Review Article

Immunotherapy of Cancer: Developments and Reference Points, an Unorthodox Approach

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Abstract

Oncology is currently a sector of medical science with accelerated progress due to rapid technological development, the advancement in molecular biology, and the invention of many innovative therapies. Immunotherapy partially accounts for this advance, since it is increasingly playing an important role in the treatment of cancer patients, bringing on a sense of hope and optimism through a series of clinical studies and cases with spectacular results. Immunotherapy, after the initial successes it experienced in the early 20th century, was forgotten after chemotherapy and radiotherapy prevailed and developed slowly in the background. Today, it is the new hope for cancer treatment, despite the unorthodox path it has followed. In this article, we study the course and key points of the discovery of immune-oncology from the oncologist's point of view. We also record the questions that have been posed about immunotherapy that sometimes lead to confusion or stalemate.

Keywords

cancer, immunotherapy, Coley's toxins, historical overview, toxicity of immunotherapy, evaluation of the response, economic burden of cancer

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Introduction

The human immune system is a complicated "organ" that, among other functions, participates in preventing neoplastic transformation and the formation of neoplasms under normal conditions. This observation is quite old, made by Paul Ehrlich in 1909, who developed the theory that the immune system may control cancers,[1] but the complexity of the mechanisms and the inability to prove theories developed in the laboratory have been the biggest obstacle in recent years for the application and nonacceptance of immunotherapy in clinical practice.[2]

Historical Overview of Cancer Immunotherapy

The journey of immunology starts with William Bradley Coley (1862-1936), who is rightly considered its father. In 1891, Coley began testing streptococcal bacteria as a cure for cancer and found that sometimes the results were impressive. However, this often had the negative effect of causing infection and soon was changed to weakened bacteria, since some cases resulted in sepsis a few days after the application of his treatment.[3] This new approach created what is known as "Coley's Toxin," which is a combination of heat-killed streptococcal organisms and *Serratia marcescens*.[4] However,

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"Coley's Toxin" received criticism from various directions, such as the *Journal of the American Medical Association* (*JAMA*), which questioned Coley's work in 1894, and James Ewing, Medical Director of the Memorial Hospital. Ewing, in particular, was against Coley's Toxin—thus declining Coley permission to use his toxins at the Memorial Hospital—and in favor of radiotherapy, which he considered as the only effective treatment for bone tumors.[4] Over the next 40 years, however, more than 1000 patients received treatment from Coley.[4-6] Some decades later, Helen Coley, his daughter, founded the Cancer Research Institute in 1953 and managed to collect and publish the course of the disease of 896 cancer patients that her father had healed with the Coley's Toxins method. She thus succeeded in restoring his reputation and acknowledging him as a pioneer in cancer immunotherapy.[7]

The idea of immunotherapy reemerged a little later when Lewis Thomas and Sir Frank Macfarlane Burnet developed the immune-surveillance theory in 1957.[8] The ability of the immune system to recognize and destroy neoplastic cells was observed in mice, which, after transplantation of cancer cells and their further removal, showed a strong immune response to tumors that were retransplanted.[9,10] But once again, the lack of strong evidence and the striking progress of surgery and radiotherapy placed immunotherapy in a secondary position. Currently, the clinical point that can confirm the theory of immuno-surveillance is to detect the presence of CD8+ T-lymphocytes in tumors, a phenomenon known as tumor infiltrating lymphocytes, which has a positive prognostic significance for several neoplasms.[11-14] Sir Macfarlane Burnet, winner of the Nobel Prize in 1960 for Physiology or Medicine, claimed that "without immunological surveillance, cancer would be more frequent and occur at younger ages than it does" in the first chapter of his book titled *Immunological Surveillance* in 1970.[15] Neoplastic cells, although recognized by the immune system, manage to escape immunological surveillance. This happens because the evolutionary pressure exerted by the immune system on cancer cells makes them develop escape mechanisms, which is explained by the 3-stage theory (the 3 Es). The first stage is Elimination, the second is Equilibrium, and the third is Escape.[16] In the first stage, the immune system, as the human body's defense mechanism, recognizes the cancer cells and leads them to apoptosis. Furthermore, there is no "visible" cancer tissue because it is a fully controlled situation. In the second stage, there is isolation between the immune system and the cancer cells. The system is in dynamic equilibrium; thus, the tumor cannot expand, because it is eliminated as soon as it grows. The third and final stage of immune surveillance is that of escape, a stage in which there is visible disease. Cancer cells have "tricked" the immune system and act almost undisturbed.[17,18]

