

San Antonio Breast Cancer Symposium (SABCS) 2017

Over 7000 attendees from over 90 countries attended the 40th annual SABCS to learn and share cutting-edge information on breast cancer research and practice. Below are some of the highlights.

CDK4/6 inhibition: flying high



In 2015, the first cyclin-dependent kinase 4/6 inhibitor (CDK4/6i), **palbociclib** (Ibrance; Pfizer) was approved with impressive data: adding palbo to letrozole doubled the progression-free survival of postmenopausal patients with hormone receptor (HR)-positive, HER2-negative, advanced breast cancer¹. In 2017, two more agents—**ribociclib** (Kisqali; Novartis) and **abemaciclib** (Verzenio; Eli Lilly)—were approved with similarly strong efficacy^{2,3}. With maturation of data for these agents showing robust benefits, the era of CDK4/6i therapy is now firmly established, as reflected in the rich set of presentations at SABCS:

- **Virtually all subgroups may benefit from CDK4/6i:** Premenopausal women responded well to ribociclib-containing therapy in the MONALEESA-7 trial⁴. Older women were shown to benefit in an FDA pooled analysis⁵. Patients with poor prognostic factors benefited from abemaciclib-containing therapy⁶. Patients with and without various mutations (PIK3CA, TP53, etc.) benefit similarly well from ribociclib + letrozole⁷. Finally, early data suggest that CDK4/6i will be effective in the neoadjuvant/adjunct setting^{8,9}.
- **Preclinical experiments show why CDK4/6i works so well:** CDK4/6i benefits may include its ability to address endocrine therapy resistance mediated by ESR1 gene fusions¹⁰ or mismatch repair deficiency¹¹. Furthermore, CDK4/6i may have an immunomodulatory mechanism: CDK4/6i may increase expression of endogenous retroviruses, which stimulates antigen presentation and other immune responses¹².
- **Preclinical work also suggests how to further extend efficacy:** Resistance to CDK4/6i + endocrine therapy has become a major research focus. Targetable mechanisms may include the PI3K pathway¹³, FGFR¹⁴, androgen receptor (AR) and/or glucocorticoid receptor (GR)¹⁵, epigenetic regulators such as bromodomain (BET) proteins¹⁶, other CDKs¹⁷, NF1 mutation (which activates the RAS/RAF/MEK pathway)¹⁸, and senescence pathways (regulated by MDM2)¹⁹. Future triple/quadruple combinations or sequential therapy may help convert HR+ advanced breast cancer into a chronically manageable disease.

Sources: 1) Ibrance PI; 2) FDA; 3) Kisqali & Verzenio PI; 4) SABCS 2017 #GS2-05; 5) GS5-06; 6) GS6-02; 7) PD4-06; 8) PD5-01; 9) Ma, 2017 Clin Cancer Res 23:4055; 10) PD8-03; 11) P4-04-01; 12) Goel, 2017 Nature 548:471; 13) PD4-04; 14) PD4-01 and GS6-05; 15) ES9-1, 2, 3; 16) P3-06-07; 17) PD4-02; 18) GS2-2; 19) P4-04-12

PARP inhibition: the next breakthrough



Although the BRCA1 and BRCA2 genes were discovered over 20 years ago, specific treatments for BRCA-mutant breast cancer have thus far been lacking²⁰. To be sure, genetic screening for BRCA has helped women make decisions for preventative surgery, but soon patients who already have BRCA-mutant breast cancer will have a set of new options. Poly-ADP-ribose polymerase (PARP) inhibitors—which have already proven highly effective against BRCA-mutant ovarian cancer²¹—now show compelling data for BRCA-mutant breast cancer:

- **Two different PARP inhibitors show strong efficacy:** Data from the OlympiAD trial of **olaparib** (Lynparza; AstraZeneca) were reported earlier²², and now equally compelling data from the EMBRACA trial were reported for **talazoparib** (Pfizer)²³. In both phase 3 trials, the ORR for PARPi was more than twice that of the physician's choice control (~60–63% vs ~27–29%). Thus both agents will likely be approved in 2018.
- **PARPi is likely to benefit a broader patient population:** The current clinical data is for patients with germline BRCA1 and 2 mutations, but the biology suggests that PARP inhibitors will similarly benefit patients with any impairment of the homologous recombination DNA repair pathway (patients with “BRCAness”), due to a phenomenon originally described by geneticists as “synthetic lethality”²⁴.
- **PARPi combinations may further improve benefits:** PARPi increases median PFS significantly but only by ~3 months versus alternative treatments^{22,23}. Resistance to PARPi may occur through reactivation of BRCA²⁴. Combination therapy may be a solution to this problem. For example, combinations of immunotherapy and PARPi are already being explored in clinical trials²⁵.

