02576548
ADC	N/A	MM-302	N/A	HER2	Failed to improve PFS
ADC	N/A	SYD 985	N/A	HER2	NCT03262935
ADC	N/A	U3-1402	N/A	HER3	NCT02980341
ADC	N/A	XMT-1522	N/A	HER2	NCT02952729
Therapeutic Antibody	N/A	ZW25	N/A	HER2	NCT02892123

Hormone & Estrogen Receptor Positive (HR/ER+) Breast Cancers

Drug target discovery: how to go about it?

Markus Warmuth, MD; H3 Biomedicine; Cambridge, MA

- Trends suggest mutations are scattered in pathway rather than in a single target
- Emergence of ER mutations correlates with resistance to AIs
- **H3B-6545** showing significant potency across panel of ER breast cancer lines after progression on an aromatase inhibitor (AI) in ER+/HER2-neg patients

Direct regulation of ER transcriptional activity by NF1

General Session Discussion

- Neurofibromatosis type 1 (NF1) is s key tumor suppressor
- NF1-deficient ER+ breast cancer tumors correlate with Tamoxifen resistance & poor outcomes

- Fulvestrant remains effective against NF1-deficient ER+ tumors, but is even more effective when combined with Ras inhibitors- apoptosis was induced *in vitro* (conducted within the confines of a lab), and tumor regression *in vivo* (conducted on people in clinical trials)
- NF1-deficient ER+ tumors may be more effectively treated by co-targeting Ras & ER

Spotlight on Endocrine Resistance Mediated by CDK4/6, FGFR, and PI3K
Shom Goel, MD, PhD; Dana-Farber Cancer Institute; Boston, MA

- CDK 4/6 inhibitors improve outcomes for patients with ER+ (e.g. **Palbociclib, Abemaciclib, & Ribociclib**)
- Combination approaches show synergy in the lab, but it can be difficult to decide which node to target (e.g. HER2, PI3K, mTORc1/2, IGF-1R) - toxicities of combos may guide choices

Gordon B. Mills, MD, PhD; UT MD Anderson Cancer Center; Houston, TX

- FGFR (Fibroblast Growth Factor Receptor) amplification occurs in ~15% of breast cancers; it may signify resistance to hormone therapy & CDK 4/6 inhibitors, suggesting that inhibitors of FGFR may be a promising target for treatment of ER+ breast cancer (e.g. **Erdafitinib (JNJ-42756493), Nintedanib (BIBF1120), AZD4547, Debio 1347, & INCB054828**)
- 188 patients were profiled for FGFR1 amplification, the majority (64%) were ER+/HER2-neg; Of the 188 ER+ patients, 66% showed intermediate to high proliferation rates
- Trials underway comparing CDK inhibitors + hormone therapy vs. FGF inhibitors + CDK inhibitors + hormone therapy (see trials listed in table below)

Todd Miller, PhD; Geisel School of Medicine at Dartmouth; Lebanon, NH

- Activated PI3K/MAPK pathway predicts lack of benefit from adjuvant Tamoxifen, but non-activated pathway predicts benefit from Tamoxifen. Thus the rationale for co-targeting PI3K & ER
- **GDC-0077** induces regression of PIK3CA-mutant breast cancer xenografts & enhances anti-tumor efficacy of Ibrance & Fulvestrant

Spotlight on Endocrine Therapy
Cynthia Ma, MD, PhD; Washington University, St. Louis, MO

- PIK3CA mutation occurs in ~40% of ER+ breast cancers; Crosstalk between ER & PI3K signaling is well established
- LORELEI trial looked at postmenopausal ER+/HER2-neg patients with operable breast cancer that received Letrozole + Taselisib vs. Letrozole + Placebo; Results showed the overall response rate (ORR) was higher in the Taselisib arm & in PIK3CA mutant ER+ breast cancer
- Pan-PI3K Inhibitors: **Buparlisib, Pictilisib**
- p110-alpha selective PI3K Inhibitors: **Taselisib, Alpelisib**
- Awaiting results for phase III trials of AI resistant HR+ MBC
    - SOLAR1: Fulvestrant + Alpelisib vs. Fulvestrant + Placebo
    - SANDPIPER trial: Fulvestrant + Taselisib vs. Fulvestrant + Placebo

