Future perspectives in cancer immunotherapy

Marinos Tsiatas[1], Giannis Mountzios[2], Giuseppe Curigliano[3]

[1]Department of Genitourinary Oncology, Athens Medical Center, Marousi, Greece; [2]Department of Medical Oncology, 251 Airforce General Hospital, Athens, Greece; [3]Division of Experimental Therapeutics, European Institute of Oncology, Milano, Italy

Correspondence to: Marinos Tsiatas. 56 Kifisias Ave & 2 Delfon Str, 151 25 Marousi, Greece. Email: mtsiatas@otenet.gr.

Abstract: The advent of immunotherapy has transformed the treatment paradigm of several solid tumors and is expected to influence the therapeutic algorithm even more in the future following the results of numerous ongoing clinical trials in a wide range of malignancies. Exploiting the anti-cancer effect of the immune system with the use of vaccines, viral vectors, and more lately with immune check-point inhibitors and chimeric antigen receptor modification, has been proven a successful therapeutic strategy in a broad spectrum of tumors. In particular, immune check-point inhibition in melanoma, non-small-cell lung cancer and renal cancer, peptide vaccination in prostate cancer and glioblastoma, and oncolytic immunotherapy in melanoma are well-established therapeutic modalities that have obtained approval by regulatory authorities and are already in clinical use. A large number of ongoing clinical trials involving thousands of patients are currently seeking to define the appropriate tumor type, therapeutic setting, treatment combination and patient populations in order to maximize clinical benefit from immunotherapeutic agents. In this context, identification of the patients whose tumors are most likely to respond to immunotherapy by the use of appropriate biomarkers will be crucial for the optimal implementation of immunotherapy into the therapeutic armamentarium.

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Advances in cancer immunotherapy in recent years, with the success of checkpoint inhibition in particular, have caused a paradigm shift in cancer management. After many years of extensive research, the basic mechanisms behind immune surveillance and tumor evasion have been elucidated and that lead to the development of effective immunotherapeutic strategies. In early clinical trials, remarkable responses have been reported but these involved a minority of patients. On the other hand, with the use of immunotherapeutic agents we witnessed an uncommon toxicity profile and we were faced with different kinetics in clinical responses, as well. In order to address these issues, we need to select the patients that will benefit the most from specific immunotherapeutic modalities, with the use of appropriate biomarkers.

Although today's enthusiasm regarding cancer immunotherapy was generated from the results of CTLA-4 and PD-1/PD-L1 inhibition in melanoma patients, several other checkpoint molecules are under investigation, such as TIM-3 and LAG-3. TIM-3, as a checkpoint inhibitor, suppresses effector T cell activation, whereas LAG-3 acts by binding to MHC molecules and also inhibits T cell activation and proliferation (1,2). LAG-3 is co-expressed with PD-1 on T cells, making it a suitable candidate for a combinatorial approach with anti-PD-1 agents. Antibodies against TIM-3 and LAG-3 are under clinical investigation showing encouraging efficacy. Several other targets of host immunity are currently being evaluated in the pre-clinical and clinical settings, including inhibitory (IDO1, B7-H3, B7-H4, VISTA, ICOS, KIR and TIGIT) and stimulatory (OX40, 4-1BB and GITR) molecules (3).

Vaccines, either preventive or therapeutic, against tumor specific or associated antigens are a promising immunotherapeutic strategy, as well. Sipuleucel-T was the first and only approved vaccine for metastatic castration-resistant prostate cancer, which confers a modest survival benefit to patients (4). GVAX, a whole-cell vaccine, showed encouraging results only in combination with CRS-207,

a Listeria monocytogenes-expressing mesothelin vaccine, in advanced pancreatic cancer patients (5). Nevertheless, the majority of vaccines used as monotherapy to treat cancer had failed and this depicts the need to develop novel vaccination strategies, using them in combination with adjuvant or other immunotherapeutic agents, such as checkpoint inhibitors, in order to address tumor-induced immunosuppression (6).

Adoptive cell transfer of tumor-infiltrating lymphocytes (TILs) was traditionally an attractive immunotherapeutic modality. Such TILs were isolated from the patient's tumor, expanded *ex vivo* and re-infused in combination with IL-2 (7). On the other hand, genetic modification and characterization of T cells with chimeric antigen receptors (CARs) allow the recognition of specific tumor antigens by T cells and the elimination of tumor cells. CARs are generated by fusing the antigen-binding region of a monoclonal antibody (mAb) to the membrane-spanning and intracellular-signaling domains, including CD28, 4-1BB and CD137 co-stimulatory molecules. They have recently shown impressive results in patients with acute and chronic lymphoblastic leukemia treated with adoptive transfer of CD19-directed autologous T cells. Recent successes suggest that the modification of T cells with CARs could be a powerful tool for developing safe and effective cancer immunotherapeutic approaches. This strategy can now be further improved and applied on patients with solid malignancies by sequencing the tumor's whole exome and identifying specific and unique neoantigens. Following that, autologous T cells can be engineered to express a CAR against the identified neoantigen. These cells, after expansion and re-infusion, may produce significant clinical responses (8).

