5th Annual Immuno-Oncology 360 Conference (IO360): Spanning Science and Business to Bring New Therapies to Patients

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OVERVIEW

The atmosphere at the 5th Annual IO360° Conference, which took place on February 6–8 at the Crowne Plaza Times Square in New York City, was truly collaborative. Co-chaired by Axel Hoos, MD, PhD (GSK), James Gulley, MD, PhD (National Cancer Institute), and Andrew Baum, MD (Citi), the conference featured almost 100 speakers and 10 plenary sessions, including 4 keynote talks and 7 panel discussions. More than 400 attendees representing the pharma, biotech, academic, regulatory, and private investment communities gathered to discuss the rapid advancement in scientific, clinical, and business developments in immuno-oncology (IO), with the goal of accelerating the development of new therapeutics for patients. Over 350 partnering meetings took place over the 3-day conference.

“360 degrees means we really want to speak to all stakeholders,” stated Dr. Hoos. The meeting is structured for the scientists to bring their most promising next-generation mechanisms that will help address these challenges. However, it is also important to look at therapies that haven’t worked, so we don’t repeat the same challenges of the past, he noted. “But IO360° is not just the science, it’s about the entire ecosystem in which the science exists, and that includes the patients and those that provide the funding to make the science happen.”

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- Axel Hoos, MD, PhD, GSK
and the CD19 Paradigm. With two CD19 CAR-T cells approved in 2017, Dr. Sadelain identified three new directions being taken to optimize CAR T-cell therapy and develop next-generation CAR Ts. The first is addressing exhaustion (loss of functionality) using genome engineering at a carefully select locus (TRAC) to create more potent CAR Ts and incorporating new designs that modify the activating portion of the CAR and balance rapid expansion and retained memory (1XX CAR). The second is gaining insight into the pathophysiology of cytokine release syndrome (CRS), including CAR T-cell-macrophage interactions, to try and reduce toxicity. The third is employing new strategies for circumventing antigen escape, such as use of radiosensitization and combinatorial targeting.

Michel Sadelain, MD, PhD, of Memorial Sloan Kettering Cancer Center, opened the meeting with a keynote, Chimeric Antigen Receptor (CAR)-T Cell Therapy versus ‘cold’ tumors,” he noted. In order to increase the efficacy of immunotherapy, a number of areas are actively being targeted, including antigen presentation, innate mechanisms of activation, the tumor microenvironment, and overcoming immunosuppression.

A variety of cells, growth factors, and cytokines in the tumor microenvironment play a pivotal role in whether or not immunotherapy is effective. Various strategies are being employed...
that attempt to modify the tumor microenvironment to overcome immunosuppressive mechanisms, such as blocking adenosine with an anti-CD73 monoclonal antibody (oleclumab, Medimmune) or an A2A receptor antagonist (CPI-144, Corvus), or inhibiting the IDO pathway (indoximod, NewLink Genetics). Other strategies are being employed to enhance the efficacy of cytokines to augment expansion and activation of T cells, such as engineering enhanced versions of the growth factors IL-2 (NKTR-214, Nektar and MDNA109, Medicenna) and IL-10 (pegilodecakin, ARMO). For example, pegilodecakin, a long-acting pegylated form of IL-10 induces hallmarks of CD8+ T cell immunity in cancer patients. According to Aung Naing, MD and Martin Oft, MD, pegilodecakin demonstrated clinical benefit in studies as a single agent and in combination with both chemotherapy and checkpoint inhibitors across several tumor types. The agent is currently being investigated in a phase 3 trial in metastatic pancreatic cancer.

