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Combination Cancer Immunotherapy — A Virtual Roundtable

By Wayne Koberstein, Executive Editor, and Llew Keltner, M.D., Ph.D., Roundtable Moderator

A Series on the Challenges and Opportunities of Using New Agents to Rally the Immune System Against Cancer.

Targets, targeting, targeted — these words get plenty of use in the biopharma industry as the field of drug discovery and development becomes more and more mechanistic. Drug targets usually consist of receptors on the surface of microbes or tissue cells, including cancerous cells, where certain compounds may bind and interfere with their growth or disease-causing activity. All such attempts to block tumor growth, however, have met with two main obstacles: tumor heterogeneity and what appears to be evolutionary ingenuity in adapting and developing resistance to drug treatment. From the earliest chemotherapy agent to present-day molecular-pathway targeting drugs, none has defeated cancer's defenses by direct, frontline assault. All along we've needed an ally, and we've known what the ally should be — the human immune system.

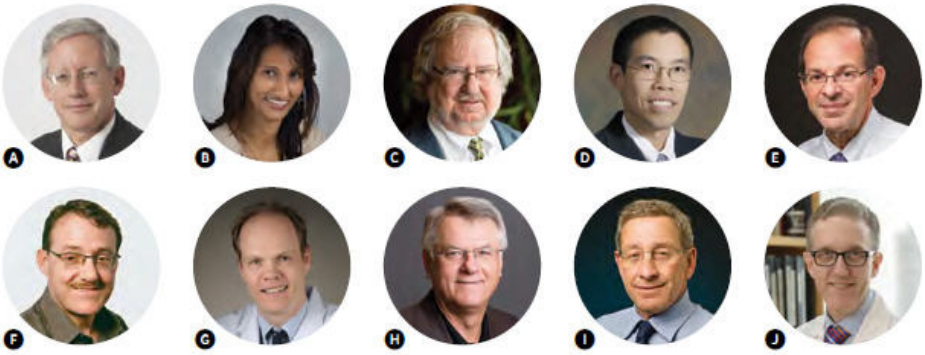
Drugs that target the immune system, not the tumor, may have entered the long war on cancer at last. Although some still dispute the validity of cancer immunotherapy, others are charging ahead. Results of large Phase 2 trials showing durable responses from a new class of drugs called checkpoint inhibitors, along with progress on the vaccine/ immunostimulator front, have fired up supporters and attracted new interest from former doubters. (See sidebar, "Brakes Off, Gas Pedal Down.")

Our virtual roundtable, a compilation of responses to questions from key experts and players in the field, considers the ramifications of a growing consensus that using cancer immunotherapies in combination, rather than as single agents, will be essential to have maximal effect for patients. In a matter of years, many cancer immunotherapies will be available, many combinations will be possible, and the choice of combinations will be quite challenging from a clinical, regulatory, and reimbursement perspective. Biomarkers and companion diagnostics may also play a big role in guiding the way, as will a deepening understanding of immunotherapy mechanisms and cancer response. But who should decide how combinations are tailored and delivered to individual patients, and on what grounds should they base those decisions?

In addition to this opinion-leader roundtable, the next phase of the series, beginning with Part Three, will offer and compare the views of company executives now working to develop and commercialize cancer immunotherapies. How well does the leading science match up with the development and commercial models of such companies? How well are companies adapting to the combination paradigm, and how may they continue to do so as the field advances?

PANELISTS

Our panel members are all leaders in cancer immunotherapy research, and most are overseeing major clinical trials in the field. Two members are especially noted below because they represent opposite, yet overlapping, opinions on the readiness of the new therapies for wide adoption by oncologists.



(A) Moderator, Llew Keltner, M.D., Ph.D.
President and CEO, Epistat

(B) Pam Sharma, M.D., Ph.D.
Scientific Director, Immunotherapy Platform and Professor, Departments of Genitourinary Medical Oncology and Immunology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

(C) James Allison, Ph.D.
Executive Director, Immunotherapy Platform and Chair, Immunology, The University of Texas MD Anderson Cancer Center, Dr. Allison pioneered the concept of "CTLA-4 blockade" and the first checkpoint inhibitor on the market, ipilimumab (Yervoy).

(D) Lawrence Fong, M.D.
Professor, Department of Medicine (Hematology/Oncology), UCSF

(E) Mario Sznol, M.D.
Professor of Medicine (Medical Oncology); Clinical Research Program Leader, Melanoma Program, Yale Cancer Center

(F) Alan Venook, M.D.
Professor, Department ofn Medicine (Hematology/Oncology), UCSF Chair of the Scientific Program for ASCO 2015 and serving on national practice-standard-setting boards, Dr. Venook is both a leading skeptic and an investigator doing exploratory trials in immunotherapy for GI cancer.