Matthew P. Goetz, MD; Mayo Clinic; Rochester, MN

- SWOG S0226 trial looked at HR+/HER2-negative MBC patients that received Anastrozole (Arimidex) + Fulvestrant (Faslodex) vs. Anastrozole alone; *Per A. Loeser- study reported the Fulvestrant/Anastrozole combo improved PFS and long-term Overall Survival (OS); there was a median OS of 49.8 months, which is the longest ever reported for this type of patient. The combination appeared to be of special benefit to patients with no prior endocrine therapy, and/or who recurred after 10 years following a diagnosis of early stage disease.*

- **Elacestrant (RAD1901)** is a selective estrogen receptor down-regulator/degrader (SERD) & as a single agent showed an overall response rate of 27.3% in heavily pre-treated ER+/HER2-neg breast cancer patients (N=22). A potentially pivotal phase 2 clinical study of Elacestrant monotherapy for women with advanced or metastatic ER+/HER2- breast cancer is expected in early 2018
- Another SERD, **GDC-0927**, also demonstrated antitumor activity in heavily pre-treated & ESR1 mutant breast cancer with no toxicity concerns
- Value of these studies suggest it may be possible to identify subgroups of patients with metastatic ER+ that can be treated with endocrine monotherapy
- Approximately 30% of TNBCs express the estrogen receptor beta (ERβ), which is different from the estrogen receptor alpha (ERα), & is what is tested for now in the clinic; ERβ is a tumor suppressor and when present in TNBC is associated with better outcomes; pre-clinical work at the Mayo Clinic shows that ERβ may be a potential drug target; Clinical trials at the Mayo Clinic are being developed & should be recruiting in late 2018. Learn more HERE

Angelo Di Leo, MD, PhD; Hospital of Prato; Prato, ITALY

- A PI3K inhibitor is the best "partner" for a CDK 4/6 inhibitor after progression on a CDK 4/6 inhibitor regimen; Pyruvate dehydrogenase kinase isozyme 1 (PDK1) inhibition re-sensitized cells to Ribociclib. https://www.ncbi.nlm.nih.gov/pubmed/28249908

Study from: Singh H, Howie LJ, Bloomquist E, Wedam S, et al.

- Compared efficacy benefit from the use of CDK4/6 inhibitors in combination with an aromatase inhibitor for the first line treatment of HR+ MBC in older women (median age = 62)
- Study suggests older women with HR+ breast cancer may receive similar benefit from CDK 4/6 inhibitors as younger women, though the treatments are slightly more toxic in patients ≥ 65. The inclusion of a greater number of patients ≥70 in clinical trials will further inform clinicians about the safety and efficacy of CDK4/6 inhibitors in older adults. More here: http://mb.cision.com/Public/3069/2410013/99eebfe249cc5306.pdf

Table 2: Novel Drugs & Corresponding Clinical Trials for HER2-neg/HR+ Breast Cancer

KEY: STK = Serine-Threonine Kinase Inhibitor; TKI = Tyrosine-Kinase Inhibitor; SERD = Selective Estrogen Receptor Down-regulator/Degrader; SERCA = Selective Estrogen Receptor Covalent Antagonists

Drug Category	Generic Name	Code Name	Brand Name	Specific Target	Clinical Trial
STK	Abemaciclib	LY2835219	Verzenio	CDK 4/6	NCT01655225 NCT02057133 NCT02308020 NCT02747004 NCT02763566 NCT02779751 NCT03099174
Misc Inhibitor	Alpelisib	BYL719		PI3K	NCT01872260 NCT02437318 NCT02506556 NCT03056755 NCT03207529

