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# Innovative immune checkpoint inhibitors (ICIs) for cancer treatment: an overview

## Abstract

Cancer immunotherapy has significantly increased patients' chances of survival andquality of life as compared to earlier standards of care (such as chemotherapy, radiation, and surgery). From the metastatic stage to the adjuvant and neoadjuvantsettings in many cancer types, immunotherapy has now firmly established itself asa novel pillar of cancer care. In this review article, we emphasise how the development of cancer immunotherapy led to findings that are today considered best practises. We also show out the existing drawbacks and restrictions of cancercheckpoint immunotherapy and the ways in which cutting-edge research is attempting to address these issues.

**Keywords:** cancer, immunotherapy, immune checkpoint inhibitors, tumor microenvironment, immunoscore

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Manal ME Ahmed
Department of Pharmacology, Medical Research and Clinical Studies Institute, Egypt

**Correspondence:** Manal ME Ahmed, Department of Pharmacology, Medical Research and Clinical Studies Institute, National Research Centre, Giza, Egypt,Tel +20-10936-27027, Email thinktankteam2014@gmail.com,mnrc98@yahoo.com

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## Introduction

The treatment of cancer patients has changed significantly thanks to the field of immuno-oncology.[1–6] In the late 19th century, William B. Coley, who is nowcommonly regarded as the father of immunotherapy, made the first attempts to use the immune system's combative capabilities to cure cancer. He saw that somepatients with substantial postoperative wound infections—a frequent occurrence when aseptic technique had not yet been optimized—would spontaneously experience regression of their unresected tumours as an orthopaedic surgeon whooperated on patients with bone sarcomas. Coley began injecting mixes of live and dead bacteria, including Streptococcus Pyogenes and Serratia marcescens, into more than a thousand patients in 1891 in an effort to cause sepsis and powerful immunological and antitumor responses. His bacterial cocktail earned the name "Coley's toxin" and is credited with being the first known active cancer immunotherapy treatment.[7,8] Coley produced long-lasting complete remissions in a variety of cancers, such as testicular carcinoma, lymphoma, and sarcoma. However, oncologists adopted surgery and radiotherapy as substitute conventional therapies early in the 20th century because Coley's toxin's lack of a recognised mechanism of action and the dangers of purposefully infecting cancer patients withpathogenic bacteria.[9]

Before Coley's toxin's methods of action could be better understood in relation to the major mediators of sepsis, it would be more than fifty years.[10–13] These mediators belong to the cytokine family, which also includes chemokines, interleukins, and interferons.[14] The rush to incorporate those fresh discoveries into cancer therapy had begun once more.[15–17] With this unique strategy, clinicians and researchers had only little success, occasionally establishing clinical remissions in metastatic renal cell carcinoma with high-dose interleukin 2 (il-2)[18] and questionable responses in stages iii and iv melanoma with interferon.[19,20] These modest successes were frequently offset by serious negative incidents. Only a tiny, carefully chosen minority of cancer patients would benefit from these innovative delivery techniques, such as pegylation, due to the unpredictable and sporadic immunological reactions they elicited in patients.

With a deeper understanding of the method by which innate immune cells destroy cancer cells—immune surveillance—the field of cancer immunotherapy experienced its next revolutionary wave.[21] The field of immuno-oncology has recently entered a new era thanks to the discovery of T cell immune checkpoints like ctla-4 [22,23] and PD-1[24–27] which also resulted in the awarding of the 2018 Nobel prize in physiology or medicine to Drs. Allison and Honjo. The key job of thosehardwired signals is to keep the delicate balance between autoimmunity and immune surveillance against invading infections or aberrant cells. The heightened autoimmunity caused by blocking certain T cell surface receptors provides an immune response against tumours but also raises the risk of autoimmune responses.

In this brief overview, we summaries the current guidelines for cancer immunotherapy, with a particular emphasis on immune checkpoint inhibitors (ICIS),their drawbacks and potential hazards, as well as intriguing innovative approaches.

