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The Phoenix Rises: The Rebirth of Cancer Immunotherapy

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The idea that the immune system can control cancer is not new. It was first theorized by Paul Ehrlich in 1909 when he suggested that cancers spontaneously arise at a high frequency in humans but are kept under control by the immune system. Over the course of a century, this idea has moved in and out of favor, and only recently has the true potential of the immune system to treat cancer been realized.

Cancer immunotherapy relies on activating an individual's own immune system to eradicate established tumors, and, in contrast to conventional cancer therapies, induces a dynamic response that can result in long-lasting remission. Current immunotherapies against existing cancers include various approaches, ranging from stimulating immune effectors to counteracting immune suppressors. Although there have been patients with certain tumor types that have achieved extraordinary survival benefits, for the majority of cancer patients, immunotherapy remains relatively ineffective. As a result, new therapies and therapeutic regimens that combine various immunological agents are being described and assessed at a breathtaking pace. These new strategies have already been shown to significantly enhance antitumor immunity; however, they can also result in increased immune toxicities. To balance the harms and benefits of these therapies, some critical questions must be addressed, including which therapies or therapeutic combinations provide the most benefit and should continue being studied, and which individuals will benefit from each of these treatments.

In this Q&A article, four experts discuss why it took so long for the promise of cancer immunotherapy to be realized, which cancers this therapeutic modality can treat, what are the most promising new therapies or therapeutic combinations, and what are the potential roles of biomarkers in guiding treatment. In addition, they will discuss the current costs of immunotherapy as well as its future potential.

The idea that the immune system could suppress cancer was first proposed over a hundred years ago, yet the field has only matured over the last decade. What took so long for the idea to become a clinical reality?

Mario Sznol: In the modern era, proof of concept for the potential of immune therapy to produce meaningful activity in advanced cancer came from the studies of interleukin-2 in the 1980s. However, activity was restricted to a small subset of patients with melanoma and renal cell carcinoma, and the toxicity of interleukin-2 precluded broad screening of activity against other solid tumors. Much of the investigational effort focused on stimulation of the immune system with cytokines and/or vaccines, which were only marginally effective. The turning point came with the introduction of agents such as anti-CTLA-4 (anti– cytotoxic T-lymphocyte associated protein 4)[7] and anti-PD-1 (anti–programmed cell death protein 1) that blocked inhibitory signals to T cells. These "immune checkpoint" inhibitors produced a greater activity in metastatic melanoma than prior agents, and, in particular, anti-PD-1 showed activity against a large number of metastatic malignancies. Therefore, the long delay before immune therapy became a broadly accepted therapeutic modality was due to the late recognition that inhibitory signals to

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[7] Nonstandard abbreviations: CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; CAR, chimeric antigen receptor; PD-L1, programmed cell death ligand 1; STING, stimulator of interferon genes.

T cells are dominant in subverting effective antitumor immune responses.

Jason J. Luke: Immunotherapy has been part of the standard of care in the treatment of cancer for several decades in the form of bone marrow transplants for hematologic malignancies; monoclonal antibodies, such as anti-CD20 (lymphoma) or anti-HER2 (breast); dendritic cell vaccines for prostate cancer; and immune adjuvants or cytokines, such as Calmette-Guerin bacillus for bladder cancer, or interferons/interleukins for melanoma and kidney cancers. The role of immune checkpoints in regulating immunity has only been known for a few decades, and the rationale for targeting them has only come to the forefront in the past several years.

Elizabeth I. Buchbinder: The ability of the immune system to control cancer relies on several factors that we understand and some we are just beginning to clarify. The immune system is an incredibly complicated system with numerous checks and balances to prevent too aggressive an immune response. Early treatments that worked on the principle of stimulating the immune system as a whole were generally very toxic. In addition, the heterogeneity observed between individual malignancies, and even within individual tumors, plays a huge role in our ability to bring about an immune response.

Padmanee Sharma: We needed to understand how T-cell responses were regulated. Jim Allison's work showed that T cells had "on" and "off" switches that controlled their responses; his work showed that it was necessary to block the "off" switches to unleash antitumor T-cell response.

Cancer immunotherapy is being portrayed as a potential cure for cancer. Do you feel that this is accurate?

Padmanee Sharma: Yes! Patients with metastatic cancers who previously had only a few months to live are now alive for years.

Elizabeth I. Buchbinder: While many patients may have marked reduction of their cancer to the point that we can no longer detect any on routine imaging or testing, it remains unknown if there are residual cancer cells that the immune system is preventing from growing. However, from a patient perspective, the long-term durable responses seen with immunotherapy are the equivalent of a cure, and thus this would be accurate.