Hormone Therapy	Enzalutamide	ASP9785/ MDV3100	Xtandi	Androgen Receptor	NCT02955394 NCT02953860 NCT03207529
TKI	Erdafitinib	JNJ-42756493		FGFR	NCT03238196
STK	Everolimus	RAD001	Afinitor	mTOR	NCT01857193 NCT02035813 NCT02057133 NCT02258451 NCT02313051 NCT02344550 NCT02387099 NCT02404051 NCT02511639 NCT02732119 NCT02871791 NCT03312738
TKI	Nintedanib	BIBF1120		VEGFR, FGFR, PDGF	NCT02389764
STK	Ribociclib	LEE011	Kisqali	CDK 4/6	NCT01857193 NCT01872260 NCT02632045 NCT02732119 NCT02941926 NCT03096847 NCT03195192
Hormone Therapy	Seviteronel	VT-464		Androgen Receptor	NCT02130700 NCT02580448
Misc Inhibitor	Taselisib	GDC-0032		PI3K	NCT01296555 NCT02285179 NCT02389842 NCT02457910 NCT02465060
STK	Vistusertib	AZD2014		mTORC1/2	NCT02299999 NCT02599714
TKI	N/A	AZD4547		FGFR	NCT01795768 NCT02465060
TKI	N/A	Debio 1347		FGFR	NCT01948297 NCT03344536
Misc Inhibitor	N/A	GDC-0077		PI3K	NCT03006172
SERD	N/A	GDC-0927		Estrogen receptor	NCT02316509
SERCA	N/A	H3B-6545		Estrogen receptor	NCT03250676
TKI	N/A	INCB054828		FGFR2	NCT02393248

Triple Negative Breast Cancers (TNBC)

- **Sacituzumab Govitecan (IMMU-132)** is an Antibody-Drug Conjugate (ADC) composed of an anti-TROP2 antibody (found on surface of many tumor cells) & a cytotoxic agent (SN-38). Sacituzumab govitecant binds to TROP2 & releases SN-38 into the cancer cell, which may inhibit the metastasis of tumor cells. Received breakthrough status in Feb 2016
- *Per A. Loeser's summary: Overall Response Rate (ORR) of 31%, including six Complete Responses (CRs) and 28 Partial Responses (PRs) in 110 patients with metastatic TNBC after receiving IMMU-132.*
- **CB-839 inhibits** glutaminase (which converts glutamine into glutamate), which can halt the proliferation & induce cell death of glutamine-dependent tumors which rely on the conversion of glutamine into glutamate for cell growth & survival. Glutaminase is highly expressed in TNBC
- **Ladiratuzumab vedotin (SGN-LIV1A)** is an ADC composed of the anti-LIV-1 antibody & a cytotoxic agent (MMAE); SGN-LIV1A binds to LIV-1 & is internalized by the tumor cell where MMAE is released which inhibits tumor cell growth & induces tumor cell death in LIV-1 positive cancer cells; LIV-1 proteins are expressed by most MBCs, including TNBC
- *Per A. Loeser's summary: In a Phase 1 study, data were reported from 53 patients (35 with TNBC) with LIV-1-expressing MBC who were treated with SGN-LIV1A. Patients received a median of four prior systemic therapies for metastatic disease. 37% achieved a partial response (PR). The disease control rate (DCR), defined as patients achieving a complete response (CR), PR or stable disease (SD), was 67% and the clinical benefit rate (CBR), defined as patients achieving CR or PR of any duration plus patients achieving SD lasting at least 24 weeks, was 47%. At the time of an interim data analysis, the estimated median progression-free survival for metastatic TNBC patients was 12 weeks, with seven patients remaining on treatment*
- **ENMD-2076** binds to Aurora A kinase which inhibits cell division & proliferation & may prevent the growth of blood vessels (angiogenesis) & induce cell death in Aurora A-overexpressing tumor cells
- In a Phase 2 study, data were reported from 18 patients with advanced TNBC or a P53 mutation with a mean of 1.7 lines of prior therapy. The primary endpoint was clinical benefit rate (CBR), which included a complete response (CR), partial response (PR), or stable disease (SD) >6 mo. PR was observed in 2 patients, & stable disease in 4 patients. Eight patients demonstrated a treatment-induced decrease in cellular proliferation (Ki-67) & microevessel density (CD34) as assessed by IHC. Dose reduction occurred in 8 patients, future clinical trials will explore lower doses
- **TZLS-214 (OH14)** is a c-FLIP inhibitor in the pre-clinical stages; Cellular [1]FLICE-like Inhibitory Protein (c-FLIP) is a master anti-apoptotic regulator and resistance factor; c-FLIP suppresses programmed cell death in tumor cells & is mediated by inhibition of HIF1a (Hypoxia-inducible factor 1-alpha); OH14 reverses the increase in HIF1a signaling seen with paclitaxel