Off-the-shelf hematopoietic cell products are being developed to address some of the limitations of patient-sourced cell therapies, such as heterogeneity, single-patient manufacturing, need for sufficient cells, extended production time, and cost. For example, engineered CAR natural killer (NK) cells, derived from induced pluripotent stem cells (iPSCs), are being developed that incorporate several individual components that together help to enhance persistence and anti-tumor efficacy (FT596, Fate Therapeutics). Multi-combinatorial strategies such as this may be key in reigniting the endogenous immune system and improving efficacy in the solid tumor space.
Genentech’s Priti Hegde, PhD, opened the Translational Science and Emerging Biomarkers plenary, part 1, with a keynote, Biomarker Signaling: Turning Cold Tumors Hot. Individual cancer types can be characterized along the tumor immunity continuum based on immune phenotype (ie, inflamed or non-inflamed) and tumor mutational burden (TMB). How can we generate an immune response signal in non-inflamed tumors when most do not achieve the TMB threshold that selects for benefit? Dr. Hedge highlighted two approaches: adaptive immunity, which has the potential to drive memory response, and synthetic immunity, which has the potential to sustain efficacy and drive log kill. An example of an adaptive immunity approach is neoantigen-specific T-cell therapy, in which there are limited but encouraging data demonstrating its ability to promote adaptive immunity in non-inflamed tumors. Synthetic immunity approaches include engineered T cells (eg, NY-ESO SPEAR T cells [GSK/Adaptimmune], BMCA CAR-T cells) and bi-specific biologics (eg, antibodies, BITEs® [Amgen], ImmTAC® [Immunocore]), in which there is proof of concept that these approaches are feasible in solid tumors and checkpoint inhibitor-refractory hematologic malignancies.

One may also need to address underlying biology to turn cold tumors hot. According to Dr. Hegde, the future of immunotherapy may be highly personalized and one will need to look at a variety of markers in biopsy specimens using a variety of techniques. This will only be possible if we have: 1.) a tissue-conserving, regulatory-grade decentralized platform to be able to run all of these assays in trials, and 2.) trial designs and statistical analysis plans that enable diagnostic signal-seeking validation and a path for registration.

The remainder of the plenary reported on translational data and evolving biomarkers and applications to help support decision making for IO drug development.
Negative results from the phase 3 study of the therapeutic prostate cancer vaccine PROSTVAC (Bavarian Nordic) show that a combinatorial approach may be needed with vaccines. Similarly, oncolytic viruses may need multiple transgenes and mechanisms to reverse complex immunosuppressive microenvironments. To address this issue, T-Stealth™ oncolytic viruses (BeneVir) can incorporate multiple genes, evade clearance by the innate and adaptive immune systems, and be combined with other drugs and IO agents.

Advances in PET imaging and radiomics provide a quantitative, non-invasive way to assess the dynamic changes of the immune system. For example, CD8 PET (Imaging Endpoints) may help distinguish between hot and cold tumors and address fundamental questions regarding the role of CD8 cells in the tumor microenvironment.

Other unique biomarkers and applications under investigation include MultiOmyx™ (NeoGenomics), a proprietary multi ‘omic’ technology that enables detection and visualization of up to 60 biomarkers on a single slide; immunosequencing (immunoSEQ, Adaptive Biotechnologies), a clinical diagnostic for monitoring clonal expansion and predicting/evaluating response to therapy, and use in combination with cellular immunology and computational biology (MIRA) to map T-cell receptors; and CANscript™ (Mitra Biotech), a personalized ex vivo histoculture approach that can be used...
to evaluate drug-induced modulation of the tumor microenvironment and predict clinical performance. (Other presenters in this plenary included: Genentech, NanoString Technologies, IGM Biosciences, Parker Institute for Cancer Immunotherapy, Janssen Research and Development, Cofactor Genomics)

The **IO Novel Technologies and Innovative Solutions** plenary showcased companies that have technologies and solutions that will help stakeholders in the IO field advance developments for cancer therapeutics. Presenters included Advaxis, Bioxcel Therapeutics, IAG, Provecs Medical, Rgenix, and Sensei Biotherapeutics.