Mario Sznol: Cancer immunotherapy as a cure for a subset of patients with advanced malignancies is already a clinical reality. Our approaches will improve and the number of patients cured with immune therapy will increase over time. However, optimal therapy and "cure" for many patients will require multimodality approaches, including targeted therapies, chemotherapy, radiation, and surgery. And sadly, not all patients and not all types of cancer will be responsive to immune therapies and will not be cured (although, some may receive significant survival benefit). Of all the available modalities for treating cancer, immune therapies have the highest potential for producing long-term remissions.

Jason J. Luke: Yes, to a degree, however with nuance. There is no question that subsets of patients have long-term durable benefit from immunotherapy. Bone marrow transplants are an obvious example of this. In the realm of solid tumors, it has been known for a long time that approximately 10% of patients receiving interleukin-2 for melanoma or kidney cancer have had long-term benefit (>10 years). This has been improved with checkpoint blockade with examples in melanoma of 22% 5–10-year survival with anti-CTLA-4 and 34% 5-year survival with anti-PD-1. The obvious inverse of these statements, however, is that the majority of patients are not cured with these treatments, and it should be pointed out that most of the combination regimens being proposed to date are likely to further improve the benefit in those patients who were most likely to benefit in the first place. A great focus must be given in expanding the total population of patients benefiting from immunotherapy.

Some cancers, such as melanoma, are considered to be more immunogenic and thus respond more favorably to immunotherapy than others. Will we be able to

translate our success with melanoma to other nonimmunogenic cancers?

Jason J. Luke: Yes, this is already happening. This can be seen with the approval of anti-PD-1 in non–small cell lung cell cancer, renal cell carcinoma, urothelial bladder cancer, Hodgkin lymphoma, and head and neck squamous cell carcinoma. This has been particularly striking in lung cancer where this disease was thought until recently to be "nonimmunogenic," but it is now standard practice to treat a subset of patients with immunotherapy instead of chemotherapy until demonstration that the immunotherapy is ineffective. More broadly, even in tumor types that have not had initial success with checkpoint immunotherapy such as colon cancer, many groups are piloting novel approaches to drive T-cell infiltration into nonimmunogenic tumors so as to be able to use drugs we already have (anti-PD-1 and anti-CTLA-4) with the hopes of engendering long-term responses.

Padmanee Sharma: Absolutely! For example, we're already making some progress in prostate cancer.

Elizabeth I. Buchbinder: Some of the nonimmunogenic tumors present huge barriers to immunotherapy by having little that the immune system recognizes as nonself and/or by surrounding the tumor with supportive stroma or other immune inhibitory factors. There are many avenues of research trying to overcome these boundaries, and it will require a balance to overcome the tumor protective features without causing too much collateral damage to normal tissue.

Mario Sznol: The division of cancers into "immunogenic" vs "nonimmunogenic" is probably too simplistic. Lung cancer was considered a nonimmunogenic tumor until responses were first observed with anti-PD-1. While it may be true that some tumors do not present any antigens recognized by the host T-cell repertoire (possibly the better definition of truly nonimmunogenic), it may still be possible to target other determinants with engineered CAR (chimeric antigen receptor) T cells. The National Cancer Institute Surgery Branch presented proof of concept that rare tumor antigen–specific T cells could be found in epithelial tumors with low mutation burdens, and when expanded and reintroduced to patients in the setting of prior lymphoablation, the tumor-specific T cells could mediate clinically relevant antitumor activity.

Many individuals with immunogenic cancers do not respond to immunotherapy treatment, while some individuals with nonimmunogenic cancers do. Do we understand why this is? How large of a challenge does this pose in deciding whom to treat with immunotherapies?

Elizabeth I. Buchbinder: As we treat more and more patients with immunotherapy, we are discovering the complexities involved in this process. Responses to immunotherapy depend upon characteristics of the tumor, host immune system, prior antigen exposure, and characteristics of the individual patient. While some factors like tumor PD-L1 (programmed cell death ligand 1) expression, high mutational load, and T-cell infiltration may help select the best responders, the fact that some patients lacking these factors still respond suggests that we cannot yet exclude patients based upon these factors. However, in the future we are likely to use these and other factors to help select which immunotherapy or combination may be best for an individual patient.