Targeting DNA repair deficiency in triple negative breast cancers (TNBC)
Samuel Aparicio, PhD; The University of British Columbia; Vancouver, CANADA

- **CX5461** is a transcription inhibitor that binds to & inhibits RNA polymerase I which prevents ribosomal RNA synthesis- a process that plays a key role in cell proliferation & survival

[1] FLICE is FADD (Fas-associated death domain)-like IL-1beta Converting Enzyme

- CX 5461 interferes with the DNA repair pathways of triple negative breast cancer & is in phase 1/2 clinical trials (see table below)

New clinical approaches for TNBC
Melinda Telli, MD; Stanford University School of Medicine; Stanford, CA

- Clinical progress is being made with several agents in Phase 3 testing; the results of these trials have potential to change treatment landscape in near term
- PARP inhibitors are in advanced clinical development for BRCA1/2+ metastatic breast cancers: **Veliparib, Olaparib, Niraparib, Talazoparib**; BRCA mutations make cancers unable to repair DNA double-strand breaks; These cancers depend on PARP for DNA repair, therefore inhibition of PARP further suppresses these tumors
- Potential targeted approaches from Phase 1/2 studies include:
    1) Anti-PD-1/L1 Antibodies- **Atezolizumab, Avelumab, Durvalumab, Pembrolizumab.** Showing improved efficacy when combined with other therapies e.g. chemo, PARP, Tyrosine-Kinase Inhibitors & Serine-Threonine Kinase Inhibitors
    2) Antibody Drug Conjugates (ADC)- in clinical trials for the use of ADCs in metastatic TNBC by Yardley D, et al JCO 2015, Forero A, et al SABCS 2016, & Bardia A, et al JCO2017, the overall response rate (ORR) = 28% with **Glembatumumab vedotin**, 37% with **Ladiratuzumab vedotin**, & 30% with **Sacituzumab govitecan**
    3) Androgen Receptor Antagonists - **Bicalutamide, Enobosarm, Enzalutamide, Seviteronel**
    4) AKT Inhibitors- **AZD5363** in early clinical trials; The PI3K/AKT pathway is frequently activated in TNBC; AKT activation can occur through PTEN loss, PIK3CA mutation, AKT mutation or amplification.
    5) ATR Inhibitors- **M6620 (VX-970) & AZD6378**
- There is a need to investigate regulatory issues pertinent to new drug development → Chemo add-on strategies in absence of good rationale; Evaluation of novel therapies where chemo is not the best comparator

Important TNBC study from: Stover DG, Parsons HA, Ha G, Freeman S, et al.

- "Genome-wide copy number analysis of chemotherapy-resistant metastatic TNBC from cell-free DNA." Primary & metastatic TNBC have remarkably similar copy number profiles yet we identify alterations enriched & prognostic in mTNBC. Collectively, these data have potential implications in the understanding of metastasis, therapeutic resistance, and novel therapeutic targets

Table 3: Novel Drugs & Corresponding Clinical Trials for Triple Negative Breast Cancer (TNBC)

KEY: STK= Serine-Threonine Kinase Inhibitor; TKI= Tyrosine-Kinase Inhibitor; ADC= Antibody-drug conjugate; ATR= Ataxia Telangiectasia & Rad3-related; GITR= Glucocorticoid-Induced Tumor Necrosis Factor Receptor