(G) Tim F. Greten, M.D.
Head, Gastrointestinal Malignancy Section Investigator, Thoracic and Gastrointestinal Oncology Branch, Center for Cancer Research, National Cancer Institute

(H) Walter Urba, M.D., Ph.D.
Director, Providence Cancer Center

(I) Neil Berinstein, M.D.
Director, Translational Research, Ontario Institute for Cancer Research (OICR)

(J) Jedd Wolchok
Chief, Melanoma and Immunotherapeutics Service, Memorial Sloan-Kettering

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We gathered the KOL (key opinion leader) responses in two ways — one, by an exchange of written questions and answers; the other, by in-person interviews — so some participants will inevitably sound more formal or informal than others. Another caveat: KOLs often disagree not just on theory but on facts. And where there is factual disagreement, there is error. Someone has to be wrong. In fact, if we show nothing else about this field, we will certainly reveal how many issues still need to be settled.

QUESTION: Cancer has shown an amazing ability to frustrate molecular-targeted therapies through mutation and adaptation. Why will cancer immunotherapy not be subject to the same ability of cancer to defeat interventions — in this case, to find a way around the therapy-induced immune responses in unpredicted ways?

Keltner (Moderator): Most of our panelists see immunotherapy as a durable new paradigm for cancer treatment, though probably not one without surprises and setbacks during a period of experience and learning, not just about therapeutic results, but also about the mechanisms. The first two panelists to speak represent opposite poles of opinion, though both are dedicated researchers in the field.

ALLISON: A paradigm shift has begun, where you no longer focus so much on targeting specific mutations in the tumor, but you focus more on unleashing the immune system to attack the cancer. That's the new biology that has to be taken into account. You can't just look at the oncogenes and the "driver" mutations in tumor cells. In fact, those may be less relevant, and it may be more important to engage the immune system to recognize the hundreds of mutations that are inherent in all cancer cells, including driver and passenger mutations. What we need companies to do — as we are trying to do with the immunotherapy platform at MD Anderson — is to look beyond results with targeted therapies and chemotherapies. Just hitting the clinical endpoints with those agents is sufficient to move ahead, but we need to understand the salient molecular basis for the responses that are durable, as we have seen with immunotherapy, so we can begin to figure out the rational combinations and discover new targets. Unless the basic science keeps moving forward, the whole field will just stall out. In combining therapies, everyone wants a clear recipe — one from column A, one from column B — but to get there we need a better understanding.

VENOOK: The main issue is that cancer immunotherapy has just recently been shown to work. It is true that there appears to be efficacy in melanoma and prostate cancer, but at great expense and really in narrow areas. I am all for developing immunotherapy, but it is just fascinating to me that people think it is an amazing sea change and works in all the ways it is being applied. It's hype beyond hype. Acknowledging there is now some proof of concept, I am much more optimistic than I might have been before. I hope it does work, but the problem will be knowing that the immune cells you affect have the capacity to do what you want them to do, that they are not already affected by the presence of cancer, chemotherapy, growth factors, or something else. None of the studies in my area of GI oncology have been positive, so far at least, so I remain skeptical.

SZNOL: What's already been published on checkpoint inhibitors is very significant and very good. I have a hard time believing the kinds of responses we're seeing in the clinic will just go away. It is reasonable for Dr. Venook to be a skeptic because he is a GI oncologist and we have not made many inroads against GI malignancies yet. But we have generated enough data and treated enough patients to know what kind of activity to expect. No, we haven't cured cancer. We have made new inroads, but not solved the problem yet. All the excitement here is related to two targets: CTLA-4, and PD-1/PD-L1. There are many other targets, so it is amazing how much success we have had with just those two. When we have other agents and start doing combinations, if even 20 percent of them work, it will still be amazing. Some patients are already deriving enormous benefit they would not have had with any other kind of therapy.

With anti-PD-1, for example, we are seeing activity across a half-dozen different malignancies, and in patients who are not responsive to other treatments. It is appropriate to be excited, not just about what anti-PD-1 or anti-CTLA-4 can do alone, but also the potential for manipulating the immune system in many different ways. We may incrementally improve outcome in many cancers. Some of the responses we see now are amazing —not only does the disease go away, but we don't have to treat the patients anymore.

"The main issue is that cancer immunotherapy has just recently been shown to work."

