

Clarion's Highlights from the
AACR 2017 Annual Meeting

Clarion attended this year's AACR Annual Meeting, at which a record-breaking 21,900 attendees convened for thousands of posters and talks. The following are just some of the key themes that emerged.



New Hope for Early Detection

This year, the AACR shined a spotlight on several new approaches for early cancer detection.

Liquid biopsies—the testing of blood for cancer biomarkers—was at the center of the spotlight, and the basis for this year's Team Science Award. Liquid biopsies have diverse applications besides early detection, including measuring drug sensitivity and identifying resistance mutations, and they may involve diverse analytes, including circulating tumor cells (CTCs), cell-free circulating tumor DNA (ctDNA), and exosomes. (Exosomes are nanovesicles that bleb off cells—including cancer cells—and enter the bloodstream, bringing with them samples of cytoplasmic RNA and protein.)

Impressive results were reported monitoring for cancer recurrence following surgery or other treatment. Researchers at the VCU Massey Cancer Center (Serrano, Abstract #3800) found that changes in the miRNA profile of exosomes can provide an early signal of recurrence. Scientists at Stanford (Diehn, Session SY08) developed highly sensitive ctDNA assays that can identify lung cancer recurrence 6 months before traditional imaging scans. Thus we are nearing a time when a simple blood draw may detect traces of cancer to enable early intervention and better outcomes.

Locally released tumor DNA. The Pap smear transformed cervical cancer from the top cancer killer of women in the US to a disease that is usually detected early and cured. New molecular methods now can improve detection of ovarian and endometrial cancers as well, by analyzing released tumor DNA (rtDNA) in the Pap smear fluid (Vogelstein, Session PL02). The combination of liquid biopsy and local rtDNA testing seems to be more robust than either alone.

Synthetic biomarkers. An alternative approach to early detection involves artificial nanoparticles designed to react with tumor-specific proteins. A synthetic biomarker developed at MIT (Bhatia, Session PL04) reacts with cancer proteases such as MMP-9 to release fluorescent compounds that are detectable in the urine. The signal amplification of this approach seems to enable a level of sensitivity far better than is possible with endogenous biomarkers.

The further refinement and combination of these new diagnostic technologies offer the hope that many more cancers will be diagnosed early, when they are curable. As Vogelstein emphasized, this line of research deserves at least as much effort and resources as the development of novel therapeutics.

Additional Sources: NIH RePORT on cervical cancer; CDC Cervical Cancer Statistics; MIT News April 10, 2017



Drugging the "Undruggable" and Overcoming Drug Resistance

New insights were presented on a wide array of cancer targeted therapies, but here we highlight advances in addressing key challenges of hard-to-treat targets (KRAS and others) and treatment durability limited by drug resistance.

Inhibiting KRAS: The RAS genes are among the first oncogenes discovered, and yet have proven among the most difficult to target. Promising preclinical data were presented for two novel RAS inhibitors using distinct pharmacologic approaches: ARS-1620, an irreversible blocker of G12C-mutant KRAS through a covalent bond with the cysteine residue (Liu, session SY28); and DC070-547, a potent blocker of RAS-RAF and RAS-EGFR interactions (Zhu, Abstract #4972). Inhibiting downstream effectors such as ERK (e.g., by LY3214996; Bhagwat, Abstract #4973) is also active in RAS-mutant in vitro and xenograft models. Clinical validation is still required, but multiple shots on goal offer unprecedented hope.

Degrading oncoproteins: A Celgene presentation (Chamberlain, Abstract #SY37-02) highlighted a novel approach to target proteins for proteasomal degradation. The method uses Celgene's expertise at modulating the E3 ubiquitin ligase Cereblon—the target of approved IMiD agents such as lenalidomide—and is able to target proteins otherwise difficult to inhibit, such as GSTP1 (glutathione-S-transferase) and Ikaros transcription factors. Thus the approach provides not only a promising drug candidate (CC-885), but proof of principle for a new way of developing targeted therapies.

Overcoming resistance: As multiple speakers discussed (e.g., Sawyers, opening plenary; Shaw, plenary session PL03), targeted therapy resistance may involve secondary mutations of the target (e.g., T790M mutation in EGFR-mutant lung cancer), activation of bypass pathways (e.g., glucocorticoid receptor [GR] upregulation in castrate-resistant prostate cancer [CRPC]), or conversion to a different cell lineage (e.g., from NSCLC to SCLC). Each mechanism requires distinct treatment approaches. For example, next-gen EGFR inhibitors overcome T790M mutation, while BET inhibition may prevent the epigenetic upregulation of GR in CRPC. Continued molecular investigations will no doubt reveal new ways to overcome or prevent drug resistance and extend the durability of targeted therapy.

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Continued Rise of the Immunotherapy Tide

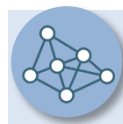
Immuno-oncology continues to be the hottest therapeutic approach and was the focus of >500 posters and talks which attracted the attention of academics as well as industry representatives throughout the conference.

