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Current Progress in Immune Checkpoint Inhibitors for Cancer Immunotherapy: a Post Event Report of ICI2017

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Abstract:

Tumor immunotherapy has entered a phase of rapid development with a shift in emphasis away from classical vaccination approaches against tumor-associated antigens (TAA) towards a focus on various strategies to modify the functions of T cells, as well as to understand and modulate the immunosuppressive nature of tumor microenvironment (TME). With such a paradigm shift, recent international conferences such as "Immune Checkpoint Inhibitors (ICI) Boston" provided unparalleled depth of insights on factors that influence combination efficacy, role of TME, identification of translational biomarkers, latest preclinical modeling approaches, as well as the scientific rationale of targeting novel immune checkpoint pathways. Here I summarize some of the highlights at ICI2017.

INTRODUCTION

The annual Immune Checkpoint Inhibitors (ICI) conference has successfully run for the 3rd time in Boston! Defying a late-coming snowstorm in the New England area, participants warmly exchanged fresh data on the success and challenges of checkpoint inhibitors as novel cancer immunotherapy during the meeting on March 15-16, 2017. The attendees for ICI Boston 2017 were mainly from pharmaceutical / biotech industry (61%) and academia (15%), a majority of them are VP or C-level officers (25%) or Directors (56%). The conference provides an unparalleled opportunity in networking, generating business leads and collaboration, providing solutions and insights to optimize the development of immuno-oncology therapeutics. Below are some take home messages from my two-day conference. **Wenda Gao, Ph.D., Director of R&D, Antagen Pharmaceuticals, Inc.**

DEEP LEARNING ALGORITHM PREDICTS RESPONSE TO CHECKPOINT INHIBITORS

Why only 20-40% of patients benefit from checkpoint inhibitors, e.g., anti-PD-1, is a disturbing question equally perplexing physicians and basic researchers. We know certain solid tumors are "hot", i.e., inflamed with great infiltration of immune cells, whereas some other tumors are "cold, Antarctically cold", joked by **Angie Park**, Senior Director of Immunotherapy & Stem Cell Biology at OncoMed, Inc. We also know that hot tumors respond to checkpoint inhibitors whereas cold tumors normally don't. But what parameters should clinicians use to define hot vs. cold and predict the responsiveness? Now, we might be at the dawn of the advent of AlphaGo in the ICI field.

Parker Cassidy, Chief Commercial Officer of Mitra Biotech, introduced their CANscript™ Dynamic tumor phenotyping technology. This sophisticated clinical data-trained algorithm combines the advantages from using cell lines, organoids, genetically-modified mice, patient-derived xenograft and humanized mouse models. CANscript™ replicates the complete tumor ecosystem, including stroma, growth factors and immune compartment, and generates M-Scores for each tested treatment in 7 days upon specimen receipt. When the M-Scores are >25, there is response to treatment, and when the M-Scores are ≤25, there is no response. After the experimental endpoints and actual outcomes of clinical treatment are fed to the proprietary algorithm, machine learning takes place. So far, there is already over 90% correlation, and the algorithm will only become stronger and stronger.

Along the same line, **Carl Morrison**, President & CSO of OmniSeq presented Multianalyte Algorithmic Analysis (MAAA) to predict response to ICI. MAAA includes RNA-seq, DNA-seq, IHC, PCR and FISH elements. After incorporating machine learning model, 4-gene model and immune function model into Bayesian model averaging, the positive prediction value for responders (clinical benefit) is 88.9%, while the negative prediction value for non-responders (no clinical benefit) is 90%.

Regardless which route to take, dynamic phenotypic tests or genotypic and biomarker tests, the field should soon get ready to embrace such a scenario that after a week long wet lab tests, the AI can inform the physician what is the best immunotherapy for the patient and what the response would be.

LESS IS MORE: A GOOD EXAMPLE OF REDUCING OFF-TARGET EFFECT

After decades of technology development, bispecific antibodies are endowing immunotherapy more deadly firepower. The "off-target" effect of such dreadful weapon should be tackled to ensure clinical safety. CD47, a "Don't-Eat-Me" signal on normal cells, particularly on young but not senescent RBCs to avoid being engulfed by macrophages, is a checkpoint signal hijacked by tumor cells for immune escape. Anti-CD47 as an ICI has a side-effect of causing anemia. When developing antibodies recognizing an antigen highly expressed on tumor cells yet also present at lower levels on normal tissues, such as CD47, the conventional wisdom is to select antibodies with higher affinity, hoping them to be more enriched at the tumor vicinity. Yet, **Marie Kosco-Vilbois**, CSO of Novimmune SA, told the surprised audience a successful story just being the opposite.