### Plenary Keynote: Evaluation and Forecast of the IO Space

Andrew Baum, MD (Citi) opened the **Financial and Commercial Implications** plenary with a keynote, *Evaluation and Forecast of the IO Space*. He started off by discussing key questions on healthcare investors’ minds. According to Dr. Baum, “what investors don’t like very much about IO is that the technology cycles are short, so you can go from here to zero very quickly very easily.” He cited ipilimumab and the fact that it was quickly eclipsed by anti-PD(L)-1 agents. Another issue is the “paradox of choice,” as there are so many different modalities. “It’s almost overwhelming,” he noted, “especially for someone that doesn’t have a deep scientific background to interpret a phase one trial.” Other questions involve primary and secondary resistance, cell therapy manufacturing constraints, minimizing/managing toxicity, and financial toxicity. However, despite these questions, “the good news is the amount of capital, the enthusiasm, and the scientific advancement all mean that we’re going to make huge strides in IO, I have no doubt.”

Dr. Baum stressed the importance of learning from historic disappointments and noted that we need better biomarkers, better trials, and patience so that the benefits can be extended to more patients. He ended his presentation with a slide showing Citi’s top 10 novel IO targets for 2020, in which IL-2/IL-15 took the top spot.
Khalil Barrage (Invus) agreed that the IO revolution has led to unprecedented investor enthusiasm for oncology, unlocking massive commercial opportunities. However, the discovery of checkpoints and their curative potential has led to a hype in IO drug discovery, resulting in risky behavior. In addition, the flood of capital has lowered potential returns and there are a lot of IO agents in development with poorly validated rationale. As a result, Invus’ approach to investing incorporates strategies such as diversification, selectivity, exploring synergistic opportunities, investing where innovation is happening, paying a premium for validated approaches when warranted, and assessing reimbursement.

The plenary concluded with a panel discussion on monetizing science: the preparation of an IPO, straight licensing with the transition to a public company, and decision-making on prioritization within portfolios. Key takeaways included strategies for building out scientific and executive talent, the importance of having a scientific advisory board to test out the research, and being prepared to be a public company.

**Day Two**

The *Trends and Collaborations* plenary featured presentations by three major industry media companies in the IO field, which discussed new trends and their effect on the investment landscape.

Biocentury analyzes IO trends at recent medical meetings using machine learning, began Simone Fishburn, PhD, VP and Executive Editor. Despite the huge focus on PD(L)-1, academics and companies are aggressively looking for, and finding new targets, with LAG3 topping the list in company oncology pipelines in 2019. CAR T activity is moving into solid tumors, with new constructs and multiple tumor antigens targeted. Immunometabolism and tumor mutation burden are hot topics.

Funding for IO start-ups is outstripping other areas, both inside and outside oncology, drawing traditional and corporate investors.
According to John D. Carroll (Endpoints News), these trends are supported by global data published by the Cancer Research Institute, which show there were 3,394 IO agents representing 417 targets in the pipeline in 2018, representing a 67% increase over 2017.

According to Dr. Hoos, who moderated the session, partnering activities in this space have increased dramatically but there has been much competition, duplicative effort, and siloed activity. It is only recently that companies have started working together, each providing their unique contributions, which will accelerate progress. From a partnering perspective, the NY State Center for Biotechnology is tumor and target agnostic. Among the academic Center and the companies represented on the panel (BMS, GSK, Pfizer, and Merck), there appear to be both proactive and reactive approaches, with some moving away from me-too programs and focusing on those that can produce large effects. Approaches combining IO and non-IO agents are being explored by most in the current wave and are starting to play out.

How is all this affecting the investment landscape? According to Jeff Bockman, PhD (Cello Health BioConsulting), IO dominates oncology growth, but not sales. And although IO deals have shown evidence of slowing, whether due to maturation, saturation, or fatigue, oncology and IO investments remain robust.

The Business Development plenary, hosted by Solebury Trout, included panel discussions on partnering, fundraising, and rationale investing. The first panel discussed IO partnering strategies from the viewpoint of pharma and academia.
The next panel, which was designed for small and emerging biotechs, discussed fundraising in the current IO space and offered a number of suggestions. For example, panel members stressed the importance of continuous exposure at conferences and road shows and focusing on key selling points and positioning as a private company. Companies should rely on their ecosystem—their board, investors they’ve worked with in the past, KOLs, etc.—to communicate their message. Rather than starting at with the top firms, start at the bottom with KOLs, then the equity arms of foundations, then build upon that. Lastly, companies should introduce themselves earlier than they need to so that funders can follow them.