Drug Category	Generic Name	Code Name	Brand Name	Specific Target	Clinical Trials
Misc Inhibitor	Alpelisib	BYL719	N/A	PI3K	NCT02506556 NCT03207529
Therapeutic Antibody	Atezolizumab	MPDL3280A	Tecentriq	PD-L1	NCT02322814 NCT02323191 NCT02605915 NCT02655822

					NCT02708680 NCT02849496 NCT03125902 NCT03202316 NCT03206203
Therapeutic Antibody	Avelumab	MSB0010718C	Bavencio	PD-L1	NCT01772004 NCT02554812 NCT02994953 NCT03217747
Hormone Therapy	Bicalutamide	ICI 176,334	Casodex	Androgen Receptor	NCT02299999 NCT02605486 NCT03090165
Therapeutic Antibody	Durvalumab	MEDI4736	Imfinzi	PD-L/CD80	NCT02299999 NCT02318277 NCT02484404 NCT02586987 NCT02628132 NCT02658214 NCT02725489 NCT02802098
Hormone Therapy	Enobosarm	GTx-024	Ostarine	Androgen Receptor	NCT02971761
Hormone Therapy	Enzalutamide	ASP9785	N/A	Androgen Receptor	NCT02457910 NCT02689427 NCT03207529
Therapeutic Antibody	Glembatumumab vedotin	CDX-011	N/A	Glycoprotein Non-Metastatic gene B (gpNMB)	NCT01997333 NCT03326258
STK	Ipatasertib	GDC-0068	N/A	AKT	NCT03337724
ADC	Ladiratuzumab vedotin	SGN-LIV1A	N/A	LIV-1	NCT01969643 NCT03310957
Misc Inhibitor	Lurbinectedin	PM01183	N/A	Pol II	NCT02454972 NCT02684318
Hormone Therapy	Mifepristone	RU 486/ RU-38486	Mifeprex	Progesterone Receptor	NCT02788981
Misc Inhibitor	Niraparib	N/A	N/A	PARP 1/2	NCT02657889
Misc Inhibitor	Olaparib	AZD2281	N/A	PARP 1/2/3	NCT02299999 NCT02484404 NCT02498613 NCT02511795 NCT02898207 NCT03057145 NCT03162627 NCT03286842 NCT03330847 NCT03344965
Therapeutic Antibody	Pembrolizumab	MK-3475	Keytruda	PD-L1	NCT02971761

ADC	Sacituzumab govitecan	IMMU-132	N/A	TROP2	NCT01631552 NCT02574455
Hormone Therapy	Seviteronel	VT-464	N/A	Androgen Receptor	NCT02130700 NCT02580448
Misc Inhibitor	Talazoparib	BMN-673	N/A	PARP	NCT02034916 NCT02358200 NCT02401347
Misc Inhibitor	Taselisib	GDC-0032	N/A	PI3K	NCT02457910 NCT02465060
Misc Inhibitor	Veliparib	ABT-888	N/A	PARP	NCT02465060 NCT02511795 NCT02595905 NCT02849496
STK	Vistusertib	AZD2014	N/A	mTORC1/2	NCT01884285
TKI	N/A	AZD1775/ MK1775	N/A	WEE1	NCT03012477 NCT03330847
STK	N/A	AZD5363	N/A	AKT 1/2/3	NCT02299999 NCT02465060
STK	N/A	AZD6738	N/A	ATR	NCT03330847
Misc Inhibitor	N/A	AZD8186	N/A	PI3K	NCT01884285
Misc Inhibitor	N/A	CB-839	N/A	Glutaminase	NCT02071862
Misc Inhibitor	N/A	CORT125134	N/A	Glucocorticoid Receptor	NCT02762981
Misc Inhibitor	N/A	CX5461	N/A	Pol I	NCT02719977
STK, TKI	N/A	ENMD-2076	N/A	Aurora A	NCT01639248
Therapeutic Antibody	N/A	INCAGN01876	N/A	GITR	NCT03126110 NCT03277352
STK	N/A	M6620/VX-970	N/A	ATR	NCT02157792