Initially, two of Novimmune's monospecific anti-CD47 antibodies showed hematoxicity and poor PK due to the ubiquitous expression of the target. When treating B cell malignancies with NI-1701, an anti-CD47/CD19 bispecific (BiAb), Novimmune scientists intentionally knocked down the affinity of anti-CD47 to such a level that the BiAb now fails to bind normal tissue cells that do not express the tumor associated antigen (TAA), CD19. But on TAA+CD47+ tumor cells, the BiAb can bind synergistically and anti-CD47 moiety can still exert its blocking effect. This enhanced selectivity reduces the vast "sink effect" by tissue-expressed CD47, and the BiAb demonstrated excellent in vivo efficacy. No hematological toxicity was observed in nonhuman primates.

The same principle is reminiscent of recent efforts in the ICI field to screen for TAA-specific Mabs only at acidic pH. The hypoxic tumor microenvironment (TME) has a low pH (6.5-6.9), compared with that of normal tissues (pH7.2-7.4). A TAA-targeting Mab that binds less well at neutral pH but more strongly at lower pH would translate into better tumor tissue specificity and in vivo efficacy. This "less is more" unorthodoxical thinking should be borne in mind for drug developers to fully utilize the characteristics of TME.

TUMOR MICROENVIRONMENT IS THE BARRIER TO OVERCOME FOR A SUCCESSFUL IMMUNOTHERAPY

Even if there are tumor-infiltrating lymphocytes (TILs) in the inflamed tumor bed, are they performing the job they are supposed to perform? Probably not, without exogenous help. **Kris Sachsenmeier** of AstraZeneca told the audience that once entered TME, these TILs are choked by smog of soluble inhibitory molecules, one of which is the potent immunosuppressive metabolite adenosine (ADO). "Supra-physiologic" ADO contents in TME can reach 50–100 μM, whereas extracellular ADO concentrations in normal tissues are only in the range of 10–100 nM. AstraZeneca and several companies in the field are thus developing Mabs blocking CD73, an ectoenzyme highly expressed in tumor tissues that catalyzes the transition of AMP to ADO. The Mab MEDI9447 inhibits the enzymatic activity of CD73, enhances T cell proliferation in mixed lymphocyte reaction, and synergizes with anti-PD-1/CTLA-4 in stimulating TNF-α and IFN-γ production. Anti-CD73 and anti-PD-1 in combination produced better results than single arm alone in controlling tumor growth and establishing immunological memory. In anti-PD-1 resistant tumor models, knockouts of CD73 and ADO receptor (A2AR) showed additive effects.

However, the real mechanism of action (MOA) is still puzzling, as the antibody effect seems to be dependent on its Fc isotype and the ability to engage the ADCC/ADCP-enabling receptor FcγRIV in mice. When administrating high doses of anti-CD73 in vivo, one would expect to see that the ADO reservoir in normal tissues will be hit hard first, before seeing any impact on ADO level in TME with 1,000-fold high concentration.

As ADO is involved in maintaining vasculature tone and many other physiological functions, the field is biting the nail awaiting a Yes or No answer on the necessity of neutralizing CD73 enzymatic activity. In the end, its MOA could be as simple as deleting CD73+ tumor cells through ADCC or ADCP.

The suppressive nature of TME may very well be manifested by previously under appreciated CAFs – carcinoma associated fibroblasts, which are linked with anti-PD-1 failure. **Viviana Cremasco** from Novartis reported that stromal cells positive for both Podoplanin (PDPN) and fibroblast activation protein-α (FAP) are CAFs. The hematopoietic lineage of FAP+ CAFs can develop into tumor-promoting M2 macrophages. Depleting FAP+ CAFs that comprise only 2% of all cells in TME, e.g., in diphtheria toxin treated DTR-FAP mice, can revert the suppression on tumor-infiltrating CD8+ T cells and lead to rapid tumor shrinkage.