Alan Venook, M.D., Professor, Department of Medicine (Hematology/Oncology), UCSF

GRETEN: I'm not saying that Provenge or ipilimumab are the best therapeutics, but they have definitely changed many people's view of immunotherapy, and there are increasing results indicating that, indeed, patients may benefit. Obviously, we still mainly see the results in patients with melanoma, non-smallcell lung cancer, and prostate cancer. Alan Venook, like myself, is interested in GI cancers, where we have no clear results yet. It seems some mechanisms that work in non-small-cell lung cancer may not work in GI cancers. But I would also challenge anybody who does not believe in immunotherapy and wants us to focus more on toxic chemotherapy or targeted therapies — shouldn't we explore the new approaches? In GI cancer, there have been no significant advances in the past 10 years.

Obviously tumors can adapt; there's no question it is a potential danger. Years ago, people used peptide vaccines, aiming but mainly failing to induce a response against a very specific epitope. Yet a few patients actually responded to those treatments, and a retrospective analysis indicated the reason was not because they developed responses against the peptides used for the vaccination, but to other epitopes derived from the tumor antigens expressed in the tumors, indicating the treatment induced a wider immune response. If you have an immune response against marginal antigens on different epitopes, the tumor is less likely to develop escape mechanisms.

Keltner: Some evidence now suggests the failure of early cancer vaccines was really due to the inability of administered antigens to elicit adequate CD8+ T cell antitumor responses, or to defective delivery of the antigens. For example, the data from simple raw peptide delivery of survivin compared to the recent (ASCO 2013 & 2014; AACR 2014) data on highly adjuvanted, depot delivery of the same survivin peptides is quite dramatic. (See sidebar, "Cancer Vaccines — A New Wave.")

URBA: Cancer immunotherapy is subject to some of the same frustrations faced by the use of molecular-targeted therapies. A close examination of tumors shows many mechanisms of escape from immune-mediated killing, for example, loss of tumor antigens or MHC-restricting elements. The major advantage of immunotherapy is this: like the tumor, it is adaptive. Over time the immune system can learn to recognize different antigens. The phenomenon of epitope spreading is an example of how the adaptive immune response could overcome the tumor's loss of an antigen to which it had been immunized. Another potential benefit of immune therapy is one can target a protein that is essential for the growth of the tumor, and if the tumor escapes by altering that key oncogenic protein, it is possible the tumor will be unable to maintain its malignant phenotype.

Keltner: "Epitope spreading" may be a potential benefit of the use of correctly formulated and delivered cancer vaccines in combination with checkpoint inhibitors — as long as the target antigens are fundamentally necessary for cancer-cell survival or malignancy.

QUESTION: Why should cancer immunotherapies be used in combinations rather than as single agents? Is it possible to envision a single, effective immunotherapeutic agent?

Keltner: Many more than two constituents will possibly be needed to fully engage the immune system. In fact, some agents that have a negligible effect when administered alone may actually be quite active in the presence of others. But the current celebratory blush over surprisingly dramatic and durable responses in Phase 2 trials has some KOLs hedging their bets about single agents versus combinations.

WOLCHOK: It is not really a one-size-fits-all paradigm. There are some patients who have had long-term benefit, in fact, complete remissions from single agents, ipilimumab, or an anti-PD-1 drug, so some patients may not need a combination. It is very hard to make conclusions prospectively at this point.

SZNOL: Of course, the immune system is very complex. It would be hard to believe that just a single target would cover all scenarios, but that being said, a single-agent PD-1, PD-L1, or anti-CTLA-4 blockade or even interleukin-2 can produce amazing, durable responses in a subset of patients. It would be ideal if we could identify people for whom either single-agent or combination therapy is needed; we're not that good yet. For the majority of patients, combinations would probably be better.

ALLISON: Because a single drug will only work in some patients, two or more is inherently better — but only if you understand how they work. If they have overlapping fundamental mechanisms, they are probably not going to combine well. The best combination I've seen so far is ipilimumab, which is an anti- CTLA-4, which enables co-stimulation, and anti-PD-1 such as nivolumab, which enables T cell receptor signaling. It seemed to us they would be at least additive, and it looks like they worked even better than that.