Since tumor-host interactions are complex, the strategy to target only one of them may be inadequate. Therefore, immunotherapy in combination with other therapeutic strategies or the administration of different immunotherapeutic modalities together may act synergistically and might restore immune responses more efficiently. The combination of ipilimumab with nivolumab in melanoma showed impressive results leading to accelerated approval from FDA in September of 2015 (9). To date, this is the first and only approved immunotherapeutic combination and is currently being tested in other tumors (10). Several other combinations with checkpoint inhibitors, such as TIM-3, LAG-3 and OX-40, exhibited impressive results in pre-clinical models and are being tested in early-phase trials. Growing knowledge regarding the effects of chemotherapy, radiotherapy and targeted therapy on immunomodulation allowed the design of other immunotherapy combinatorial approaches showing very encouraging results in phase I trials (11).

The aforementioned immunotherapeutic strategies are the result of the application of the accumulated knowledge regarding the tumor-immune system interactions. These approaches are totally different compared to conventional therapies, in terms of efficacy or toxicity, there is therefore a need for the development of new tools for the conduct of such research. Durable responses and the novel kinetics of response observed with immunotherapeutic agents require the definition of new efficacy endpoints in clinical trials. The introduction of immune-related response criteria (irRC) and exploratory endpoints, such as landmark survival, and their adoption from regulatory authorities will be essential for better and faster reporting of efficacy in future clinical trials (12-14).

In order to increase the percentage of patients responding to immunotherapeutic agents, reliable biomarkers are needed. The first immune biomarker used in immune-oncology clinical trials is tumor PD-L1 protein expression that helps identify patients, which are more likely to benefit from anti-PD-1/PD-L1 agents. However, due to the fact that PD-L1 protein expression is inducible and the existence of several assays with different cut-off points for positivity, their utility is controversial and still under discussion (15). In addition to PD-L1, other potential biomarkers that can identify responders include the tumor immune infiltrate score (immunoscore), consisting of the frequency of $CD3^+$ and $CD8^+$ cells (16) or the tumor mutational load that may indicate higher rates of host immune responses to several neoantigens, thus leading to increased responses to checkpoint inhibition (17,18).

Most of the clinical success in the immunotherapy landscape is still based on the universal checkpoint modulatory antibodies, but this success is anticipated to expand to other modalities, as well. It is important to remember that immune-oncology agents across different modalities can show distinct clinical efficacy and safety profiles, but also, potential synergistic effects. For combination therapies, investigations may be designed with an understanding of the underlying mechanisms of action, the expected clinical profiles and the potential synergistic activity of the agents involved (19). The resulting effect of these combinations may well exceed expectations for individual agents in terms of pharmacokinetics and pharmacodynamics, which renders combinations very

appealing for the clinical trial arena. Ultimately, such combinations may hopefully revive the potential for cure, either at a functional level by turning cancer into a controllable chronic disease (similar to the way retroviral drug combinations work) or by the true eradication of the disease, which may indeed now be a realistic goal for a clinically significant number of advanced cancer patients (19).

In conclusion, novel immunotherapeutic agents, used alone or in combination with conventional therapies and demonstrating unique survival benefits, have the potential to transform cancer to a chronic disease and this is now the reality for many cancer patients treated with such agents. However, we need to further improve our immunotherapeutic modalities in order to maximize efficacy and minimize toxicity and this could only be achieved through well-designed clinical trials. Indeed, there are countless studies in several tumors and in different settings that are in progress today and *Table 1* shows that by citing a list of ongoing trials only in the field of breast cancer. The immune-oncology field is rapidly evolving and current excitement is not expected to dissipate but rather continue to increase in the following years, as new effective strategies keep constantly emerging.

Table 1 Ongoing clinical trials involving immune checkpoint inhibitors for breast cancer treatment. Last update: January 2016