Many at the conference, even CAR-T experts, shared the same viewpoint that converting tumors from cold to hot relies on manipulation of TME and immune checkpoint pathways. **Prasad S. Adusumilli** at Memorial Sloan Kettering Cancer Center presented data on the importance of intracellular co-stimulatory domains in constructing the second generation CAR-T, targeting mesothelin (MSLN). CAR-T with 4-1BB co-stimulatory domain (MBBz) is much more effective than that with CD28 co-stimulatory domain (M28z). CAR-T infusion causes upregulation of PD-L1 and PD-L2 in TME. The longer functional persistence of MBBz CAR-T cells seems to correlate with their lower PD-1 expression than that on M28z CAR-T cells. Exogenous treatment with PD-1 antibody or endogenous expression of a dominant negative PD-1 ectodomain can rescue the M28z CAR-T cells. Thus, checkpoint blockade might very likely converge with CAR-T immunotherapy.

FIRST-IN-CLASS SMALL MOLECULE ICI OPENS UP NEW VENUES

All are welcome, big or small, in the arena of immune checkpoint inhibitors! The field should soon witness the break of antibody dominance by small chemical antagonists. **David Tuck**, CMO of Curis Inc., introduced CA170 and CA327, small molecule ICIs developed by functional screening to identify compounds capable of selectively rescuing T cell proliferation and activation in the presence of co-inhibitory molecules. CA170 antagonizes PD-L1 and VISTA to the same level by anti-PD-1 and anti-VISTA, and is orally bioavailable in multiple species. CA170 is superior to anti-PD-1 in syngeneic mouse tumor models sensitive to anti-PD-1. In syngeneic mouse tumor models where anti-PD-1 is ineffective but the alternative non-redundant VISTA pathway is active, CA170 daily oral treatment suppressed tumor growth to the similar extent as to anti-VISTA. CA170 is in Phase I clinical trial. Likewise, CA327 inhibits PD-L1 and TIM3, and its IND-enabling studies are ongoing.

Taken together, the advantages of small chemical ICIs are oral bioavailability with much reduced infusion cost, patient convenience and access, clean off-target profile, and flexibility in dosing and combination. With the delineation of interaction and structures of immunoglobulin superfamily members, the chemistry of small molecule antagonism seems to extend to multiple immune checkpoint inhibitors. While the effector functions of antibody Fc, such as CDC, ADCC and ADCP, cannot be simply imparted by these chemical antagonists, antibodies do have a disadvantage due to their supersize, i.e., difficult to penetrate deep into the solid tumor. In this sense, size does make a difference, and those small combatants could be crucial to winning the war against cancer.

NEXT TIDAL WAVE OF CHECKPOINT INHIBITORS PLAY DUAL ROLES

What's next after PD-1? **Frédéric Triebel**, CSO/CMO of Prima Biomed, informed the audience that the trajectory of the PubMed articles on "LAG-3 cancer" would be similar to that of "PD-1 cancer", with the former trailing after the latter in about 8 years apart. LAG-3 is structurally similar to CD4. After binding to MHC Class II, it positively stimulates APC for antigen presentation to CD8+ CTLs, and negatively inhibits T cell activation, just as PD-1 and CTLA-4 do. But unlike antibodies against these forerunners, anti-LAG-3 can have either antagonist or agonist effects. Even LAG-3Ig can serve as an agonist of MHC Class II and a soluble antagonist of surface bound LAG-3, leading to T cell activation and proliferation. A synergistic combination of LAG-3Ig and anti-PD-1 is "pushing the gas (by LAG-3Ig) and releasing the brake (by anti-PD-1) on CD8+ T cell response".

Anti-GITR antibody being developed by Merck Research Laboratory, as put by investigator **Amy Beebe**, also plays similar dual roles but on different T cell populations. It provides a positive co-stimulatory signal to primed effector T cells, while at the same time leading to localized depletion of GITR-positive Treg cells in tumor, at least in mouse models. Because the antibody would introduce foreign amino acid sequences in the CDR region, and because of the known effect of GITR on B cell stimulation, the challenge of an agonist GITR antibody is the high ADA response that impedes multiple uses. In this sense, GITRL-Fc being developed by OncoMed, Inc., could be more promising. **Angie Park** from OncoMed argued that agonist mAbs, dependent on dimerization by Fc, are poor agonists for trimeric TNF ligand receptors. Using the natural ligand GITR-L in the trimeric form would be more potent with less ADA concern. Indeed, data showed that GITRL-Fc is more potent than agonist GITR antibody in activating effect T cells, and it can also deplete Treg in tumor.