### Checkpoint inhibitors overview

Cancer immuno-editing is the process by which different immune system components safeguard the host against the establishment of primary tumours or promote tumour escape, or both, by either sculpting tumour immunogenicity or attenuating antitumor immune responses.[28–30] Immune checkpoints, which are immunological-cell surface receptors that regulate either the activation or suppression of immune responses, strictly regulate the process. On the one hand, activating the immune system is what is needed to prevent tumour growth, but it is also what causes autoimmunity. By upregulating immune activation at different stages of the immunological cycle, the discovery and development of monoclonal antibodies against the inhibitory immune checkpoints ctla-4[31,32] and PD-1[33,34] have produced remarkable antitumor responses. Immune checkpoint inhibitor treatments are now frequently recommended for a variety of cancer types (Table 1). Additionally, other clinical trials that are still in progress evaluate how additional agonistic or inhibitory checkpoints may impact outcomes connected to tumours (Table 2). The potential of the checkpoints varies. For instance, the clinicalactivity of the agonistic OX40 antibody is minimal, whereas the CD28 antibody, even at very low dosages, caused significant cytokine syndrome and required the IC hospitalization of the first six healthy volunteers treated.[35,36] In light of this, clinical research is still ongoing to determine the best ICI treatment combination tocause the ideal level of immunological activation.

**Table 1** Indications for currently approved immune checkpoint inhibitors in advanced-stage cancers

| Agent | Melanoma | NSCLC | RCC | SCHNN | Bladder | Merkel cell carcinoma | Hepatocellular carcinoma | Hodgkin lymphoma |
|---|---|---|---|---|---|---|---|---|
| **CTLA-4 inhibitor** | | | | | | | | |
| Ipilimumab | All lines of Tx | | | | | | | |
| **PD-1 inhibitors** | | | | | | | | |
| Pembrolizumab | All lines of Tx | All lines of Tx | 2nd line Tx | | 2nd line Tx | | | After ASCT |
| Nivolumab | All lines of Tx | 2nd line Tx | | 2nd line Tx | | | 2nd line Tx | After ASCT |
| **PD-L1 inhibitors** | | | | | | | | |
| Atezolizumab | | 2nd line Tx | | | 2nd line Tx | | | |
| Avelumab | | | 2nd line | | | 2nd line Tx | | |
| Durvalumab | | After CTxRT in stage III | Tx | line Tx | 2nd line Tx | | | |
| **Combination CTLA-4 and PD-1 inhibition** | | | | | | | | |
| Ipilimumab nivolumab | 1st line Tx | | 1st line Tx | | | | | |

**Source:** Health Canada's Drug Product Database (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug- products/drug-product-database.html).

NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma (clear cell); SCCHN, squamous-cell carcinoma of head and neck; Tx, treatment; ASCT, autologous stem-cell transplantation; CTxRT, chemoradiotherapy.