Clinicaltrials.gov identifier	Phase	Intervention/contents	Status	Drugs	Responsible party
Advanced/metastatic breast cancer					
NCT02467361	1/2	A study of an inhibitor of STAT3 and cancer stem cells self-renewal in combination with immune checkpoint inhibitors	Recruiting	BBI608 (napabucasin), ipilimumab, nivolumab, pembrolizumab	Boston Biomedical, Inc.
NCT02484404	1/2	PD-L1 blockade in combination with PARP-inhibition or anti-angiogenetic drug for advanced solid tumors and recurrent ovarian cancer	Recruiting	MEDI4736, cediranib, olaparib	National Institutes of Health Clinical Center (CC), National Cancer Institute (NCI)
NCT02309177	1	PD-1 blockade in association with chemotherapy for solid tumors (cohort expansion for HER2-negative breast cancer)	Recruiting	Nab-paclitaxel, nivolumab, gemcitabine, carboplatin	Celgene Corporation
NCT02404441	1/2	PD-1 blockade for advanced malignancies (cohort expansion for TNBC)	Recruiting	PDR001	Novartis (Novartis Pharmaceuticals)
NCT02518958	1	PRIMETIME: RRx-001 plus nivolumab in advanced solid tumors and lymphoma	Recruiting	RRX-001, nivolumab	EpicentRx, Inc.
NCT02303366	Pilot study	BOSTON II: Stereotactic ablation for oligometastatic breast neoplasia in combination with MK-3475 (MAb anti PD-1)	Recruiting	MK-3475, radiosurgery (SABR)	Peter MacCallum Cancer Centre, Australia
NCT02546531	1	FAK inhibitor agent in combination with pembrolizumab and gemcitabine in patients with advanced cancer (expansion cohort for pancreatic cancer)	Recruiting	Defactinib, pembrolizumab, gemcitabine	Washington University School of Medicine
NCT02643303	1/2	*In situ* vaccination with an anti-CTLA-4 agent and IV anti PDL-1 blocker plus a Toll-like receptor agonist for advanced cancers	Not yet recruiting	Durvalumab, tremelimumab, poly ICLC	Ludwig Institute for Cancer Research
NCT02129556	1/2	PANACEA: anti-PD-1 in trastuzumab-resistant, HER2-positive breast cancer	Recruiting	Pembrolizumab, trastuzumab	International Breast Cancer Study Group-IBCSG

Table 1 (*continued*)

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Clinicaltrials.gov identifier	Phase	Intervention/contents	Status	Drugs	Responsible party
NCT02411656	2	PD-1 blockade for metastatic inflammatory breast cancer	Recruiting	Pembrolizumab	M.D. Anderson Cancer Center
NCT02452424	1/2a	Double immune suppression blockade by combining a CSF1R inhibitor with an anti-PD-1 (cohort expansion for TNBC)	Recruiting	PLX3397, pembrolizumab	Plexxikon
NCT02628132	1/2	PD-L1 blockade in combination with chemotherapy in metastatic TNBC		Durvalumab, paclitaxel	AstraZeneca
NCT01386502	1	PD-1 blockade and p53 genetic vaccine for advanced solid tumors	Withdrawn prior to enrollment	p53: 264-272 peptide, pidilizumab (CT-011)	National Institutes of Health Clinical Center (CC)
NCT02648477	2	PD-1 blockade and doxorubicin or anti-estrogen therapy for TNBC or HR+ HER2-negative metastatic breast cancer	Not yet recruiting	Anastrozole, doxorubicin hydrochloride, exemestane, letrozole, pembrolizumab	City of Hope Medical Center
NCT02555657	3	KEYNOTE-119: PD-1 blockade *vs.* chemotherapy for metastatic triple-negative breast cancer	Recruiting	Pembrolizumab, capecitabine, eribulin, gemcitaine, vinorelbine	Merck Sharp & Dohme Corp.
NCT02644369	2	INSPIRE: PD-1 blockade for advance solid tumors (cohort expansion for TNBC)	Not yet recruiting	Pembrolizumab	University Health Network, Toronto
NCT02646748	1b	PD-1 blockade in combination with JAK-1 or PI3K inhibitor (triple-negative breast cancer)	Not yet recruiting	Pembrolizumab, INCB039110, INCB050465	Incyte Corporation
NCT01375842	1	A study of engineered anti-PD-L1 antibody in patients with locally advanced or metastatic solid tumors or hematologic malignancies	Recruiting	Atezolizumab	Genentech, Inc.
NCT02303990	1	RADVAX: PD-1 blockade and hypofractionated radiotherapy to an isolated index lesion for advanced and metastatic cancers	Recruiting	Pembrolizumab, radiotherapy	Abramson Cancer Center of the University of Pennsylvania
NCT02425891	3	IMpassion130: PD-L1 blockade plus chemotherapy as first-line for locally advanced or metastatic TNBC	Recruiting	Atezolizumab, nab-paclitaxel, placebo	Hoffmann-La Roche
NCT01772004	1	JAVELIN solid tumor: treatment with an anti PD-L1 drug	Recruiting (breast cancer cohort is closed)	Avelumab	EMD Serono
NCT02605915	1b	Anti PD-L1 drug plus anti-HER2 blockade or dual-blockade for HER2-positive breast cancer (metastatic or early breast cancer >2 cm)	Recruiting	Atezolizumab, carboplatin, docetaxel, pertuzumab, trastuzumab, trastuzumab emtansine	Hoffmann-La Roche
NCT01975831	1	PD-L1 and CTLA-4 blockade for advanced solid tumors (non-TNBC)	Recruiting	MEDI4736, tremelimumab	Ludwig Institute for Cancer Research