Some patients who did not respond to CTLA-4 blockade did respond to PD-1 blockade, and vice versa; thus, it makes sense to put them together. But whatever the response rate, the survival rates may be higher. Response was dosedependent, so there may be another inhibitory factor. When we were doing studies with anti-CTLA-4 biomarkers, we found a population of immune cells, the ones that actually show the antitumor activity, expressing a molecule called ICOS. ICOS is a positive test for CTLA-4 (Ng Tang et al, "Increased frequency of ICOS+ CD4 T cells as a pharmacodynamic biomarker of anti-CTLA-4 therapy," Cancer Immunology Research, 2013); it is genetically in the same family with CD28 and CTLA-4. But when you block CTLA-4, the cells that express ICOS appear. If you give a signal to the ICOS molecule, it boosts the anti-CTLA-4 response. You can find new targets just by studying the mechanisms.

URBA: Not only do I believe that it is possible to envision a single, effective immunotherapeutic agent, but in fact, they currently exist. Rituximab, trastuzumab, ipilimumab, and anti- PD-1 are all examples. So are vaccines against hepatitis B and HPV. But, except for the prophylactic vaccines, none of these strategies are optimally effective by themselves, and that is why combination therapy will be required. Tumors from each patient, and even individual tumors within patients, have their own genetic composition. This leads to a unique repertoire of potential tumor rejection antigens and to individual evolutionary changes to adapt to the host's immune response. Add to this the heterogeneity of patients' immune responses, and you can immediately see the complexity of the tumor host response. There will be multiple problems to address from the presence of adequate numbers of antitumor T cells, the balance of checkpoint inhibitors, the presence of immunosuppressive cells and/or cytokines (perhaps produced by the tumors), and a host of other factors in the tumor microenvironment. This is likely not only to require combinations of immunotherapy, based on the biology of the patient's tumor, but also combinations with other therapies, including chemotherapy and radiotherapy.

GRETEN: Now is the time to evaluate possible combinations, because we are just about to get the first clinical data from the checkpoint agents tested alone, and a few combinations are being tested; this includes, for instance, checkpoint inhibitors with other enhancers of immune responses. But they are not being tested in combination with chemotherapy. My fear is, if you only combine checkpoint inhibitors with other immunotherapy agents, it may actually lead to premature negative data because there is insufficient immunological understanding behind it, including how the non-immune-based therapies affect immune responses. It is important to ensure the needed T cells are not depleted by the chemotherapy or any other agent combined with immunotherapy.

"I'm not saying that Provenge or ipilimumab are the best therapeutics, but they have definitely changed many peoples' view of immunotherapy."

Tim F. Greten M.D., Head, Gastrointestinal Malignancy Section Investigator, Thoracic and Gastrointestinal Oncology Branch, Center for Cancer Research, National Cancer Institute

FONG: We have developed a method for cataloging the T cell repertoire, the T cells circulating within a patient. [Improved Survival with T Cell Clonotype Stability After Anti–CTLA-4 Treatment in Cancer Patients, Cha, et al., www.ScienceTranslationalMedicine.org, 28 May 2014, Vol 6 Issue 238, 238ra70.]. We use a next-generation sequencing approach to study the immune cells in the patient rather than looking for mutations in the cancer. That allows us to discriminate among the millions of T cells in a person's body — and see what happens to them when you give patients some of the checkpoint inhibitors. We found melanoma or prostate cancer patients who had improved survival after receiving anti-CTLA-4 antibody were maintaining a baseline of high-frequency T cells [i.e., the most common T cells, which may include "clonotypes" capable of recognizing tumors], whereas patients without survival gains had shuffled all their T cells around, replacing their initial high-frequency T cells with other T cells. Achieving prolonged survival seems to depend on whether there is a preexisting immune response. Some patients may lack this response, which is the context where it is important to use a combination therapy that helps them to generate these T cells.

Keltner: Without major progress, immune-response detection may have little practical effect on the use of combinations versus treatment with a single agent. Patient segmentation is often murkier in practice than in theory. Most cancer patients' immune systems are compromised, so physicians will likely want to cover more than one base in any immunotherapeutic regimen — making combinations SOP. Yet immuneresponse testing will continue to grow in use and sophistication, if only to pursue the goal all of the panelists share: understanding immune and immunotherapeutic response in cancer at an ever-higher degree of resolution.

BERINSTEIN: Cancers have evolved very sophisticated biologic mechanisms to suppress effective immune eradication. Thus, successful cancer immunotherapy needs to incorporate a solid understanding of the different suppressive mechanisms in play for different cancers and different stages of cancer progression, as well as the potential antigen targets for immune rejection. It needs to utilize therapeutic platforms that can generate robust antitumor immune responses, which often require breaking immune tolerance to self-antigens. It also needs effective immune modulators that are safe and can inhibit the immune-suppressive environment of both the tumor and sometimes the patients themselves. These complex tasks are a tall order for a single agent. For this reason, it is likely that the most successful cancer immunotherapy will be a combination of two or more therapies that are very effective in doing their part, rather than a single, do-it-all treatment.