The last panel focused on understanding IO investment decisions. Most investors feel that this an exciting time, with a bright future for many modalities. However, the massive wall of data coming is making it hard to pick winners, analogous to trying to drink from a firehose. The investors on the panel rely on a wide variety of indicators, such as the asset’s chance of success and market, whether the data supports a high-risk prospect, or whether an agent has a broad application or has a niche in the IO space. Equally important is a company’s track record in handling their catalysts and their visibility to investors.

The plenary ended with a fireside chat with Ilia Tikhomirov, MBA, CEO of Forbius. Presented by Solebury Trout, the discussion focused on lessons learned in financing the company, with a view towards an IPO. For companies looking for series A funding, Mr. Tikhomirov highlighted the fact that Forbius had established networks as a spinoff and stressed the need to think through product ideas and where they are heading. There are some very generous programs available, so Forbius strategically pursued both dilutive and nontraditional financing in parallel to strike a balance. Those with clear direction can try Forbius’ high-risk strategy, and Mr. Tikhomirov expects to see more stories like Forbius’ in coming years. As industry costs are dropping, companies can be quickly launched with limited capital, like IT companies have done in the past.
The afternoon began with a keynote, “Evolving I-SPY2 to Optimize Breast Cancer” led by founder and co-principal investigator Laura Esserman, MD, MBA, of University of California, San Francisco. According to Dr. Esserman, we are at an inflection point in breast cancer: it has evolved from one disease to many, screening has changed the spectrum and distribution of tumor types, agents and trials are evolving, and there is an opportunity today to use early endpoints to enable interventions to rapidly evolve.

The I-SPY series of trials are changing the way new therapies are developed for breast cancer, helping make available better and more personalized treatments, faster. The basic principles of I-SPY are: testing drugs where they matter most (ie, early stage disease), changing the order of therapy to learn about response early in the course of care, building an efficient engine to evaluate drugs and accelerate knowledge turns, using imaging and biomarker guidance, and being collaborative by design. I-SPY2 is a platform trial for neoadjuvant treatment of locally advanced breast cancer. A biopsy is used to assess subtype and serial MRI and pathology informs adaptive randomization per subtype. The protocol and the Master IND are structured to enable seamless addition and release of investigational agents over the course of the trial. The primary endpoint is pathologic complete response (pCR), which is a highly significant predictor of event-free and distant disease-free survival, and is assessed in 10 pre-specified biomarker signatures. The information from 8 biomarker groups (standard, qualifying and exploratory) is maximized to inform drug assessment.

According to Dr. Esserman, “if we want innovation to continue, we have to change our design.” The focus of new drug development should be early disease, early recurrence risk: a curable population. “Clearly getting a person from high risk of metastatic disease to pCR—excellent survival—is a huge win.” It is also a huge economic win.

The goal of I-SPY2+ is to get 90% of patients to pCR without standard chemotherapy, with targeted de-escalation and escalation of therapy based on response. Dr. Esserman closed with one last piece of advice for drug developers: “Don’t shy away from finding out which subtypes your drug works for. Don’t be afraid to change the paradigm.”
The afternoon continued with two concurrent tracks. The first track, "Translational Science and Emerging Biomarkers Part II," was led by Ian McCaffery, PhD of Janssen and continued to focus on biology and application to help predict responses to immunotherapy. Technologies discussed included HexaBody Technology to enhance antibody therapeutics (GenMab), antibody-drug conjugate (ADC) mechanisms of action to inform combinations (Seattle Genetics), multi-dimensional predictive immune modeling (Cofactor Genomics), single cell proteomics (IsoPlexis), the ImmunoID NeXT Platform for biomarker discovery (Personalis), MDNA55, a locally administered IL-4-guided toxin (Medicenna), and a toll-like receptor 9 (TLR9) agonist in Spherical Nucleic Acid format (Exicure).