**Table 2** Agonistic and antagonistic immune checkpoint modulators currently under investigation[37]

| Target | Drug | Company | Clinical phase |
|---|---|---|---|
| Costimulatory or agonist antibodies | | | |
| 4-1BB (CD137) | Utomilumab | Pfizer Canada, Kirkland, QC | I |
| | Urelumab | Bristol–Myers Squibb, New York, NY, U.S.A. | I/II |
| | INBRX-105 | Inhibrx, San Diego, CA, U.S.A. | I |
| ICOS (CD278) | GSK3359609 | GlaxoSmithKline, Mississauga, ON | I/II |
| | JTX-2011 | Jounce Therapeutics, Cambridge, MA, U.S.A. | I/II |
| GITR (CD357) | TRX 518-001 | Leap Therapeutics, Cambridge, MA, U.S.A. | I/II |
| | MK-4166 | Merck, Kenilworth, NJ, U.S.A. | I |
| | BMS-986156 | Bristol–Myers Squibb, New York, NY, U.S.A. | I/II |
| | INCAGN01876 | Incyte Biosciences International, Wilmington, DE, U.S.A. | I/II |
| CD70 | ARGX-110 (cusatuzumab) | Argenx, Breda, Netherlands | I/II |
| CD27 | CDX-1127 (varlilumab) | Celldex Therapeutics, Hampton, NJ, U.S.A. | I/II |
| OX40 (CD134) | PF-0451860 | Pfizer Canada, Kirkland, QC | I/II |
| | MEDI0562/6469/6383 | AstraZeneca Canada, Mississauga, ON | I |
| | GSK3174998 | GlaxoSmithKline, Mississauga, ON | I |
| | BMS-986178 | Bristol–Myers Squibb, New York, NY, U.S.A. | I/II |
| CD40 | CP870893 | Pfizer Canada, Kirkland, QC | I |
| | APX005M | Bristol–Myers Squibb, New York, NY, U.S.A. | I/II |
| Co-inhibitory or antagonist antibodies | | | |
| VISTA (B7-H5) | CA-170 | Curis, Lexington, MA, U.S.A. | I |
| CCR4 (CD194) | Mogamulizumab | Kyowa Kirin, Tokyo, Japan | I/II |
| B7-H3 (CD276) | MGD009 | Novartis Pharmaceutical, Ottawa, ON | I |
| | 8H9 | Y-mAbs Therapeutics, New York, NY, U.S.A. | I |
| TIM-3 | TSR-022 | Tesaro, Waltham, MA, U.S.A. | I |
| | MBG453 | Novartis Pharmaceutical, Ottawa, ON | I/II |
| | Sym023 | Symphogen A/S, Ballerup, Denmark | I |
| | MEDI9447 (oleclumab) | AstraZeneca Canada, Mississauga, ON | I |
| LAG-3 (CD223) | BMS-986016 (relatlimab) | Bristol–Myers Squibb, New York, NY, U.S.A. | I/II |
| | IMP321 (eftilagimod alpha) | Prima BioMed, Sydney, Australia | I |
| | LAG525 | Novartis Pharmaceutical, Ottawa, ON | I/II |
| KIR (2DL1–3) | Lirilumab | Bristol–Myers Squibb, New York, NY, U.S.A. | I/II |
| IDO-1,2 | Indoximod | NewLink Genetics, Ames, IA, U.S.A. | II |
| | Epacadostat | Incyte Biosciences International, Wilmington, DE, U.S.A. | II |
| TIGIT | Tislelizumab | BeiGene, Beijing, P.R.C. | I/II/III |

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Table Continued...

| Target | Drug | Company | Clinical phase |
|---|---|---|---|
| | BMS-986207 | Bristol–Myers Squibb, New York, NY, U.S.A. | I/II |
| | MTIG7192A | Genentech, San Francisco, CA, U.S.A. | II/III |
| | AB154 | Arcus Biosciences, Hayward, CA, U.S.A. | I/II |
| A2aR | Ciforadenant | Corvus Pharmaceuticals, Burlingame, CA, U.S.A. | I |
| Transforming | M7824 | EMD Serono, Rockland, MA, U.S.A. | I/II |
| growth factor β | Galunisertib | Eli Lilly and Company, Indianapolis, IN, U.S.A. | II |
| CD47 | TTI-621 | Trillium Therapeutics, Mississauga, ON | I |
| CD73 | MEDI9447 (oleclumab) | AstraZeneca Canada, Mississauga, ON | I |
| Other pathways | | | |
| Toll-like receptors | Poly-ICIC* | Ludwig Institute for Cancer Research, New York, NY, U.S.A. | I |
| | MGN1703 (lefitolimod) | Mologen, Berlin, Germany | I |
| | SD-101 | Dynavax Technologies Corporation, Emeryville, CA, U.S.A. | I/II |
| | DSP-0509 | Boston Biomedical, Cambridge, MA, U.S.A. | I/II |
| | Rintatolimod | Hemispherx Biopharma, Philadelphia, PA, U.S.A. | II |
| | CMP-001 | Checkmate Pharmaceuticals, Cambridge, MA, U.S.A. | II |
| Interleukin 2 receptor | NKTR-214 | Nektar Therapeutics, San Francisco, CA, U.S.A. | I/II/III |
| | RO6874281 | Hoffmann–La Roche, Basel, Switzerland | I/II |
| | THOR-707 | Synthorx, La Jolla, CA, U.S.A. | I/II |
| Arginase inhibitors | CB-1158 | Incyte Corporation, Wilmington, DE, U.S.A. | I/II |
| Oncolytic peptides | LTX-315 | Lytix Biopharma, Oslo, Norway | II |
| Interleukin 10 | AM0010 (pegilodecakin) | Eli Lilly and Company, Indianapolis, IN, U.S.A. | I/II |

*Poly-ICIC, polyinosinic-polycytidylic acid–poly–L-lysine carboxymethylcellulose.

