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REVIEW ON IMMUNO-ONCOLOGY AGENTS FOR CANCER THERAPY

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ABSTRACT - Cancer therapy consists of four main types of treatment: surgery, radiation therapy, chemotherapy and targeted therapy. Over the past decade, immunooncology (IO) has been developed as a new and important approach to cancer therapy by stimulating the body's own immune system to kill cancer cells. This newly recognised method of cancer treatment is rapidly developing, and many approvals from the Food and Drug Administration of the United States and the European Medicines Agency will be accelerated in 2019. In particular, immune control point inhibitors have been remarkably successful in multiple malignancies and are the most established treatment class of immunooncology agents to date. Biomarkers for programmed death ligand 1 (PD-L1) checkpoint targets have been developed and are now mandatory before treatment with Pembrolizumab (Keytruda, Merck) for lung cancers in non-small cells, gastric cancer, head and neck squamous cell carcinoma, and before treatment with atezolizumab (Tecentriq, Roche) for urothelial carcinoma . Although IO agents are rapidly changing the standard of care for cancer patients, there are still many challenges to overcome in terms of managing their toxicities and ensuring that health systems such as the NHS can afford the high cost of these treatments. The IO pipeline also includes chimeric antigen receptor T-cell therapies and cancer vaccines, both of which show great promise for the future but have their own unique toxicity and cost-effectiveness issues.Cancer immunotherapy has reached a critical point today, with immune checkpoint inhibitors and two CAR-T products being approved on the market for the treatment of 16 types of cancer and one tissue-agnostic cancer indication. Expanding the indications of immuno-oncological agents and overcoming treatment resistance are facing increasing challenges.The China Cancer Immunotherapy Workshop in 2019 was held to discuss current challenges and opportunities in immuno-oncology. At this conference, concepts and strategies for the development of immunooncology were proposed, focusing solely on correcting immunological defects in the tumor microenvironment. New targets such as Siglec-15 and new directions including neoantigens, cancer vaccines, oncolytic viruses, and cytokines have been reviewed. New immunotherapies have been discussed in the fields of overcoming primary and secondary resistance to existing immune control point inhibitors, activating endocrine cells, and targeting immune suppression mechanisms in the tumor microenvironment. In this paper, we highlight the evolution of ancient and new waves of immunotherapy and provide perspectives on the latest movement of the current impulse in cancer immunotherapy.

KEYWORDS-Neoantigen,Biomarkers, Cancer, Immune checkpoint inhibitors, Immuno-oncology .

INTRODUCTION- The field of immuno-oncology has transformed the care of cancer patients. William B. Coley, widely regarded as the father of immunotherapy, first tried to use the power of the immune system to treat cancer at the end of the 19th century[1]. Since the approval of ipilimumab in 2011, the immune control marker inhibitor (ICI) has been a major factor in the treatment of cancer[2] .Currently, 11 immune control marker inhibitors (Table 1) and 2 cell antigen receptor T cell (CAR-T) products have been approved for the treatment of 16 types of malignant diseases and 1 tissue-agnostic indication[2,3] .In 2018, James Allison was awarded the Nobel Prize in Physiology or Medicine for conceptualizing cancer immunotherapy by focusing

on the immunosuppressive signal mediated by cytotoxic T lymphocyte-associated protein 4 (CTLA-4)[3] .This conceptual breakthrough led to the subsequent revolutionary development of immunological control point inhibitors [4].In addition, Tasuko Honjo, a co-nobel prize winner, showed that a basic mechanism activated induced cell death in lymphocytes, mediated by program cell death 1 (PD-1)[5], Honjo then showed that the PD-1 pathway is an important negative regulator of the function of T cells[6,7]. Although Allison and Honjo's discoveries were really decisive, the IO revolution, like any other scientific breakthrough, took place in "a village". For example, Lieping Chen first cloned Programmed Cell Death 1 Ligand 1 (PD-L1, also known as B7-H1)[8] and showed its inhibition function[9] and showed that blocking this pathway may have a therapeutic potential [10]. Other non-scientific collaborators included Gordon Freeman, who collaborated with Hoyo to determine the receptor-ligand relationship between PD-1 and PD-L1[11] and Pierre Goldstein, who first cloned CTLA-4[12], Tak Mak and Arlene Sharpe, who showed the inhibitory function of CTLA-4 [13]. The IO Village has also included many clinical investigators who masterfully designed and completed the ICI clinical trials and integrated ICI in current standard clinical practice[14].As a witness to the prosperity of cancer immunotherapy, the Chinese American Hematologist and Oncologist Network (CAHON) has since 2017 organized the annual Chinese Cancer Immunotherapy Workshop in partnership with the National Medical Product Administration of China (NMPA) and later joined Tsinghua University to provide update and education to doctors, scientists and drug developers[15].The fifth China Cancer Immunotherapy Workshop was held in Tianjin on June 29-30, 2019,and it proved again to be an international forum on the dis-cussion of the cutting edge of cancer immunotherapy.There were 4 major themes in the 2019 conference. The first theme was centered on current challenges in ICI development, and new visions for the future of this field.The second one focused on the development and application of cell therapy, where new IO agents continue to rapidly emerge [14,15].The third theme covered new immunotherapy strategies driven by advances in basic immunology research. The last topic highlighted the regulatory challenges and solutions of Chinese NMPA, the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in clinical research and development of cancer immunotherapies[15]. Here, we use the China Cancer Immunotherapy Workshop 2019 program as a general framework for critically reviewing the latest concepts and advances in treatment in an increasingly exciting and complex field of immunooncology[16].