The second track, "Clinical Operations for IO Trials," was led by Jacqueline Karmel of Roche and was designed for clinical trial operation executives who wanted to learn what it takes to execute an IO clinical trial. Topics discussed included an end-to-end clinical trial operations case study (Genentech), operationalizing a complex phase 1 basket trial in IO (TRAP-001, EMD Serono), and clinical trial design for immunotherapies. The track ended in a panel discussion on the operational challenges with obtaining IO data and utilizing it to advance science. (Other presenters included: IQVIA, Memorial Sloan Kettering Cancer Center, Sidney Kimmel Center for Prostate and Urologic Cancers, BMS, Covance, PRA Health Sciences, Medidata)

According to Qi Liu, PhD at the FDA, current image-based endpoints (ie, ORR, PFS) may not adequately capture the clinical benefit of IO agents. As a result, emerging trends include use of immune response criteria, machine learning to unlock the power of imaging data, radiomics, and new techniques. The IO Imaging Aspects plenary wrapped up the afternoon with a discussion of novel imaging approaches.

There are unique challenges with use of imaging-based response assessments at IO clinical sites as a result of complex protocol requirements. According to Kelie Luby (Mint Medical), some of these challenges can be addressed by keeping the information mobile and relevant, avoiding distillation of protocol-defined response criteria, and including a concise summary of criteria in the protocol. Likewise, image-related risks can be minimized by use of clear protocols, properly configured and implemented image processing and
Radiomics are being used in conjunction with immune-related endpoints to obtain more information from images to improve reliability, as well as better differentiate between pseudoprogression and true disease progression. Molecular imaging, such as the CD8 PET discussed earlier, is also an evolving area. Similarly, whole body imaging using PD-L1 adnectin PET (BMS) represents an opportunity to noninvasively assess all of a patient’s tumors for PD-L1 expression with a single PET scan, helping guide treatment decisions and assess treatment response. It involves use of a novel engineered radiolabeled anti-PD-L1 target-binding protein.

Day Three

Day three opened with the inspirational story of patient advocate Judy Perkins. Diagnosed initially with early stage-breast cancer, her cancer recurred 10 years later as metastatic disease. After numerous failed chemotherapy and hormonal therapies, Judy educated herself and learned of an immunotherapy trial at the NCI. The treatment involved collecting her tumor-infiltrating lymphocytes (TILs), identifying the ones that could recognize her cancer, and expanding those cells in the lab. Four months later, Judy received an infusion containing billions of the selected cells and the cancer regressed. Judy has the distinction of being the first person to be declared free of metastatic breast cancer after a course of immunotherapy.

According to Judy, her local oncologist initially tried to dissuade her from participating in the trial. She closed with some sage advice to patients who might be in the same position: “I say the same thing to everybody dealing with cancer or any issues--find out as much as you can about your specific disease. Go a comprehensive cancer center to gain access to not just one mode of therapy but several modes..."
of therapy. Find out about clinical trials and whether you can participate in them. The magic is out there and you might as well try and find it.”

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- Judy Perkins, Metastatic Breast Cancer Veteran & Patient Advocate

Next up on the morning’s agenda was a panel discussion on how to combine IO modalities in a cost-effective, patient beneficial manner. The right combinations are difficult to identify but must be hypothesis- and biomarker-driven. First and foremost, the molecular pathobiology of a patient’s tumor needs to be characterized. One would then want to know if the tumor has been seen by the adaptive immune system: is it infiltrated by T cells and, if so, do they have an exhausted phenotype? What immunosuppressive factors are present in the tumor microenvironment? However, sampling problems are an important issue. Is the sample representative? What is the spatial arrangement of the cell types present? Biopsies are critical, but also limiting and confounding. Being able to look in the blood is ideal, but it doesn’t provide all the answers. Lastly, how can all this information be assembled? (Companies participating on this panel: Agenus, IONpath™, Stanford University, Cello Health BioConsulting, Biodesix, Torreya Partners, Strata Oncology)