On December 23, 1971, the United States of America President at the time, Richard Nixon, declared the war on cancer by signing a $1.6 billion contract for the development of new anticancer drugs, in front of dozens of cameras. From this point onward, a successful course begins to emerge in several areas of immunotherapy as well as in modern medical science.[19]

In 1976, the strategy of using weakened bacteria to treat malignancies reappeared with Bacille Calmette-Guérin as a means of preventing the recurrence of noninvasive bladder cancer. Bacille Calmette-Guérin treatment was so effective that it is still used.[20]

In 1986, the US Food and Drug Administration (FDA) granted permission to administer interferon-α to cancer patients. In 1995, interferon-α2 was approved for adjuvant treatment of patients with stage IIB/III malignant melanoma, while in 1998, interleukin-2 was approved for patients with metastatic renal cancer and malignant melanoma. Particularly in the case of melanoma, 16% of the patients achieved durable responses beyond 2½ years claiming the "passport" of healing and driving the medical community into frantic enthusiasm.[21,22] The press of that time was talking about a revolution in cancer treatment, but the difficulty of using it due to serious side effects soon led the oncologists and their patients to avoid it as a "forbidden fruit" since there was no biomarker for selecting this 16% who would have the ultimate benefit of the treatment versus those who would undergo the sacrifices of serious adverse effects.[23]

A vaccine called Sipuleucel-T was approved by the FDA against castration-resistant prostate cancer in 2010. The manufacturing process is quite difficult (ex vivo) since it requires peripheral blood to be taken from the patient 3 days in advance and the activation of its mononuclear cells with a prostatic acid phosphatase (PAP-GM-CSF), ensuring a minimum of 50×10^6 autologous CD54+ cells when retransfected into the donor. This option is currently available only in the United States, and the end point for its choice as a treatment is for the patient to be asymptomatic, with a small burden of disease and without visceral metastases. A phase III, multicenter study enrolled 512 patients, with 341 assigned to receive Sipuleucel-T and 171 assigned to receive placebo. The median overall survival was 4.1 months longer in the drug arm than in the placebo arm, and this was found to be statistically significant.[24]

However, enthusiasm for immunotherapy came from a new category of immunomodulating drugs—the checkpoint inhibitors (Table 1). These antibodies block the suppression of antitumor immunity, leading to activation of T cell responses. The start was made by ipilimumab, an anti-CTLA-4 monoclonal antibody that was approved in March 2011 by the FDA for patients with metastatic malignant melanoma. Ipilimumab was the first anti-CTLA-4 antibody that had succeeded in a randomized phase III study in comparison with GP100, a glycoprotein 100 peptide vaccine, in pretreated patients with metastatic melanoma. Six hundred and seventy-six patients had been enrolled in this study, 403

Table 1. Immune Checkpoint Inhibitors.

Type	Role	History	Drugs	Approved
Anti-CTLA-4	Cytotoxic T lymphocyte-associated protein 4 (CTLA-4) plays a role in the regulation of T-cell activation and enhance immune responses, including antitumor immunity.[62-64]	In 1987, CTLA-4 was identified by Pierre Golstein and colleagues. The negative regulator role of CTLA-4 in T-cell activation in mice has been published in November 1995 from the laboratory of Tak Wah Mak and Arlene H. Sharpe.[62-64]	Ipilimumab	2011
			Tremelimumab	
Anti-PD-1	Programmed cell death protein 1, (PD-1) has a role in regulating the immune system's response and downregulating the immune system.[65,66]	Yasumasa Ishida, Tasuku Honjo, and colleagues discovered the PD-1 at Kyoto University in 1992 and in 1999 demonstrated that mice where PD-1 was knocked down were prone to autoimmune disease.[65,66]	Nivolumab	2014
			Pembrolizumab	2014
Anti-PD-L1	Programmed death-ligand 1 (PD-L1) plays a major role in suppressing the immune system during particular events.[67,68]	The molecule renamed as PD-L1 because it was identified as a ligand of PD-1 (L = ligand). PD-L1 was characterized at the Mayo Clinic as an immune regulatory molecule.[67,68]	Atezolizumab	2016
			Durvalumab	2017
			Avelumab	2017

of which received ipilimumab plus GP100, 137 patients of which received ipilimumab, and 136 patients received GP100. The median overall survival in the ipilimumab plus GP100 arm was 10.0 months, in the ipilimumab arm it was 10.1 months, and 6.4 months in the GP100 arm. There was no difference between the ipilimumab plus GP100 arm and in the ipilimumab alone arm ($P = .76$).[25]