Noteworthy Clinical Trials & Results

- I-SPY2 trial studied whether adding experimental agents to standard neoadjuvant medications increased the probability of pathologic complete response (pCR) over standard neoadjuvant chemotherapy. I-SPY2 model also matched these therapies with biomarker subsets (TNBC, HER2+, HER2+/HR-neg, HR+/HER2-neg).
- I-SPY2 demonstrates that achieving a pathologic complete response (pCR) strongly predicts prevention of later recurrence of incurable metastatic disease. The data support the use of pCR as a primary endpoint for accelerated approval of new drugs. The I-SPY2 model also allows for smaller, faster, and more focused phase 3 trials of new therapies for patients with TNBC & HER2+ breast cancer.
- Six drugs have graduated from I-SPY2 & are identified as excellent candidates for phase 3 trials in their corresponding tumor subtype (see table below); several others are still being evaluated.

Drug	**Predictive probability of success in phase 3**	**Biomarker signature that graduated**
Veliparib (ABT-888)	88%	TNBC
Neratinib (Nerlynx)	79%	HER2+/HR-neg
MK-2206	87%	HER2+/HR-neg
Trastuzumab emtansine or TDM-1 (Kadcyla)	94%	HER2+
Pertuzumab (Perjeta)	90%	HER2+
Pembrolizumab (Keytruda)	99%	HER2-neg

- NeoALTTO: Can we identify biomarkers associated with treatment response in patients with HER2+ early breast cancer treated with neoadjuvant anti-HER2 therapy? Pathological complete response (pCR) rate was associated with high expression of ERBB2/HER2 and low expression of ESR1. Additional results showed higher pCR rates in HR- vs. HR+ & across all treatment arms; HER2+ & TNBC patients had highest pCR rates. Findings support the relevant role of immune and stroma signals in determining the response to anti-HER2 treatments.

- SOLD (Suppression of Ovarian Function Trial): Assessing duration of adjuvant trastuzumab-9 weeks vs. 1 year, combined with adjuvant taxane-anthracycline chemotherapy for early HER2+; 1 year of trastuzumab (Herceptin) remains standard, 9 weeks of Herceptin did not meet inferiority endpoint.

- PANACEA: Trastuzumab (Herceptin) + Pembrolizumab (Keytruda) in HER2+ breast cancers resistant to Herceptin or TDM-1 showed that patients w/ PDL1+ tumors met endpoint with an overall response rate of 15% & an average disease control duration of 11.1 months. Higher levels of sTILs (stromal Tumor Infiltrating Lymphocytes) were associated with improved response & disease control.

- APHINITY Phase III: Chemo + Trastuzumab (Herceptin) + Pertuzumab (Perjeta) vs Chemo + Trastuzumab (Herceptin) + placebo. The addition of Pertuzumab to Trastuzumab lowered the chance of developing invasive breast cancer by 19% compared to trastuzumab alone, but only in patients with node-positive disease.

- ExteNET Phase III: Neratinib vs. placebo after adjuvant treatment with trastuzumab (Herceptin) in patients with early stage HER2+ BC. After 5 yrs., treatment with Neratinib resulted in a 27% reduction of risk of invasive disease recurrence or death vs. placebo. A retrospective analysis looked at benefit of Neratinib after trastuzumab-based therapy in HER2+ patients with PIK3CA mutations, but the current data do not support PIK3CA alterations as a predictive biomarker.

- NALA is an ongoing phase III trial (NCT01808573) that randomized 600 HER2+ MBC patients to receive either Neratinib (Nerlynx) + Xeloda or Lapatinib (Tykerb) + Xeloda. Results expected in 2018.

- MONARCH-3: randomized 493 postmenopausal women with advanced HER2-neg/HR+ breast cancer to receive Abemaciclib or placebo + a nonsteroidal aromatase inhibitor as a 1st line therapy. Abemaciclib + a nonsteroidal aromatase inhibitor was effective as initial therapy, significantly improving progression-free survival (PFS) and objective response rate (ORR) and demonstrating a tolerable safety profile. Abemaciclib was FDA approved in Sept 2017 for women with HER2-neg/HR+ MBC and has demonstrated clinically that it crosses the blood-brain barrier.