Joining the group with similar dual MOA on activation of Teff and reduction of Treg is ICOS. **Beth Trehu** from Jounce Therapeutics, Inc. presented data on JTX-2011, an agonist mAb that targets ICOS. All these agents with dual activities synergize with anti-PD-1 in preclinical tumor models. Along with others, such as anti-TIM-3, as well as agonist anti-CD27 introduced by Conference Chair Dr. **Jannie Borst**, Head of Immunology Division at Netherlands Cancer Institute, they form the next tidal wave of ICIs with novel MOA that tip the balance between effector T cells and suppressive Treg cells.

MYRIAD POSSIBILITIES FOR COMBINATION THERAPIES, BUT RATIONALE OUTWEIGHS RANDOM MATCHMAKING

Both **Jon Wigginton**, CMO of MacroGenics, Inc. and **Geoffrey Gibney**, Associate Professor and co-Leader of Melanoma Disease Group at Medstar Georgetown University Hospital delivered basically the same theme: Combinations of immune checkpoint blockade require thorough safety evaluation, and improved strategies for management of supra-additive immune-related AEs and biomarkers to predict toxicity risks are needed. **Philip Gotwals**, Executive Director of Exploratory Immuno-Oncology at Novartis Institutes for BioMedical Research, Inc., proposed that testing of combination regimens should focus on mechanism-based approaches supported by clear preclinical rationale. There are multiple stages that immuno-therapeutics can target to, e.g., at immune priming, T cell modulation (e.g., checkpoint), T cell engagement (e.g., CAR-T) and tumor microenvironment.

For example, the STING (Stimulator of Interferon Genes) receptor is generally expressed at high levels on innate immune cells. Once activated, it primes broad immune responses, inducing the expression of interferons and chemokines. In preclinical tumor models, the STING agonist ADU-S100 alone demonstrated superior anti-tumor responses. When combined with checkpoint inhibitor anti-PD-1, abscopal CD8-mediated rejection of distal tumor can be observed. **Sarah McWhirter**, Director of STING Program at Aduro Biotech, further elaborated the scientific rationale of activating STING: Tumor-derived DNA stimulates STING to produce IFN-β, a cytokine signature in the TME of T cell inflamed human tumors. STING plays a critical role in activating immune cells in TME to prime CD8+ T cells recognizing any individuals' unique neo-antigens. However, while Aduro's ADU-S100 elicits TNF-α-mediated durable anti-tumor immunity with memory response, the efficacy requires intra-tumor injection route. Nonetheless, for patients developing resistance to checkpoint inhibitors, STING agonists may provide an immune reboot.

Other targets to correct the immunosuppressive tumor microenvironment are being tested in combination with checkpoint inhibitors, for instance, A2A receptor (compound CPI-444) and IDO (compound Epacadostat). These clinical trials are ongoing. It has been noted that currently there are more than 1,700 PD-1/L pathway related combination clinical trials. Are all these based on good scientific rationales? In the end, some companies are just burning money to prove certain marriages are simply not working.

SUMMARY

Tumor immunotherapy has entered a phase of rapid development with a shift in emphasis away from vaccination studies to a focus on various approaches to modify the functions of T cells. The therapeutic efficacy of CAR-T has thus far been limited mainly to certain hematologic malignancies, suggesting that the microenvironments of solid tumors may have unique impediments to the functions of effector T cells. An especially notable characteristic of checkpoint inhibitors are their durability, which contrasts with the relatively limited duration of responses to "targeted" cancer therapies that interfere with specific signaling pathways mediating the carcinogenesis process. The intermittent, but remarkable, successes of CAR-T cell therapies and checkpoint inhibitors in patients with solid tumors highlight our ignorance: We do not know the reasons for the failures.

The next phase in the development of cancer immunotherapy, however, must achieve an understanding of why T cell checkpoint antagonists are ineffective in the majority of cancer patients. Simply combining various regimens is not enough. Do they not respond because their immune systems do not recognize antigens associated with cancer cells, or because of the occurrence of another type of immune suppression? The "cancer immunoediting" hypothesis predicates that the host immune response rapidly selects for cancer cells that are not immunogenic, thereby enabling cancer to escape immune control. So far, the partial success of checkpoint antagonists suggests the opposite. Understanding the existence of an immunosuppressive process in the tumor microenvironment that is so stringent that it masks potentially effective antitumor immune responses, even in the presence of CAR-T and/or T cell checkpoint antagonists, and developing ways to revert this process is the key to establishing a long-lasting response to tumors toward "curing" cancer.