A year later, a study was published in the *New England Journal of Medicine* involving the use of ipilimumab plus dacarbazine on previously untreated metastatic melanoma. This was a phase III randomized study, in which 250 patients received ipilimumab with dacarbazine (dacarbazine was considered the gold standard for untreated metastatic melanoma at that moment) and 252 patients received dacarbazine with placebo. Dacarbazine was the gold standard at the moment for untreated metastatic melanoma. The study was positive in its primary endpoint. Overall survival (OS) was statistically, significantly longer in the ipilimumab with dacarbazine arm compared with dacarbazine and placebo with 11.2 months versus 9.1 months, respectively.[26] Four years later a pooled analysis of long-term survival data from phase II/III trials of ipilimumab in unresectable or metastatic melanoma of 1800 patients showed a plateau in the Kaplan-Meier curve: 22% of the patients would achieve long-term tumor regression after 3 years of treatment.[27]

Ipilimumab was approved in 2015 for patients with complete resection of high-risk adjuvant melanoma through a randomized, double-blind phase III study (EORTC 18071), which consisted of a 10 mg/kg dosing, initially applied 4 times every 21 days, then every 3 months and gradually up to 3 years. Recurrence-free survival (RFS) was the primary endpoint of this study, and OS, distant metastasis-free survival (DFS), and safety were the secondary endpoints. The median RFS was 9 months longer in the drug arm than in the placebo arm. However, 5 patients died due to drug-related adverse events in the ipilimumab group (approximately 1%), but the tested dose was 3 times higher than the approved one (3 mg/kg vs 10 mg/kg), based on preliminary results presuming that higher dose would be more effective. The researchers concluded that additional assessment was needed based on the risk-benefit ratio on DFS and OS endpoints to define its definitive value.[28] In November 10, 2016, the same researchers published the results of their 5-year study: the ipilimumab arm showed a positive RFS of 40.8% compared with a 30.3% in the placebo arm ($P < .001$); the 5-year OS rate was 65.4% in the first group versus 54.4% ($P = .001$) in the second; and the 5-year DFS rate was 48.3% in the ipilimumab group compared with a 38.9% rate ($P = .002$) in the placebo group.[29]

The Current State and Issues

Moving forward to the current state of play, the new immunotherapeutic drugs gradually began to present positive results in clinical trials and receive therapeutic approvals (Table 2). The start was made in 2014 with pembrolizumab and 2 months later with nivolumab. These drugs are anti-PD-1 and received approval from the FDA for the treatment of metastatic melanoma as a breakthrough therapy first or as a second-line therapy, that is, after progression in ipilimumab

Table 2. Immunotherapy Treatments with FDA approval in solid tumors.

