T-cell-based Immunotherapy: Adoptive Cell Transfer and Checkpoint Inhibition

Roch Houot¹,², Liora Michal Schultz³, Aurélien Marabelle⁴, and Holbrook Kohrt⁵

Abstract

Tumor immunotherapy has had demonstrable efficacy in patients with cancer. The most promising results have been with T-cell-based therapies. These include adoptive cell transfer of tumor-infiltrating lymphocytes, genetically engineered T cells, and immune checkpoint inhibitor antibodies. In this review, we describe the different T-cell-based strategies currently in clinical trials and put their applications, present and future, into perspective. Cancer Immunol Res; 3(10); 1115–22. ©2015 AACR.

Introduction

T cells are believed to play a major role in immunosurveillance and tumor eradication. On the basis of this paradigm, over the past quarter century, therapies have been developed to generate, educate, and/or enhance T cells against tumors (Fig. 1). Although the initial demonstration that T cells had the potential to treat cancer comes from allogeneic stem cell transplantation, here we focus on autologous T cells, which can be manipulated in two ways to treat cancer: either ex vivo using adoptive cell transfer (ACT) or in vivo using T-cell targeting antibodies.

The first adoptive transfer approach consists of the infusion of autologous lymphocytes with antitumor properties. These lymphocytes can be derived from unmodified (i.e., naturally occurring) T cells isolated from resected tumors (tumor-infiltrating lymphocytes, TIL) or genetically engineered T cells recognizing tumor antigens (T-cell receptors (TCR) or chimeric antigen receptors (CAR)). The second approach consists of direct in vivo stimulation of lymphocytes in patients using antibodies, including checkpoint inhibitors and bispecifics (Fig. 2). Each of these strategies has its own characteristics (Table 1): the identification of a tumor antigen (Ag), whether it is needed or not, the type of tumor Ag that is targeted (surface vs. intracellular), the nature of the T-cell response that is generated against the tumor (monoclonal vs. polyclonal), the durability of immune protection (short term/passive vs. long lasting/active), and the methods of production of the “drug” (off-the-shelf vs. customized, personalized vs. “universal”). On the basis of these characteristics, some T-cell therapies may be more applicable than others, depending on the type of tumor. Here we also compare and contrast the potential benefit and toxicities of monotherapy versus combinatorial approaches (adoptive T cells and checkpoint inhibitor antibodies; Table 2).

Adoptive T-cell Transfer

Adoptive T-cell Transfer offers several advantages. Antitumor T cells with high-avidity recognition of tumor antigens can be expanded in vitro in large numbers, genetically engineered, and/or activated ex vivo to acquire antitumor functions. In addition, the host can be manipulated before cell transfer to eliminate suppressor cells (such as T-regulatory lymphocytes and myeloid-derived suppressor cells) and promote in vivo expansion of transferred lymphocytes (through “homeostatic expansion”) by eliminating endogenous lymphocytes that can behave like a cytokine sink that competes for the same survival and stimulatory factors (notably cytokines such as IL7 and IL15). The lymphocytes infused during ACT function as “living drugs” that can induce long-term protection.

Tumor-infiltrating lymphocytes

Tumor-infiltrating lymphocytes are a heterogeneous cell population found within neoplastic lesions and are mainly composed of T cells. A fraction of TILs express TCRs directed against unique or shared tumor-associated antigens and exert cytotoxic effects against malignant cells. These TILs can be isolated from resected tumors, selected and expanded ex vivo.