The morning continued with a new plenary for 2019, Next Generation Cell Therapy. According to co-chair Dr. Gulley, “cell-based therapy has been the latest wave to crash on the shore of cancer treatment.” It’s clear there is substantial activity in hematologic
malignancies, but it’s less clear what is needed to achieve the same effect in solid tumors, so this is where there is much interest. The question is how to reproduce what was seen in melanoma studies but extend the benefit to a greater proportion of patients. The new technologies and targets discussed in this plenary aim to do just that.

NY-ESO SPEAR T-cells (GSK794, GSK/Adaptimmune) are an engineered T-cell product consisting of patient cells that are genetically modified to express a TCR that recognizes NY-ESO-1, a tumor-specific antigen found on many malignancies. TCR technology offers an advantage over CAR T-cell therapy in that it provides access to both extra- and intracellular domains. Promising early results have been seen in synovial sarcoma, a cancer for which there are no effective therapies after failure of first-line chemotherapy.

As noted earlier, off-the-shelf allogeneic products offer a number of advantages over autologous CAR T-cells. Allogeneic CAR T-cells (UCART) developed using the TALEN gene editing platform are being investigated in ALL, AML, and multiple myeloma (Cellectis). The next logical step is to edit multiple genes to create T cells with desired features, such as the ability to prevent or overcome resistance.
TILs may offer an advantage over other cell-based therapies in treating solid tumors in that they target multiple tumor antigens and there is a minimal chance of unpredicted or off-target effects. The technology used to develop the TILs that Judy Perkins received has been licensed (Iovance) and signals of efficacy have been seen in cervical, head and neck, and lung cancers. Importantly, the timeline for creating the product has been shortened from 5 to 6 weeks to 22 days and the end result is a cryopreserved product.

This plenary closed with a panel discussion on technical and clinical improvements to cell based IO therapeutics that will lead to more effective and durable therapies. Many of the strategies previously discussed were highlighted, including a shift to off-the-shelf and TCR products and addressing antigen loss with dual targeting or combination products. In order to move forward, we need to address roadblocks like the bottleneck when moving from in vitro/vivo models to the clinical setting as well as understand cell phenotypes and how the process used to create the product may change the cells, improve manufacturing automation, and improve safety. Ultimately, we need to mainstream cell therapies so that more patients will have access. (Companies participating on this panel: Chardan, Neon Therapeutics, Tmunity, Precision BioSciences, GSK)
The conference concluded with the **IO Clinical Development** plenary, which discussed recent IO clinical data. The plenary began with an overview of outcomes data for the PD-1 inhibitor pembrolizumab (Merck). Monotherapy activity has been demonstrated in more than 25 cancer types. The agent has received 18 US approvals across more than 11 indications, including approval in microsatellite instability-high (MSI-H) cancer. Pembrolizumab is now moving into earlier lines of therapy and next generation biomarkers are beginning to help identify promising combinations.

To summarize, “2018 has given us remarkable insights to produce more patient benefit in immuno-oncology,” said Dr. Hoos. However, there is still a lot of unmet need. As a result, “we need to investigate new concepts to expand the benefit beyond PD(L)-1.” Cell therapy has really broken ground, expanding itself to the next generation of engineered products, and we are beginning to extend the benefit from liquid to solid tumors and overcoming the barriers, such as T-cell exhaustion, that hamper long-term efficacy. All in all, the outlook for patients is promising.

Updates were also provided for ADU-S100/MIW815, a first-in-class STING agonist (ADURO), a BCMA BiTE® (Amgen), and combination immunotherapy targeting PD-1 and the glucocorticoid-induced tumor receptor (GITR, Regeneron).

The **6th annual Immuno-Oncology 360°** summit will take place on **February 26-28, 2020** in New York City.

You can also join us at the **4th annual IO Combinations 360°** summit, **June 20-21, 2019** in Philadelphia, PA.
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