Jason J. Luke: Tumors from patients with cancers can be broadly classified into those that demonstrate evidence of a spontaneous immune infiltrate (T-cell–inflamed) and those that do not (non–T-cell–inflamed). While some tumor types demonstrate higher levels of spontaneous T-cell inflammation (melanoma and kidney for example), some fraction of tumors from all cancer histologies demonstrates this. Numerous groups have already published pan-cancer analyses of T-cell inflammation that can act as an initial road map for the effectiveness of current immunotherapies. Over time, this will need to be refined as combination regimens come forward and our mechanistic understanding of what initiates T-cell inflammation improves. These mechanisms may include, but are not limited to, tumor mutational load/neoantigen burden, tumor-intrinsic oncogenic signaling pathways, and tumor extrinsic mechanisms such as germline polymorphisms in immune genes and environmental exposures such as the contents of the human microbiome.

Padmanee Sharma: We are still trying to understand why some patients respond and others do not. There are some clues, including mutations in tumor cells that permit immune evasion and other immune checkpoints that we are planning to target in new clinical trials.

Mario Sznol: As noted before, we cannot truly characterize tumors as immunogenic vs nonimmunogenic because we cannot routinely and accurately assess the presence, magnitude, or quality of tumor antigen–specific T-cell responses in individuals. Tumors that respond to immune checkpoint inhibitors likely have ongoing and potentially effective tumor-specific T-cell responses that are inhibited by reversible mechanisms addressed by the specific administered agents. There are several reasons why patients might not respond, including the absence (lack of priming or destruction) of tumor antigen–

specific T cells, exclusion of T cells from the tumor microenvironment, or other immune suppressive factors within the tumor microenvironment not addressed by the specific administered agents. It is also possible that additional signals, for example, for proliferation or activation, are required before a threshold antitumor response is generated. The greatest challenge to development of more effective immunotherapies is the development of biomarkers that identify the critical signals or factors missing (or required) for effective antitumor immunity.

There are numerous immunotherapies available or being investigated. What do you feel is the most promising new therapy, or therapeutic combination, being developed or tested right now?

Elizabeth I. Buchbinder: There are so many promising immunotherapies being developed at this time that this question is probably the most challenging and might have a different answer on a different day. One immunotherapy that I find very exciting at this time is the development of vaccines based upon cancer neoantigens. This technology creates specific vaccines to novel antigens found only in the tumor itself, and can be combined with other immunotherapies to bring about a targeted immune response. I am also very excited about the different injectable therapies that are entering clinical testing given the opportunity to convert an immunologically bland tumor into a reactive one that would then respond to other immunotherapies.

Jason J. Luke: Building off a rational categorization of cancer immunity by the T-cell–inflamed and non–T-cell–inflamed phenotypes, we can consider priority combinations in each setting. For patients whose tumors demonstrate robust T-cell inflammation, combination strategies directed toward interferon-γ associated gene expression make a great deal of sense. An example of this is anti-PD-1 in combination with indoleamine-dioxygenase inhibition. This combination has moved rapidly into a registrational phase III study, and may become the standard of care in short order. Alternatively, in patients whose tumors do not have T-cell inflammation, investigators should consider approaches that may drive an inflammatory phenotype (with examples including oncolytic viruses, toll-like receptor or STING (stimulator of interferon genes) agonists, or even radiation) before the administration of checkpoint immunotherapy.

Mario Sznol: Based on activity reported in either randomized trials or phase 2 studies across several different malignancies, the most promising combination to date is anti-CTLA-4 plus anti-PD-1. The activity is explained, in part, by the critical and nonredundant roles of PD-1 and CTLA-4 in controlling host immunity.

Padmanee Sharma: Combination therapy with genomically targeted agents plus immune checkpoint therapy.

What role do you see for biomarkers in cancer immunotherapy, and, of all the biomarkers being studied, developed, or used, which do you think are the most promising?

Padmanee Sharma: Biomarkers will be important to help determine which patients would benefit from monotherapy and who would need combination therapy. Important biomarkers include CD8 tumor-infiltrating T cells and mutation status of tumors.

Jason J. Luke: Many biomarkers are being developed but those that currently appear to be the most promising include gene expression profiling around interferon-γ, mutational density/neoantigen prediction, PD-L1 immunohistochemistry, and T-cell receptor sequencing. Of these, gene expression profiling appears the most promising since it gives the most robust description of the intratumoral immune response. All of these technologies can tell us who is most likely to benefit, but the broad power of expression profiling can suggest tumors where checkpoint immunotherapy is least likely to have activity.