Category	Drug	Type of Cancer	Doses
CTLA-4	Ipilimumab	Metastatic melanoma	3 mg/kg every 3 weeks for a maximum of 4 doses
		Adjuvant therapy for melanoma stage III (TNM)	10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years
PD-1	Nivolumab	Adjuvant therapy for melanoma stage III	240 mg (flat dose) once every 2 weeks or 480 mg (flat dose) once every 4 weeks until disease recurrence or unacceptable toxicity for up to 1 year
		Metastatic melanoma	240 mg (flat dose) once every 2 weeks or 480 mg (flat dose) once every 4 weeks
		After PD in first line in NSCLC	240 mg (flat dose) once every 2 weeks or 480 mg (flat dose) once every 4 weeks
		After PD in first line in renal cancer	240 mg (flat dose) once every2weeks or 480 mg (flat dose) once every 4 weeks (as a single agent)
		After PD in first line in head and neck cancer	240 mg (flat dose) once every 2 weeks or 480 mg (flat dose) once every 4 weeks
		After PD in first line in bladder cancer	240 mg (flat dose) once every 2 weeks or 480 mg (flat dose) once every 4 weeks
		Metastatic colorectal cancer with microsatellite instability-high or mismatch repair deficient progressed following conventional chemotherapy	240 mg (flat dose) once every 2 weeks
		After PD in sorafenib in advanced hepatocellular carcinoma	240 mg (flat dose) once every 2weeks or 480 mg (flat dose) once every 4 weeks
		Hodgkin lymphoma, classical that relapsed or progressed after autologous HCT	240 mg (flat dose) once every 2 weeks or 480 mg (flat dose) once every 4 weeks
		Small cell lung cancer progressed following platinum-based chemotherapy and one other line of therapy	240 mg (flat dose) once every 2 weeks or 480 mg (flat dose) once every 4 weeks
	Pembrolizumab	Metastatic melanoma	200 mg once every 3 weeks
		After PD in first line in NSCLC	200 mg once every 3 weeks
		First line in NSCLC (PD-L1 > 50%)	200 mg once every 3 weeks
		After PD in first line in head and neck cancer	240 mg (flat dose) once every 2 weeks or 480 mg (flat dose) once every 4 weeks
		After PD in first line in bladder cancer	200 mg once every 3 weeks
		After PD in first line in cervical cancer PD-L1+	200 mg once every 3 weeks
		Hodgkin lymphoma, classical refractory, or has relapsed after 3 or more lines of therapy	200 mg once every 3 weeks
		After PD in first line in gastric cancer PD-L1+	200 mg once every 3 weeks
		After PD in second line in primary mediastinal large B-cell lymphoma	200 mg once every 3 weeks
		Microsatellite instability—high cancer that has progressed after prior treatment and who have no satisfactory alternative treatment options	200 mg once every 3 weeks
PD-L1	Atezolizumab	After PD in first line in bladder cancer	1200 mg every 3 weeks. *Note*: Select previously untreated, cisplatin-ineligible patients for atezolizumab therapy based on the PD-L1 expression on tumor-infiltrating immune cells.
		After PD in first line in NSCLC	1200 mg every 3 weeks
	Avelumab	After PD in first line in bladder cancer	10 mg/kg once every 2 weeks
		Merkel cell carcinoma	10 mg/kg once every 2 weeks
	Durvalumab	After PD in first line in bladder cancer	10 mg/kg once every 2 weeks
		Locally advanced, unresectable stage III NSCLC who have not progressed following chemoradiotherapy	10 mg/kg once every 2 weeks
CTLA-4 + PD-1	Ipilimumab + nivolumab	Metastatic melanoma	Nivolumab (1 mg/kg every 3 weeks) plus ipilimumab (3 mg/kg every 3 weeks for 4 doses) followed by nivolumab 3 mg/kg every 2 weeks
		First line in advanced renal cell carcinoma	Nivolumab (3 mg/kg every 3 weeks) plus ipilimumab (1 mg/kg every 3 weeks for 4 doses) followed by nivolumab 3 mg/kg every 2 weeks

(continued)

Table 2. (continued)

Category	Drug	Type of Cancer	Doses
		Metastatic colorectal cancer, (microsatellite instability-high or mismatch repair deficient)	Nivolumab 3 mg/kg once every 3 weeks (in combination with ipilimumab 1 mg/kg) for 4 combination doses, followed by 240 mg (flat dose) once every 2 weeks nivolumab monotherapy
		Renal cell cancer, advanced (previously untreated)	Nivolumab 3 mg/kg once every 3 weeks (in combination with ipilimumab) for 4 combination doses, followed by 240 mg (flat dose) once every 2 weeks or 480 mg (flat dose) once every 4 weeks (nivolumab monotherapy)
PD-1 + chemotherapy	Pembrolizumab + pemetrexed + carboplatin	First line in NSCLC	Pembrolizumab 200 mg once every 3 weeks (in combination with pemetrexed and either cisplatin or carboplatin) for 4 cycles, followed by pembrolizumab monotherapy of 200 mg once every 3 weeks (with or without optional indefinite pemetrexed maintenance therapy) until disease progression, unacceptable toxicity, or (in patients without disease progression) for a total duration of pembrolizumab therapy of up to 35 cycles or 24 months

Abbreviations: FDA, Food and Drug Administration; CTLA-4, cytotoxic T lymphocyte-associated protein 4; TNM, tumor, node, and metastases; PD, progression disease; NSCLC, non–small cell lung cancer; HCT, hematopoietic cell transplantation; PDL-1, programmed death-ligand 1.

or after progression of ipilimumab and vemurafenib (BRAF inhibitor) in patients with a BRAF mutation and, following, for first-line treatment with ipilimumab.[30-36]

It would not be an exaggeration to say that these new immunotherapy drugs are very aggressive and that they have been or are currently being tested in all types of cancer. In cancers such as sarcoma there are studies with drug combinations that are very promising.[35]