Durability for immune checkpoint inhibitors (ICIs): In the first report of long-term survival in advanced NSCLC with an ICI, **nivolumab** produced a 5-year survival rate of 16%, roughly 4 times the historic rate with chemo (Brahmer, Abstract #CT077). This provides the best evidence to date that ICIs may cure a subset of lung cancer patients. On a related note, a phase 1 study of **atezolizumab** monotherapy in triple-negative breast cancer reported that while only 10% of patients had an objective response, those who did had 2-year OS rates of 100% (Schmid, Abstract #2986).

ICIs efficacious in Merkel cell carcinoma (MCC): In an update from the JAVELIN Merkel 200 trial, **avelumab** monotherapy demonstrated a 33% ORR (11% CR rate), with 86% of responses lasting ≥ 6 months (Kaufman, Abstract CT079), providing the basis for its first FDA approval. **Nivolumab** was also highly active in MCC (Topalian, Abstract CT074).

Novel combinations and mechanisms: IDO inhibitors showed remarkable efficacy and safety in multiple indications. In one single-arm phase 2 study in patients with advanced melanoma, **indoximod + pembrolizumab** had an ORR of 52%, a significant improvement over 34% ORR seen with pembrolizumab alone in the KEYNOTE-006 trial (Zakharia, Abstract CT117). In a phase 1/2a trial in advanced solid malignancies, the novel IDO inhibitor **BMS-986205** was described as having “best-in-class” activity, with no grade 3 events in the monotherapy lead in, and no grade 4 or 5 events with the combination of **BMS-986205 + nivolumab** in expansion cohorts (Siu, Abstract CT116). Early clinical efficacy data, although very limited, suggest that this combination is one to watch in the future. A new oncolytic virus approach also seems promising: combining intratumoral **coxsackievirus A21 (CVA21)** + systemic **ipilimumab** led to an ORR of 50% in immunotherapy-naïve and pretreated advanced melanoma patients in a phase 1b trial (Curti, Abstract CT114).

Tumor mutational burden (TMB) as an immune biomarker: TMB continues to show promise as a predictor of response to ICIs. For example, analysis of the CheckMate 026 trial (first-line NSCLC), the trial with the most patients evaluated for TMB to date, showed that patients with both high TMB and $\geq 50\%$ PDL1 expression had the greatest benefit from **nivolumab** (Peters, Abstract CT082). Foundation Medicine's FoundationOne test has been validated for analyzing TMB and predicts ICI response across multiple tumor types (Lieber, Abstract #2987), but is less predictive of NSCLC response than others, perhaps due to the immunomodulatory effects of specific mutations such as STK11 (Stephens, Abstract SY40-02). Thus TMB is likely best utilized in combination with other biomarker assessments.



Connecting the Dots Between Big Data and Clinical Outcomes

This year's AACR showcased advances by several collaborative initiatives aiming to marry large-scale genomics with clinical data, opening new fronts toward personalized care in oncology.

Pan-cancer Analysis of Whole Genomes (PCAWG): Introduced at AACR 2015, PCAWG is an international consortium with the goal of identifying patterns in cancer whole genomes. The project has now assembled and analyzed the genomes of over 2800 patient samples across >20 tumor types, and 17 working groups are developing insights from their analysis of the data, including methodological best practices and discovery of new cancer biology and new cancer targets (Stein, Brooks, Van Loo, and Getz, Session SY10; Davidson et al, Abstract #389).

Project GENIE: AACR's Project GENIE is a newly minted international data-sharing project including ~19,000 somatic tumor genotype reports and real-world patient data contributed by eight leading cancer institutions. Although the scope and methodology for genotyping varied widely across the institutions, the project already demonstrates clinical utility for rationally matching patients to clinical trials and to treatment regimens, and for gaining insight into new biomarkers such as tumor mutational burden (Sawyers, Cerami, Schram, Micheel, and Baras, Abstracts LB-102 thru 105).

Industry collaboration: An example is the collaboration of Foundation Medicine and Flatiron Health to form a “clinico-genomic database” for precision medicine. This database currently holds data for 20,000 patients, and already provides real-world validation—based on long-term outcomes—of a set of therapeutic algorithms (Stephens, SY40-02).

Moving forward: Joe Biden returned to AACR this year and called out additional initiatives such as the NCI Genomic Data Commons and the collaborative Blood Profiling Atlas in Cancer. Although these and other programs may be threatened by budget cuts, the potential impact for patients provides a compelling argument for further investment.

Additional Sources: Flatiron/FMI press release Nov. 3, 2016

Prepared by Dennis Chang, Jesse Wolinsky, Natalie German, and Bigyan Bista

CLARION | Healthcare, LLC

One Financial Center, Suite 1610 Boston MA 02111 Ph: 617.757.7850, www.clarionhealthcare.com