Mario Sznol: Biomarkers are, of course, critical for development of immune therapies. There are a very large number of potential combinations, and it is highly likely that any combination would only address a subset of patients. Gene expression studies of whole tumor (large biopsies) may provide the greatest information for any single test, but current technologies cannot assess and interpret all the relevant information in tumor (and possibly peripheral blood), which would include quality and quantity of the tumor antigen–specific response. In addition, it will be difficult to assess the critical and nonredundant signals required by an individual (based on their specific tumor–host relationship) to produce effective antitumor responses.

Elizabeth I. Buchbinder: Biomarkers in cancer immunotherapy have the potential to predict response to immunotherapy, help guide treatment selection, predict the likelihood of severe toxicity, and detect mechanisms of resistance to immunotherapy. At this time, the majority of biomarkers for cancer immunotherapy are still in very early stages of development. The most robust of these biomarkers is PD-L1 testing, although we are still working out how best to use this in patient care. I think the most promising biomarkers are those that will help de-

termine mechanism of resistance to immunotherapy, and help guide future combinations and salvage therapies.

These new therapies have a high cost associated with them, both societal (e.g., financial) and individual (e.g., potential for severe adverse events). At this point in time, do the benefits of cancer immunotherapy outweigh the harms, and what is being done to reduce these costs?

Mario Sznol: There is no question that benefit outweighs risk (considering only adverse events, not cost) for these agents in almost all settings. A subset of patients with otherwise very poor prognosis can be converted into long-term survivors, and some patients can be cured. Clearly the high cost of the agents is a problem, particularly when used in unselected populations amongst which only a small subset might obtain substantial survival benefit. Aside from influencing the amount charged for the agents, the only hope for reducing cost is to find improved biomarkers for selection and to better define optimal length of therapy.

Elizabeth I. Buchbinder: At this point in time, the potential for patients to develop durable long-term responses from cancer treatment make the benefit of these treatments outweigh the harms. However, we need to continue working on methods to recognize and control immune toxicities early to avoid long-term consequences and harm. There are several active trials looking at combining therapies aimed at reducing toxicity with active immunotherapy. In addition, the financial impact of this therapy can be large, and efforts are needed to develop less expensive therapies and treatment algorithms that help control cost.

Jason J. Luke: There is no doubt that these therapies are very expensive, and this is a relatively urgent societal issue that must be addressed. At this time, however, there is also no doubt that they are worth the cost given the potential for long-term survival and societal productivity. As the use of these agents expands there should be a priority to require the codevelopment of biomarkers that guide their use. That being said, there will always be a tension since it seems that the addition of immunotherapy will make any cancer therapy more effective.

Padmanee Sharma: The benefits outweigh the risks because patients are able to live for years, more than 10 years in some cases, which is a significant improvement for patients with metastatic cancer. It would be important for pharmaceutical companies to decrease costs of the drugs.

What do you foresee as the role of cancer immunotherapy in the future?

Padmanee Sharma: Cancer immunotherapy is, and will continue to be, a pillar of cancer treatment, similar to surgery and radiation therapy.

Elizabeth I. Buchbinder: Cancer immunotherapy is rapidly expanding into the treatment of numerous malignancies, and as we develop better and better drugs and combinations, I expect this to continue. Due to the fact that cancer is a very heterogeneous disease, I think there will be cancers where its benefit remains small or requires novel approaches as well as combinations with more traditional therapies. Thus, while cancer immunotherapy has huge potential, we still have a long way to go before it can be given successfully to all patients with cancer.

Mario Sznol: Cancer immunotherapy will be the predominant mode of therapy, or be a component of therapy, for the majority of patients with advanced solid tumors (and possibly also for hematological malignancies). This could take many forms and involve different types of agents. I also believe that immune therapies will be brought to the surgical adjuvant setting in many malignancies. However, cancer is a complex disease, and it is unrealistic to believe that immunotherapy alone will cure all cancers. Optimal therapies will combine immune therapy with newer agents targeted to key molecular events that maintain the malignant phenotype.

Jason J. Luke: Cancer immunotherapy will become integrated into the standard treatment paradigm for every kind of cancer. This is likely to be throughout the treatment spectrum from neoadjuvant (before surgery) through to advanced disease/palliative intent treatment. In different diseases, this will take different forms either as a stand-alone modality (as already seen in melanoma) to combination approaches (for example, with leukemia where cytoreductive chemotherapy remains an essential element of treatment to reduce cancer-related immunosuppression). A pie-in-the-sky thought surrounds whether, for some cancers, we may eventually be able to avoid surgery, radiation, or chemotherapy with the use of immunotherapy. While that is exciting to entertain, it is not anywhere in the immediate horizon.

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