Table 1 (*continued*)

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Clinicaltrials.gov identifier	Phase	Intervention/contents	Status	Drugs	Responsible party
NCT02536794	1	PD-L1 and CTLA-4 blockade for metastatic HER2-negative breast cancer	Recruiting	MEDI4736, tremelimumab	Cesar Augusto Santa-Maria, Northwestern University
NCT02513472	1/2	Eribulin mesylate in combination with anti-PD-1 blocker for metastatic TNBC	Recruiting	Eribulin mesylate, pembrolizumab	Eisai Inc.
NCT02447003	2	KEYNOTE-086: PD-1 blockade as monotherapy for metastatic TNBC	Recruiting	Pembrolizumab	Merck Sharp & Dohme Corp.
NCT02649686	1b	PD-L blockade for patients with HER2-positive breast cancer under trastuzumab treatment	Recruiting	Durvalumab, trastuzumab	NCIC Clinical Trials Group
NCT01644968	1	Targeting OX40 in advanced carcinoma, sarcoma or lymphoma	Recruitment status unknown	Anti-OX40, tetanus vaccine, KLH (keyhole limpet hemocyanin)	Providence Health & Services
NCT01862900	1/2	Stereotactic body radiation (SBRT) on liver or lung lesions plus an anti-OX40 antibody in breast cancer patients with metastatic lesions	Recruiting	MEDI6469, SBRT (15, 20, 25 Gy)	Providence Health & Services
NCT02205333	1b/2	A Combination study of OX40 blocker with therapeutic immune agents for advanced solid tumors or aggressive B-cell lymphomas	Not yet recruiting	Tremelimumab, MEDI6469, rituximab	MedImmune LLC
NCT02221960	1	Evaluation of a recombinant OX40 ligand alone or in combination with an anti-PD-L1 antibody for advanced solid tumors	Recruiting	MEDI6383 MEDI4736	MedImmune LLC
NCT02318394	1	"First time in human" anti-OX40 agonist study for advanced solid tumors	Recruiting	MEDI0562	MedImmune LLC
NCT01813539	1	CD70/CD27L blockade for advanced solid tumors	Recruiting	ARGX-110	arGEN-X BVBA
NCT02608268	1	Safety and efficacy of an anti-TIM3 antibody as single agent or in combination with a PD-1 blocker in patients with advanced malignancies	Recruiting	MBG453, PDR001	Novartis (Novartis Pharmaceuticals)
NCT02270372	1b	A combination study of MUC1 liposomial vaccine plus anti-CD27 antibody to treat advanced ovarian or breast cancer	Not yet recruiting	ONT-10, varlilumab	Oncothyreon Inc.
NCT02614833	2b	AIPAC: LAG3-Ig fusion protein as adjunctive to standard treatment for HR-positive breast cancer	Recruiting	IMP321, placebo, paclitaxel	Immutep S.A.
NCT01714739	1	Study of an anti-KIR agent administered in combination with anti-PD-1 in patients with advanced solid tumors	Recruiting	Lirilumab, nivolumab	Bristol-Myers Squibb
NCT02453620	1	Histone deacetylase inhibitor and immune checkpoint blockade for metastatic solid tumors and locally advanced/metastatic HER2-negative breast cancer	Recruiting	Entinostat, ipilimumab, nivolumab	National Cancer Institute (NCI)

Table 1 (*continued*)

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Clinicaltrials.gov identifier	Phase	Intervention/contents	Status	Drugs	Responsible party
Neoadjuvant setting					
NCT02622074	1	KEYNOTE173: PD-1 blockade plus chemotherapy as neoadjuvant treatment for TNBC	Not yet open for participant recruitment	Pembrolizumab, nab-paclitaxel, anthracycline, cyclophosphamide, carboplatin	Merck Sharp & Dohme Corp.
NCT02489448	1/2	Anti PD-L1 therapy plus nab-paclitaxel and dose-dense AC as neoadjuvant treatment for stage I-III triple-negative breast cancer	Recruiting	MEDI4736, nab-paclitaxel, doxorubicin, cyclophosphamide	Yale University
NCT02605915	1b	Anti PD-L1 drug plus anti-HER2 blockade or dual-blockade for HER2-positive breast cancer (metastatic or early breast cancer >2 cm)	Recruiting	Atezolizumab, carboplatin, docetaxel, pertuzumab, trastuzumab, trastuzumab emtansine	Hoffmann-La Roche

TNBC, triple-negative breast cancer; HR, hormone receptor; HER2, human epidermal growth factor 2; AC, adriamycin plus cyclophosphamide regimen.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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