Sources: 20) Larsen, 2014 Breast Cancer 8:145; 21) FDA; 22) Robson, ASCO 2017 #LBA4; 23) GS6-07; 24) BL1; 25) PD6-11



Immunotherapy: slow, steady progress

Immuno-oncology (I-O) is in the midst of transforming care of melanoma, lung cancer, renal cancer, bladder cancer, and several other cancer types, but not breast cancer (yet). Progress steadily continues, however: I-O was a major focus of over a hundred data presentations at SABCS, including the following:

- **Anti-PD-(L)1 monotherapy—biomarkers are critical:** Previously, **avelumab** (Bavencio; Pfizer/Serono) monotherapy had an ORR of only ~5% in a broad, refractory metastatic breast cancer (mBC) population²⁶. This year, in the Keynote-086 trial, **pembrolizumab** (Keytruda; Merck) showed an ORR of ~23% by focusing on treatment-naïve triple-negative breast cancer (TNBC) with high expression of PD-L1²⁷. Additional biomarker selection may further enhance efficacy: pembro monotherapy appears much more effective for patients with high levels of both PD-L1 and stromal tumor-infiltrating lymphocytes (sTILs)²⁷.
- **Anti-PD-(L)1 plus standard of care—benefit is incremental:** In 2015, **atezolizumab** (Tecentrig; Roche) + **nab-paclitaxel** (Abraxane; Celgene) showed promisingly high ORR (42% in 1L–3L TNBC)²⁸, but the sample size was small (n=24). This year, other anti-PD-(L)1 combinations showed more modest efficacy. **Pembro + eribulin** (Halaven; Eisai) in TNBC had 29% ORR in 1L patients (n=65) and 22% in 2L–3L patients (n=41)²⁹. **Pembro + trastuzumab** (Herceptin; Roche) in HER2+ mBC (≥2L) had only a 15% ORR even in the PD-L1 high subgroup³⁰, which was less impressive than data for next-generation HER2-inhibiting TKIs neratinib³¹, tucatinib³², and pyrotinib³³. **Pembro + abemaciclib** in HR+ mBC (≥2L) had only a 14% ORR³⁴.
- **Immunotherapy triple combinations may be required:** The tumor microenvironment (TME) in breast cancer is frequently “cold” or unreceptive to T cell activity, with multiple underlying mechanisms³⁵. Preclinical studies attempting to convert TMEs from “cold” to “hot” often find that triplet regimens are more effective than singlets or doublets. A few examples include **radiation therapy (RT) + TGFβ inhibition + anti-PD1**³⁶, **HDACi + DNMTi + anti-PD1**³⁷, and **CSF1Ri + CXCR2i + anti-PD1**³⁸.
- **ADCs may shift standard of care:** Although not acting via immune activation, antibody-drug conjugates (ADCs) showing impressive early data include **sacituzumab govitecan** (IMMU-132; Immunomedics) targeting Trop-2³⁹ and **glembatumumab vedotin** (CDX-011; Celldex) targeting gpNMB⁴⁰.

Sources: 26) Dirix, SABCS 2015 #S1-04; 27) PD6-10 and discussant (Mittendorf); 28) Adams, SABCS 2015 #P2-11-06; 29) PD6-13; 30) GS2-06; 31) P5-21-17; 32) P5-20-01; 33) PD3-08; 34) P1-09-01; 35) ES6-1,2,3; 36) PL1; 37) BS1-1; 38) BS1-2; 39) GS1-07; 40) Yardley, 2015 JCO 33:1609



Early-stage disease: seeking the most cures for the most people

Advances in treatment of mBC may be impressive, but better treatments and screening for early-stage disease are primarily responsible for the steadily declining rates of breast cancer-related deaths in developed countries over the last two decades³⁴. Further improvements will likely continue to have life-saving impact:

- **Optimizing surgery and adjuvant therapy:** Large, long-term clinical trials continue to provide insight into surgical margins³⁵, the optimal dose schedule of adjuvant therapy³⁶, and the optimal duration of therapy—which is not a one-size-fits-all approach: in some situations, ≤5 years of therapy maximizes the benefit, but in others, 10 years is recommended^{37,38}.
- **Monitoring for metastasis:** Sentinel lymph nodes (SLN) in the axilla are biopsied to test for metastasis. Radioisotopes are used to guide biopsy, but new fluorescent markers may provide superior resolution and/or lower cost³⁹. Less invasive biopsy⁴⁰ or avoiding biopsy may even be possible with new ultrasound methods⁴¹. Liquid biopsies are also an active area of research and are showing promise⁴².
- **Addressing disparities in care:** Improving breast cancer care in developing countries is a salient need⁴³. However, even in the US, the access to and quality of care vary widely: based on geographic⁴⁴, racial⁴⁵, and health insurance status⁴⁶. The problem is multi-factorial and will require multi-pronged solutions⁴⁴.

Sources: 34) ML1; 35) GS5-01; 36) GS1-01; 37) CS1-2; 38) GS3-01; 39) PD2-02,03,07; 40) PD2-04; 41) PD2-05; 42) GS6-03, PD3-03; 43) IS-1,2,3; 44) ES5-1; 45) P6-10-01, ES5-2, ES5-3; 46) P4-10-21

Prepared by Dennis Chang