On May 23, 2017, the FDA approved the administration of pembrolizumab, a PD-1 inhibitor, when faced with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) unresectable or metastatic, solid tumors.[37-42] MSI-H/dMMR appears to be a very important immunotherapy response biomarker. The analysis of the whole-exome sequences in people with MSI-H/dMMR showed a mean of 1782 somatic mutations per tumor, compared with 73 mutations per tumor in people with mismatch repair–proficient cancer. High numbers of somatic mutations and potential mutation-associated neoantigens were associated with longer PFS and objective response.[43] This is the first time that the FDA has approved treatment for any solid tumor with a specific genetic feature. The approval of this treatment depended on the pivotal data including patients from 5 trials, the KEYNOTE-016, KEYNOTE-164, KEYNOTE-158, KEYNOTE-012, and KEYNOTE-028, as well as patients with various types of cancer such as colon, endometrial, urologic, breast, thyroid, and others.[37-42]

Toxicity

Another point of interest is that of toxicity, which is different from the toxicity of chemotherapy. Common side effects of immunotherapy are fatigue, diarrhea, rash, pruritus, decreased appetite, pyrexia, cough, musculoskeletal pain, constipation, and nausea. Autoimmune adverse effects include pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, and skin toxicity.[44] Managing toxicity of immunotherapy demands a great deal of caution, since it often develops silently and is not easily reversed; this might be fatal for the patients of non-experienced doctors who fail to recognize the signs. The University of Texas MD Anderson Cancer Center conducted a retrospective study including 290 metastatic cancer patients treated with immunotherapy: 98 of the patients (34%) experienced no immunotherapy adverse event (irAE) and 15 of the patients (5.2%) developed grades 3 and 4 irAEs, the most common being enterocolitis and dermatitis. Eighty percent of these patients with grades 3 and 4 irAEs received corticosteroids and there were no deaths noted.[45] The implications of immunotherapy for survivorship care, especially in terms of long-term toxicity, are an important issue. There are many side effects from this treatment.[46,47] It is known that corticosteroids suppress the human immune system. A small dose of corticosteroids can help prevent nausea and vomiting from chemotherapeutic drugs, as well as hypersensitivity reactions from the treatment. When it comes to treating immunotherapy side effects, corticosteroids show great results but have a long duration of treatment.[48] Immune checkpoint inhibitors, when received with a high dose of corticosteroids, can show an efficacy reduction.[49] Moreover, it has been observed that mortality was higher in patients who were treated with high doses of corticosteroids compared with patients who did not receive, any but this was not statistically significant.[50]

Additional general and non-cancer-specific factors that increase the likelihood of infection are age, comorbidity, the

underlying disease, as well as the use of biological therapies. Early recognition of infection in patients receiving corticosteroids is often difficult since they may not exhibit typical signs and symptoms of infection due to inhibition of cytokine release and the relative reduction of inflammatory and febrile event.[46]

irRECIST

One of the most important issues that emerged with the use of these new drugs is the evaluation of the response. This issue was described and thoroughly studied in the KEYNOTE-001 study, in 655 patients with advanced melanoma who were treated with pembrolizumab. Seven percent of these patients had atypical responses, 8% of all patients showed pseudoprogression (5% early and 3% delayed), and 14% experienced progressive disease per RECIST 1.1 criteria, but nonprogressive disease per immune-related response criteria. All of the above have resulted in an unclear field, thus generating the need to set different criteria between the patients receiving immunotherapy and those receiving chemotherapy. The objective of the new "irRECIST" criteria is to provide a more objective indication of efficacy in therapy by taking into account several new factors such as the duration of the treatment.[51] There are 3 basic differences between RECIST 1.1 and irRECIST criteria. For irRECIST, the new measurable tumor diameters are calculated to the overall size of tumors versus the nadir diameter value. The new lesions do not necessarily imply the progression of the disease. In RECIST 1.1, partial response is an at least 30% decrease in the sum of diameter of all lesions; instead, in irRECIST ≥50% decrease of tumor burden is considered as partial response, whereas irRECIST stable disease is considered to be a 50% decrease in tumor burden versus baseline tumor diameter.[52]