- MONALEESA-7: Ribociclib (Kisquali) + Tamoxifen vs. AI + Goserelin in pre-menopausal HR+ /HER2-neg MBC patients showed median progression free survival (PFS) of 23.8 mo. vs. 13 mo. with just endocrine therapy and Goserelin alone. Ribociclib was FDA approved in March 2017 for HER2-neg/HR+ MBC.

- TRINITI-1: *Ribociclib (Kisquali) + Everolimus (Afinitor) + Exemestane (Aromasin) in HR+/HER2-neg MBC patients whose disease progressed on a prior CDK 4/6 inhibitor (any drug with -ciclib ending) or hormone therapy (e.g. Faslodex or Tamoxifen); A Clinical Benefit Rate (CBR) of 50% was seen at 6 mo. & the combo appears to be well-tolerated, with no new safety issues observed.* (*Per A. Loeser)*

- *PALOMA-3 randomized women who had experienced progression on prior endocrine therapy & were treated with Fulvestrant (Faslodex) + either Ibrance (Palbociclib) or placebo; The addition of Ibrance reduced the risk of progression-free survival (PFS) similarly by about 50% regardless of the presence of ESR1 mutations. This is significant because ESR1 mutations typically indicate acquired resistance to hormonal therapy. From: http://www.mdedge.com/oncologypractice/article/111684/breast-cancer/esr1-mutations-found-prognostic-not-predictive (Per A. Loeser)*

- *Abemaciclib (Verzenio) & Pembrolizumab (Keytruda): The combo shows early promise without additional toxicity in HER2-neg/HR+ patients with MBC who received a median of 3 prior therapies. At a 4-month analysis, the objective response rate (ORR) was 14.3%. The rationale for the combo came from preclinical data showing that Abemaciclib may increase T-cell infiltration of tumors with enhanced efficacy when combined with PD-L1 blockade (Keytruda) in the setting of anti–PD-L1 resistant disease.*
  From: http://www.onclive.com/web-exclusives/abemaciclib-pembrolizumab-shows-early-promise-for-hrher2-breast-cancer (Per A. Loeser)

- ABCSG-16 trial showed no benefit to continuing Anastrozole (Arimidex) beyond 7 years in postmenopausal HR+ breast cancers. After 5 years of adjuvant endocrine therapy (Tamoxifen or AI or Sequence), a further extension to 5 additional years did not yield additional outcome

benefit but added toxicity. Learn more: http://www.ascopost.com/News/58332?email=8f7372d195d12c0f442857beab69b2c3cfba92bcc6fff33fc410022e8890a504

- CALGB 40502: Study looked at weekly paclitaxel (Taxol) vs. weekly nab-Taxol or Ixabepilone (Ix) +/- Bevacizumab (Avastin) in chemotherapy-naive MBC. Taxol was better tolerated than both Ix and Avastin and weekly Taxol remains a standard for MBC patients, especially in HR+ disease.

- Combined TEXT & SOFT trials randomized comparison of adjuvant Exemestane + ovarian function suppression (OFS) vs. Tamoxifen + OFS in premenopausal women with HR+ early breast cancer (BC); After 9 yrs. median follow-up, adjuvant Exemestane + OFS, as compared with Tamoxifen + OFS, shows a sustained reduction of the risk of recurrence, but did not improve overall survival. Overall toxicity was NOT significantly worse with Exemestane.

- POETIC (Perioperative Endocrine Therapy Individualizing Care) randomized 4,486 post-menopausal patients with HR+ breast cancer to receive or not receive Anastrozole or Letrozole 2 weeks before surgery aka peri-operative aromatase inhibitor (POAI); No significant evidence that 4 weeks of POAI improved time to relapse (TTR) compared with no POAI, but POETIC trial will provide definitive evidence on the role of 2-week POAI-treated patients.