The initial studies, published in 1988, consisted of the administration of TILs to patients with metastatic melanomas (1). However, these cells were unable to persist in vivo, despite concomitant administration of IL2, a T-cell growth factor. This approach was significantly improved by the administration of a lymphodepleting preparative regimen consisting of chemotherapy (usually cyclophosphamide and fludarabine) with or without total-body irradiation (TBI). In recent protocols, overall response rates and complete response rates for metastatic melanoma were around 50% and 20%, respectively (2, 3). Responses were seen in all visceral sites including brain. Most importantly, these responses appeared durable. Among patients who achieve a complete tumor regression (22% of the patients, n = 20), 95% of them have ongoing complete regressions beyond 5 years and may be cured (3).
Although this strategy allows expansion and persistence of a large number of polyclonal antitumor T cells, there are several limitations to this approach. The first limitation relates to feasibility. The tumor needs to be resected for isolation and expansion of TILs. The patient needs to be "suitable" to tolerate lymphodepletion and IL2-based treatments and remain suitable during the several-week period required to expand the cells in vitro. The laboratories producing TILs need to be specialized and have highly trained personnel. The procedure is expensive. Most significantly, this approach may not be applicable in tumors other than melanoma. Indeed, the efficacy of naturally occurring TILs seems to be primarily restricted to melanoma, for reasons that are not fully understood. Melanoma is unusual among cancers in that it naturally gives rise to high numbers of antitumor T cells infiltrating into tumors. Although TILs can be isolated from many cancers, to date, only those from melanomas consistently possess specific cytolysis against the tumors from which they were generated. This may be due to the strong immunogenicity of melanoma resulting from the high frequency of mutational events. Nevertheless, some tumors might be responsive to TIL therapy, especially those expressing potentially immunogenic mutational epitopes (high frequency of somatic mutations) and those sensitive to checkpoint blockade.

Unmodified T cells can also be used to treat virally associated cancers (e.g., Epstein-Barr virus [EBV]– or human papillomavirus [HPV]–associated tumors] that express viral foreign antigens. EBV-associated tumors include Burkitt lymphoma, nasopharyngeal carcinoma, lymphoproliferative disorders, some Hodgkin and non–Hodgkin lymphoma, and gastric carcinoma. EBV expresses latency genes in transformed cells, and the viral proteins can be targeted by T cells. EBV-specific T cells can be isolated and expanded from peripheral blood. Donor and third-party (i.e., allogeneic) EBV-specific T cells have been successfully used to treat posttransplant lymphoproliferative disorders. Autologous EBV–specific T cells also demonstrated promising efficacy in EBV-associated tumors such as nasopharyngeal carcinoma and Hodgkin disease.

**Genetically modified T cells (TCRs, CARs)**

As mentioned previously, a major limitation in the more widespread application of TIL therapy is the difficulty in identifying antigen-specific T cells in other cancer types. Although naturally occurring TILs have demonstrated efficacy in melanoma, all tumor types with identifiable tumor-associated antigens can be lysed by T cells engineered to recognize tumor...
antigens. Moreover, TIL therapy makes it necessary for each patient to have a surgical resection and requires the ability to consistently generate and expand T cells while preserving anti-tumor function. To overcome these obstacles, investigators have developed approaches on the basis of genetic modification of normal peripheral-blood T cells. These modifications allow T cells to be specifically redirected to tumor antigens and trigger T-cell activation and tumor eradication upon antigen binding.

There are two common approaches for redirecting T-cell specificity: (i) gene modification with TCRs directed against tumor-associated antigens and (ii) introduction of a CAR. Different types of antigens can theoretically be used to redirect autologous T cells against tumor cells: tissue-specific differentiation antigens [such as melanocyte differentiation antigens (MDA); e.g., gp100 or MART1, in melanoma and CD19 in B-cell malignancies], cancer testis (germ cell) antigens (such as NY-ESO-1), which are detected in many tumors but not in normal adult tissues, with the exception of the testis (11), overexpressed self-proteins (such as HER2), mutational antigens (such as EBV in Hodgkin disease and HPV in cervical cancer), and viral antigens (such as gp100 in melanoma (13), carinoembryonic antigen (CEA) in colorectal cancer (14), and NY-ESO-1 (15) and MAGE-A3 (16) in melanoma and synovial sarcoma).

Genetically modified T cells (TCRs or CARs) are transfected using virus vectors (retroviruses or lentiviruses) or a transposon system (Sleeping Beauty). Following transfection, genetically modified T cells are expanded and transferred into patients treated with preconditioning lymphodepletion similar to that used with TIL protocols.