## Validation of immunoscore

Patients' chances of survival and overall quality of life have been significantly improved by cancer immunotherapy. However, not all tumours are created equal,and there are currently very few indicators of toxicity and response. Immuno- oncology is still in its relative infancy despite the quick progress achieved in the field, and there are still many problems and obstacles to be solved. With time, it became clear that the traditional methods for evaluating treatment options duringthe period of chemotherapy and targeted therapies might not apply to the novel immunotherapies.

Irecist, which accounts for the novel patterns of response seen during immunotherapy, including cancer pseudoprogression.[38] was developed by modifying the Response Evaluation Criteria in Solid Tumors (RECIST), which was usedto evaluate response to treatments. In the same way that TNM staging has been crucial in guiding treatments in the era of chemotherapy, novel tools are required in the era of cancer immunotherapy. The Immunoscore has already been validatedas adding important prognostic information to TNM staging in colon cancer.[39] Because of T-cells are currently broadly known as the Key mediators of antitumourefficacy with ICI therapy, using the Immunoscore is an attractive tool to assist guide treatment selection in other cancer types as well. However, this option does not exclude the possible use of additional parameters that might provide further insights into the specifics of each case.

## Area to work on for improvement in the immune checkpoint inhibitors' effectiveness and safety

Increasing the efficacy of combination medicines that are already well-establishedin clinical practise is getting harder. Combining ctla-4 and PD-1 inhibitors has produced an exceptional five-year overall survival rate exceeding 50% in metastatic melanoma.[40] The same combination has been linked to an intention-to-treat population overall survival rate of more than 60% at 3years in metastatic renal cell carcinoma.[41,42] Few unique combinations in the vast field of ongoing early-phaseclinical trials have attained a level of efficacy comparable to those new standards of care. Their safety profiles most definitely need to be enhanced.

In the context of melanoma, the approved induction and regimen dose of combination ICIS—ipilimumab 3mg/kg and nivolumab 1mg/kg every 3 weeks—is linked to a 59% rate of grades 3–4 toxicities.[43] Ipilimumab 1mg/kg and nivolumab 3mg/kg every three weeks were the alternative dose methods utilised in CheckMate 511, and preliminary data revealed a considerable improvement in toxicity without a loss of efficacy.[44] Predictors and cutting-edge methods to reduce those toxicities are urgently required because iraes can occasionally be linked to mortality and serious lifetime morbidity (such as de novo insulin-dependent diabetes, persistent pituitary dysfunction, or immune-related inflammatory arthropathies).

Finding innovative treatments for patients who are both primary non-responders to ICIS and those who develop secondary resistance to such therapies is another area in which there is a critical need.[45–51] Very few therapies have been examined beyond ICI failure, and clinicians frequently follow already approved standards of care for each particular cancer. Early observational data imply that ICIS exposure may modify the responsiveness to conventional treatments administered after progression. For instance, after ICI failure, extremely high chemotherapeutic response rates have occasionally been documented.[52,53] Those observations may be a byproduct of immunotherapy, which eliminated the initial inhibition that tumour cells or other immune cells had exerted, followed by the cytotoxic chemotherapy-mediated eradication of the tumour cells. On the other hand, first-line exposure to ICIS may have a negative impact on progression-free survival and the adverse event profiles linked to exposure to targeted therapies (such as BRAF inhibition in melanoma).[54–60]

## Conclusion

In conclusion, combination therapies utilizing checkpoint inhibitors rather than additional new checkpoint inhibitors may be the future of cancer immunotherapy. The current wide "shotgun" strategy, which exposes everyone within the approvedindications to ICIS, will be replaced by tailored therapies that are specific to the characteristics that make each cancer and host a particular pairing as a result of advancements in those domains.

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## Conflicts of interest

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