- EMBRACA phase 3 trial showed that patients with advanced HER2-negative breast cancer with germline (inherited) BRCA mutations had significantly prolonged progression free survival (8.6 mo.) when treated with the PARP inhibitor, Talazoparib, compared to 5.6 mo. when treated with physician's choice of chemo. The overall response rate (ORR) was 62.6% for patients that received Talazoparib and only 27.2% for patients that received chemo.

- ABRAZO phase II trial randomized 84 patients with advanced breast cancer that harbored the BRCA 1/2 mutation and had received prior therapy to receive the PARP inhibitor, Talazoparib. Response rates were 21% among patients who had responded to prior platinum therapy and 37% among patients who had received 3 or more prior lines of chemotherapy, but not a platinum agent.

- OlympiAD phase 3 trial compared PARP inhibitor, Olaparib (Lynparza), to standard chemotherapy in patients with inherited BRCA mutations with MBC that was either HER2-neg/HR+ or triple negative. Tumors shrank in about 60% of patients who received Olaparib, compared with 29% of those who received chemotherapy. At a median follow-up of about 14 months, patients who received Olaparib had a 42% lower chance of cancer progression than those who received chemotherapy.

- BRAVO is an ongoing phase III clinical trial that will randomize HER2-neg patients with inherited BRCA1/2+ MBC to receive either Niraparib (PARP Inhibitor) or physician's choice.

- SWOG1416 is an ongoing phase II clinical trial that will randomize TNBC patients or patients with inherited BRCA1/2+ breast cancer that has come back or has or has not spread to the brain to receive Cisplatin +/- Veliparib (PARP Inhibitor).

- MEDIOLA is an ongoing phase I/II clinical trial that will randomize HER2-neg MBC patients with a BRCA1/2+ mutation to receive a PARP Inhibitor (Olaparib) + an immunotherapy drug (Durvalumab).

- S1200 showed that acupuncture significantly reduced joint pain for postmenopausal women with early-stage breast cancer receiving treatment with an aromatase inhibitor; Authors feel there is now sufficient evidence to support insurance coverage of acupuncture for aromatase inhibitor (AI) induced joint pain.

FDA Updates

Adapted from notes written by A. Loeser

a. Reducing the Maximum Tolerated Dose Due to Drug Toxicities: Dr. Tatiana Prowell of the FDA strongly stated that patients do not have to use the FDA-approved dose of a drug if there is reason for using a lower, less toxic dose. She specifically stated, "Dose is something that we are increasingly recognizing as a common error that is probably the easiest to avoid. In oncology, specifically, drug developers have a tendency to move forward with the maximum tolerated dose, even though it is not clear if it is necessary or appropriate for targeted drugs. This happens even when they have data suggesting that a targeted therapy maximally inhibits or stimulates its target at a much lower dose. It results in a lot of unnecessary toxicity." Source

b. Clinical Trial Endpoints: Dr. Prowell indicated that Patient Reported Outcomes (PROs) should demand as much attention as other clinical trial endpoints, and that they can serve as a basis for selection or dismissal of drugs.

c. New Working Group: The FDA and the Clinical Trials Transformation Initiative (CTTI) will be working together to create a new working group with patient advocacy organizations to talk about patient engagement at the FDA. This initiative is part of the FDA's commitment to increasing patient involvement in the FDA's decision-making process. The new work group will create a forum to exchange information, ideas, and experiences relative to matters of interest to patients and patient advocates, and has established a new website regarding their endeavors.

d. Herceptin Biosimilar Drug Approval: On Dec. 1, 2017, the FDA approved Ogivri (Trastuzumab-Dkst) as a biosimilar to Herceptin (trastuzumab) for the treatment of patients with breast or metastatic stomach cancer whose tumors overexpress the HER2 gene (HER2+). Ogivri is the first biosimilar approved in the U.S. for the treatment of breast cancer or stomach cancer and the second biosimilar approved in the U.S. for the treatment of cancer.