**TCR T cells.** TCR T cells are T cells cloned with TCRs in which variable α- and β-chains with specificity against a tumor antigen (either from a patient or from humanized mice immunized with tumor antigens). Such T cells recognize processed peptide antigens expressed in the context of MHC.

Some of the advantages of TCR T cells arise from the fact that these cells can be produced from peripheral blood T cells (unlike TILs) and can "see" intracellular antigens (unlike CARs). However, many of the TCR T-cell trials were accompanied by on- or off-target toxicity. TCRs recognizing tumor-associated antigens expressed on healthy tissues induced on-target toxicity. MDAAs such as MART1 and gp100 are expressed by normal melanocytes present in the skin, retina, and inner ear. TCR gene therapy against MART1 and gp100 resulted in skin rash, uveitis, and hearing loss (14). Similarly, patients with colorectal adenocarcinoma who were treated with CEA TCRs experienced dose-limiting severe colitis due to the expression of CEA on normal epithelial cells throughout the gastrointestinal tract (14). The use of T cells with MAGE-A3–specific TCRs, a cancer testis (CT) antigen, also resulted in on-target toxicity. These patients experienced neurologic
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therapy-refractory diffuse large B-cell lymphoma (DLBCL). In still ongoing at 9 and 22 months), two partial responses (PR), CAR T cells induced four complete responses (CR; three of them

Abbreviations: Ag, antigen; CRS, cytogen release syndrome.

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>TILs</th>
<th>TCRs</th>
<th>CARs</th>
<th>Bispecific antibodies</th>
<th>Checkpoint Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Unmodified (naturally occurring) T cells genetically engineered ex vivo from peripheral T cells</td>
<td>T cells genetically engineered ex vivo from peripheral T cells to express recombinant TCR against a tumor Ag</td>
<td>T cells genetically engineered ex vivo from peripheral T cells to express a CAR (scFv with TCR signaling molecules) against a tumor surface Ag</td>
<td>T-cell engaging bispecific antibodies directed against a tumor surface Ag and CD5</td>
<td>Antibodies blocking inhibitory molecules on T cells to enhance their function</td>
</tr>
<tr>
<td>Requirement for tumor Ag identification</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Specificity against tumor cells</td>
<td>Polyclonal</td>
<td>Monoclonal</td>
<td>Monoclonal</td>
<td>Monoclonal</td>
<td>Polyclonal</td>
</tr>
<tr>
<td>Origin of Ag targeted</td>
<td>Intracellular and extracellular</td>
<td>Intracellular (MHC-restricted T cells)</td>
<td>Surface</td>
<td>Surface</td>
<td>Intracellular and extracellular</td>
</tr>
<tr>
<td>MHC-restricted</td>
<td>Yes*</td>
<td>Yes*</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Long-lasting protection</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Off-the-shelf</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Personalized therapy</td>
<td>Feasibility Mostly restricted to melanoma</td>
<td>On-target/off-tumor toxicity</td>
<td>On-target/off-tumor toxicity</td>
<td>Tumor escape (loss of CD3 antibody)</td>
<td>Autoimmune manifestations</td>
</tr>
<tr>
<td>Main limitations</td>
<td>+++++</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: Ag, antigen; CRS, cytogen release syndrome.
*HLA-negative tumors are not “seen,” but HLA presentation allows recognition of intracellular antigens.