Financial Impact of Drugs

A major issue for health care policy makers is the economic burden of cancer. Estimating and projecting of costs include productivity loss, morbidity for patients, families' spending or losing time, and health care expenditures.[53] In recent years, with the introduction of immunotherapy into therapeutic practice, health cost has increased dramatically, since even countries with strong economies and well-organized health care systems are unable to fully bear the huge cost that treatment incurs.[54-56] All the more questions arise globally regarding the value of these factors and the relationship between their cost and cost-effectiveness.[57] One unanswered question about immunotherapy is the duration and dose. Health care scientists, therefore, point out that costs could be reduced as soon as we can accurately determine how many treatment cycles are desirable and what the effective dose is for each patient. Continuing treatment is the standard practice for chemotherapy where the goal is to inhibit the cell cycle of the cancer cell. However, the mode of action of immunotherapy is different since the objective is to "awaken" the patients' immune system so that it may later attack their cancer.[58] The National Institute for Health and Care Excellence has reached the conclusion that nivolumab is a cost-effective treatment option for patients with nonsquamous non–small cell lung cancer, who have received prior chemotherapy. However, a present-day article published in the *Journal of the American Medical Association* (*JAMA*), titled "Adjuvant Ipilimumab for Melanoma—The $1.8 Million per Patient Regimen," reflects scientists' concerns about the costs that have begun to accrue.[59]

The Future

The future of immunotherapy is rather auspicious as its darker sides are increasingly illuminated. Currently, there are several clinical studies with combinations of immunotherapeutic drugs that are expected to give optimistic results. The benefits of immunotherapy are long-term responses and synergy with other therapies, and its disadvantages would be its efficiency in a small number of patients (approximately 22%) and the lack of a broad objective biomarker. The use of the biomarker PD-L1 unfortunately has been proven to be unsuitable and unreliable in this case. The only reason to measure it in everyday clinical practice is to use pembrolizumab as the first-line treatment in metastatic lung cancer patients with 50% expression or more.[60] The problem of measuring PD-L1 appears to be dominating in the first line of treatment, as seen from the positive results of KEYNOTE-021, a randomized, phase II, open-label study that focused on the application of carboplatin and pemetrexed, with or without pembrolizumab for advanced, non-squamous, non–small cell lung cancer. The study demonstrated better objective response in the pembrolizumab plus chemotherapy group, compared with chemotherapy alone.[61] Some immunotherapy studies have illustrated positive results[62-68] (see also Table 1), while some other have presented negative outcomes[69-79] (see also Table 3), but the important thing is that immunotherapy created a further therapeutic "bridge," from one chemotherapy to the next chemotherapy, even in cancers that until recently had no therapeutic options, significantly improving the quality of life of patients.

Conclusions

In conclusion, apart from research institutions or major cancer centers, the medical community's knowledge is weak on immunotherapy and its side effects, sometimes resulting in false expectations and therapeutic errors. However, the positive results deriving from multiple clinical studies and the

Table 3. Failed Clinical Trials.

Phase III	Indication	Drug	Primary Outcome Failed to Be Proven
CheckMate-143[69]	Recurrent glioblastoma	Nivolumab monotherapy versus bevacizumab	OS
MYSTIC trial[72]	First-line non–small cell lung cancer	Durvalumab and tremelimumab, versus platinum-based chemotherapy	PFS (OS is pending)
Keynote 040[73]	Recurrent or metastatic head and neck squamous cell cancer	Pembrolizumab versus standard chemotherapy (methotrexate, docetaxel, or cetuximab)	OS
CheckMate-214[74]	Previously untreated advanced or metastatic renal cell carcinoma	Ipilimumab and nivolumab versus sunitinib	PFS. But ORR and OS was significantly increased as well as for the intermediate- or poor-risk disease
Keynote 061[75]	Second line advanced gastric or gastro-esophageal junction cancer	Pembrolizumab versus paclitaxel	OS
JAVELIN Gastric 300[76]	Third line advanced gastric or gastro-esophageal junction cancer	Avelumab versus physician's choice of chemotherapy	OS; PFS
IMvigor211[77,78]	Platinum-treated locally advanced or metastatic urothelial carcinoma	Atezolizumab versus chemotherapy	OS
IMpassion 130[79]	First-line metastatic TNBC	Atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel	OS, but PFS was improved. Furthermore, in a subset analysis PD-L1 + tumors, atezolizumab improved both PFS and, importantly, OS

Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, objective response; TNBC, triple-negative breast cancer; PD-L1, programmed death-ligand 1.

number of patients who have been benefited from the use of immunotherapy should be taken into account. Currently, immunotherapy seeks to find its place between classical chemotherapy, targeted treatments, and combinations of them. Finally, what must not be forgotten is the importance of the human factor, such as the oncologist's acute judgment, which often needs to be individualized so that it can offer maximum therapeutic benefit to its patient. Having followed an unorthodox path from Coley up to present-day achievements, immunotherapy has not easily proven its therapeutic value but has managed to become a therapeutic option for several types of cancer at present, casting hope on its potential future achievements.

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