Plenty of competition exists among the growing variety of players to belong to the in-crowd of wide-use combinations. Our KOL panel wades more deeply into its discussion of therapeutic choices — by physicians, payers, and regulators — next month in Part Two of this series, Combination Cancer Immunotherapy — A Virtual Roundtable, Key Opinion Leaders Benchmark the Science. In the following month, Part Three will begin the next phase of the series, sharing the views and plans of company leaders in the combination cancer immunotherapy space.

BRAKES OFF, GAS PEDAL DOWN

Cancer immunotherapies of various sorts have been around for a long time, but have never met the threshold of potency necessary to defeat the disease in most patients. In the past several years, however, four new approaches have excited — and some would say mesmerized — researchers: cell-based therapy, checkpoint blockade or inhibition, immunostimulation, and cancer vaccines, with the likely combination of more than one drug in one or more of these classes.

Cell-Based Immunotherapy. Exemplified by Dendreon's Provenge (Sipuleucel-T), this personalized form of immunotherapy involves removing immune and/or tumor cells from an individual patient's blood or tissue, transforming them through a biochemical process into specialized immune cells capable of an immune response to the patient's cancer, and injecting the transformed cells back into the patients. The approach is expensive and logistically challenging, but "industrialization" facilitated through central production sites may extend its practical application.

Checkpoint Blockade/Inhibition. In "taking the brakes off" the immune system, checkpoint inhibitors block certain receptors or "checkpoints" expressed on T cells and other immune cells that allow tumors to avoid immune system detection and attack. Tumors essentially suppress the immune system by hijacking immune cell antigens, the "points" in "checkpoints," of which about two dozen have been identified. The first approved "off-the shelf" immunotherapy, Yervoy (ipilimumab), is a checkpoint "blockade" that inhibits the CTLA-4 receptor (cytotoxic T-lymphocyte associated antigen 4) on T cells, allowing the cells to proliferate and attack the cancer. Other agents in development target the PD-1 (programmed cell death protein 1) checkpoint, unleashing T cells and natural killer (NK) cells to proliferate and destroy the tumor, and PD-LI, a protein secreted by the tumor cells to the PD-1 receptor on T cells and to T reg cells that support the suppression of the immune system by the tumor. More inhibitory agents are in development for many of the other checkpoints now identified — each with its own unique role in rallying all of the immune system's armamentarium against cancer.

Immunostimulati on. Besides taking the brakes off the immune system, many researchers and companies are "stepping on the accelerator" by combining checkpoint blockade with agents that directly stimulate proliferation of T cells and other immune cells. Although the most-often discussed are agents like anti- OX40, which cause proliferation of activated CD4+ and CD8+ antitumor T cells, immunostimulators may also include chemotherapy, monoclonal antibodies such as Rituximab, and autologous stem cell transplantation. (See sidebar "Cancer Vaccines — A New Wave.")

CANCER VACCINES — A NEW WAVE
A creative approach to new cancer vaccines shows promise.

Where do cancer vaccines fit in the evolving paradigm for combination immunotherapy? The CAR-T (Chimeric Antigen Receptor Therapy) and autologous T cell technologies have shown that highly activated and targeted T cells can be home to tumors and provide a clinical benefit. The idea of activating T cells by using a vaccine technology is intuitive, particularly when combined with other immunotherapies that act on the tumor microenvironment and address its immune suppressive mechanisms, provided a meaningful T cell response is induced.

Not surprisingly, vaccines are generally believed to be ineffective; they only weakly activate T cells, and their use as monotherapies without addressing the immune-suppressive mechanisms has been an overwhelming weakness. But a new wave of rationally designed cancer vaccines has emerged, and the early data is intriguing.

The implementation of innovative technologies including viral vectors, DNA technologies, novel adjuvants, and formulations has demonstrated an ability to induce antigentargeted T cell responses in cancer patients. Signals of clinical activity that conform with traditional endpoints in statistically modeled randomized studies, including response rate or disease progression evaluations, are emerging.

Going forward, the demonstration of a T cellbased mechanism of action in a meaningful number of cancer patients early in development will be an important gating event. Technological advancements in monitoring T cells will allow a sophisticated and rational evaluation of vaccines. A cancer vaccine may still be the underdog that enables highly effective combination immunotherapies.

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