In early-phase clinical trials, the most promising results of CARs have been obtained in B-cell malignancies with CAR T cells with specificity for CD19. In lymphoma, anti-CD19 CAR T cells were promisingly efficacious (18). Specifically, anti-CD19 CAR T cells induced four complete responses (CR, three of them still ongoing at 9 and 22 months), two partial responses (PR), and one stable disease (SD) out of seven patients with chemotherapy-refractory diffuse large B-cell lymphoma (DLBCL). In chronic lymphocytic leukemia (CLL), of 23 patients treated with CD19 CAR T cells, 5 (22%) achieved a CR and 4 (17%) achieved a PR, for an overall response rate of 39% (19). However, the most spectacular results have been observed in acute lymphoblastic leukemia (ALL). By infusing CD19-targeting CARs in 30 patients (25 children and 5 adults) with relapsed or refractory ALL, Maude and colleagues reported a 90% complete remission (20). CAR T cells were also able to eradicate leukemia in the cerebrospinal fluid. Sixty-seven percent of the patients remained in remission at 6 months. Prolonged persistence of CD19 CARs (for years) has been observed. In July 2014, FDA granted breakthrough therapy designation to CD19 CARs for relapsed/refractory ALL. In solid tumors in general, the clinical results have been disappointing so far, due to either lack of efficacy or limiting toxicities. Nevertheless, promising results were achieved by Pule and colleagues with CARs directed to GD2 in neuroblastoma. Three of 11 patients with active neuroblastoma achieved CR (21, 22). CARs have also been developed that recognize many other targets, including HER2 for colorectal cancer (23), folate receptor-α for ovarian cancer (24), and carbonic anhydrase IX (CAIX) for renal cell carcinoma (25), but failed to show significant antitumor effect. CARs to a multitude of different antigens are currently under development.

CAR technology offers many advantages. Similar to TCRs, CARs can be produced from peripheral blood T cells. However, in contrast to TCR T cells that are restricted to a single type of MHC molecule, CARs can be used to treat all patients in an HLA-unrestricted manner. In addition, they can target tumors that have downregulated HLA class I molecules or fail to process or present proteins. Despite promising efficacy, extensive use of CAR therapy may be limited by a number of issues. The first issue relates to on-target/off-tumor toxicity. To date, most CAR trials have targeted overexpressed antigens, nonmutated self-proteins.
Toxicity On-target/off-tumor effect IrAE: Nonspecific manifestations of CRS include fever, increased cytokine concentration, pancytopenia, hypotension, hypoxia, and neurologic symptoms. It usually correlates with tumor burden, T-cell proliferation, and clinical response. CRS can be effectively treated with glucocorticoids and/or, preferentially, antibody to IL-6 receptor (tocilizumab). Another issue with CAR therapy is tumor escape by loss of target expression. Indeed, T-cell–driven selective pressure allows emergence of CD19-negative populations leading to tumor escape. This has been observed in several patients with ALL treated with CD19 CARs.

Although very promising, engineered T cells are facing several limitations including toxicity, applicability, and sometimes limited efficacy. Several approaches are trying to obviate these limitations. Regarding safety, toxicities may be limited by careful choice of target antigens to avoid off-tumor but on-target adverse effects. Ideal targets should be tumor-specific antigens. In case of antigens shared with normal tissues, these should not be present on tissues of vital organs. The identification of appropriate tumor antigens is perhaps the greatest challenge now facing researchers in the field of ACT. Toxicities may also be limited through on-demand cell destruction of engineered T cells by incorporation of suicide genes. These strategies include Herpes simplex virus thymidine kinase (HSV-TK) and inducible caspase-9 (26). Regarding applicability of engineered T cells, strategies are being developed to generate "universal" T cells that could be manufactured from one donor and administered to multiple patients. For instance, this could be done by eliminating the expression of endogenous TCR to generate T cells devoid of alloreactive TCRs (27).

**Checkpoints Blockade**

Multiple inhibitory mechanisms restrain endogenous TILs and modified T cells used for adoptive therapy from effectively

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Table 2. Comparison of ACT, checkpoint blockade, and combinatorial adoptive T-cell and checkpoint blockade therapy

<table>
<thead>
<tr>
<th>Impact of combination therapy</th>
<th>Checkpoint blockade</th>
<th>Adoptive T-cell therapy (ACT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Most experience and efficacy demonstrated with hematologic malignancies (CD19-expressing tumors)</td>
<td>Most experience and efficacy demonstrated with solid tumors (malignant melanoma, RCC, NSCLC)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>On-target/off-tumor effect CRS</td>
<td>IrAE: Nonspecific autoreactive T-cell activity</td>
</tr>
<tr>
<td>Effector cell source</td>
<td>CAR/TCR: Autologous: (Pre-stem cell transplant: patient-derived T cells; post-stem cell transplant: patient-derived engrafted donor T cells that have been tolerated) Allogeneic third-party T cells: Require HLA matching TIL: Tumor-derived</td>
<td>Recruits patients' own T cells without need for apheresis and ex vivo cell manipulation</td>
</tr>
<tr>
<td>Need for antigen specificity</td>
<td>Requires T-cell specificity to cancer-associated antigen: CARs: Different constructs for different tumor types TILs: Patient specific</td>
<td>Effective across tumor types despite varying antigen expression profile</td>
</tr>
<tr>
<td>Scalability</td>
<td>Complicated ex vivo cell manipulation: TIL: TIL isolation and expansion CAR: Apheresis, T-cell transduction (retroviral, lentiviral, sleeping beauty, gene editing via CRISPER) and expansion</td>
<td>Off-the-shelf</td>
</tr>
<tr>
<td>Time for treatment preparation</td>
<td>Time lag introduced to allow for ex vivo cell manipulation and expansion</td>
<td>Readily available</td>
</tr>
</tbody>
</table>

Abbreviations: CRS, cytokine release syndrome; IrAE, immune-related adverse event.
eradicating tumor. Beyond well-documented inhibitory cells including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSC) that are upregulated in the tumor microenvironment, T cells have intrinsic regulatory mechanisms that abrogate their effector function. Activated T cells upregulate surface inhibitory receptors including cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed death ligand 1 (PD-1), and upon binding to their respective ligands, they transmit inhibitory signals to the T cells and attenuate T-cell activation. These receptors act as checkpoints that protect the host from unopposed T-cell activation. Many tumor types take advantage of these inhibitory pathways to circumvent T-cell–mediated destruction. Disrupting these receptor–ligand interactions using blocking antibodies removes this inhibition and enables enhanced T-cell–mediated antitumor activity. This approach to immune therapy is referred to as checkpoint blockade.

One benefit of checkpoint blockade as compared with T-cell therapy is the ease of generalizability to a spectrum of malignancies. Unlike adoptive T-cell therapy that relies upon the presence of cancer-specific antigens and requires ex vivo manipulations, checkpoint blockade can be achieved with the use of an off-the-shelf monoclonal antibody that can be applied across tumor types.

CTLA-4 blockade

CTLA-4 is a member of the CD28:B7 immunoglobulin family and acts as a surface inhibitory receptor found on effector T lymphocytes and Tregs (29). Antibodies blocking CTLA-4 receptor–ligand engagement were the first checkpoint blocking antibodies to be approved for clinical use in melanoma in 2011. Long-term follow-up of earlier studies show that 15% of treated patients survive 5 years, indicating that responses can be durable (30).

The survival improvement seen with antibodies to CTLA-4 in melanoma stimulated further investigation of CTLA-4 blockade in other solid and hematologic malignancies, including prostate cancer, non–small cell lung cancer (NSCLC), RCC, pancreatic cancer, ovarian cancer, glioblastoma, acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS) with encouraging preliminary results. CTLA-4 blockade is also being explored in children with refractory malignancies, including Wilms tumor, bone and soft-tissue sarcomas, neuroblastoma, and lymphomas. Currently, more than 100 trials investigating CTLA4 blockade are ongoing or in the pipeline (clinicaltrials.gov).

The effect of CTLA4 blockade, unfortunately, is not restricted to tumor-specific T cells. The appropriate inhibition of autoreactive T cells can be disrupted, leading to unwanted immune-mediated toxicities, including immune-related adverse events (irAE) most commonly affecting skin (rash, pruritus, vitiligo), bowel (diarrhea, colitis), liver (hepatitis, transaminitis), and endocrine glands (hormonal imbalance; refs. 31, 32).

PD-1 blockade

The PD-1 receptor is expressed on the cell surface membrane of activated T cells. Interaction with ligands PD-L1 (often upregulated on tumor cells including urothelial, ovarian, breast, cervical, colon, pancreatic, gastric, melanoma, glioblastoma, and NSCLC) and PD-L2 (found on antigen-presenting cells including macrophages, mast cells, and dendritic cells; ref. 33) results in an inhibitory signal to the T cell. Preclinical data demonstrating PD-1 expression by TILs, PD-L1 upregulation on certain tumor cells, and mouse models that showed enhanced antitumor immunity through PD1 blockade (34) led to clinical trials of PD-1 blocking agents in 2007 and to FDA approval in 2014 for use in treating melanoma (pembrolizumab, nivolumab).

PD-1 blockade has since been shown to affect RCC, NSCLC, Hodgkin disease, and uroepithelial bladder cancer. The responsiveness of NSCLC was notable, as unlike melanoma and RCC, NSCLC has not previously demonstrated responsiveness to immune therapy. A recent trial in relapsed/refractory Hodgkin disease showed remarkable effects of PD-1 blockade with objective responses in 87% of patients (n = 23; ref. 35). In contrast to most successes with PD-1 blockade, which have been in solid tumors, these results showed an effect of PD-1 blockade in hematologic malignancies.

More than 100 trials are investigating the use of PD-1 blockade agents as monotherapy or in combination with chemotherapeutic agents, targeted therapies, or alternate immunotherapy modalities for multiple tumor types (clinicaltrials.gov). To date, more than 7,000 patients, with multiple indications, including NCSLC, RCC, and malignant melanoma have participated in trials of PD-1 blockade and have tolerated the agent well. To date, the toxicity profile of PD-1 blockade has been less severe than CTLA4–mediated irAE, consistent with PD-1 knockout mice having a milder autoimmune phenotype than CTLA4 knockout mice (36).

Conclusions and Future Directions

Adoptive cell transfer and checkpoint blockade have both had striking success to date, but both treatment modalities are in their infancy, with much untapped potential. Methods to further optimize outcomes are in order. There is a strong rationale to combine checkpoint inhibition with adoptive T-cell therapy. Adoptive T cells require a permissive environment to allow for maximal antitumor effect. Checkpoint blocking antibodies remove T-cell inhibition; however, their effectiveness relies upon the presence of functional tumor-specific T cells. Providing both tumor-specific T cells and removing T-cell inhibitory stimuli through checkpoint blockade may offer outcomes superior to those achieved with either agent alone (Table 2).

The antitumor efficacy of combinatorial therapy with CAR T cells and checkpoint blockade using PD-1 blocking antibodies was investigated preclinically using a transgenic Her2 mouse model treated with Her2-specific CAR T cells alone, mAb to PD-1 alone, or a combined approach. Her2-specific CAR engagement with tumor Her2 antigen has triggered PD-1 upregulation on CAR T cell (37). PD-1 blockade enhanced proliferative and functional capacity of Her2-specific T cells and enhanced regression of established tumor when compared with arms treated with anti-Her2-specific CARs alone (37). An alternative approach to merging CAR technology with checkpoint blockade is being explored preclinically, in which a chimeric protein is generated that fuses an extracellular and transmembrane domain of CTLA-4 or PD-1 to a cytoplasmic-activating signal domain (such as CD28). This innovative chimera, upon binding ligand, transforms the inhibitory CTLA-4 or PD-1 signal into a positive stimulatory signal. CTLA-4/CD28 chimera maximized T-cell antitumor function in preclinical lymphoma and melanoma syngenic mouse models (38). T cells modified to express PD-1/CD28 chimeric molecules exhibited enhanced cytokine secretion, upregulation of activation markers, and
improved proliferation upon coculture with tumor cells in vitro when compared with control cells, and superior in vivo anti-tumor function in two xenograft models of human melanoma tumors (39). These innovative chimeric proteins can be cotransduced with tumor-targeting CARs to combine tumor T-cell specificity, T-cell activation, and abrogation of checkpoint inhibition in a single genetically modified T-cell. However, preclinical data are encouraging, currently no clinical trials in practice are offering combinatorial therapy with CARs and checkpoint blockade. Studies combining genetically modified T cells specific for the NY-ESO-1 antigen expressed on some solid tumors in combination with ipilimumab are in the pipeline. The extent of possible antitumor effects and toxicities of such combinations has yet to be fully explored.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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