Table-1: Immune checkpoint inhibitors and their US FDA/EMA/China NMPA approved Indication

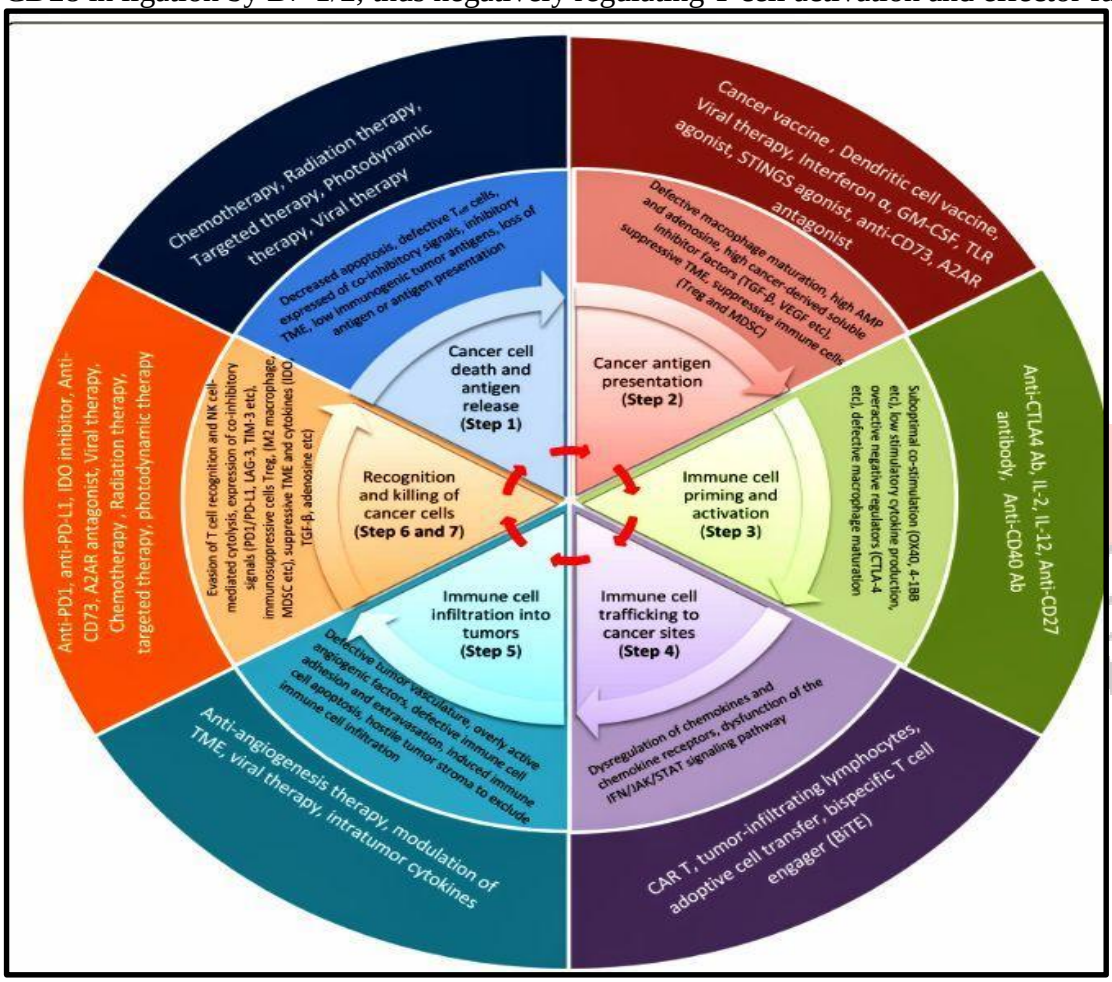
Immune checkpoint inhibitor	Targets	US FDA/EMA approved indications	China NMPA approved indications
Pembrolizumab	PD-1	Melanoma, non-small cell lung cancer, head and neck cancer, Hodgkin's lymphoma, urothelial carcinoma, MSI-H/dMMR* colorectal cancer, MSI-H/dMMR cancers, gastric cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, small cell lung cancer, esophageal carcinoma, endometrial cancer	Melanoma, non-small cell lung cancer
Nivolumab	PD-1	Melanoma, non-	Non-small cell lung

		small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, urothelial carcinoma, MSI-H/dMMR colorectal cancer, hepatocellular carcinoma, small cell lung cancer	cancer
Atezolizumab	PD-L1	Urothelial cancer, non-small cell lung cancer, breast cancer, small cell lung cancer	Non-small cell lung cancer
Durvalumab	PD-L1	Urothelial carcinoma, non-small cell lung cancer	-
Avelumab	PD-L1	Merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma	-
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma	-
Ipilimumab	CTLA4	Melanoma, metastatic, renal cell carcinoma, MSI-H/dMMR colorectal cancer	-
Toripalimab	PD-1	-	Melanoma
Sintilimab	PD-1	-	Hodgkin's lymphoma
Camrelizumab	PD-1	-	Hodgkin's lymphoma
Tislelizumab	PD-1	-	Hodgkin's lymphoma

Information through 8 to 15

OVERVIEW OF CHECKPOINT INHIBITORS -Cancer immuno-editing is the process by which various components of the immune system protect the host from the development of primary tumors or increase the evacuation of tumors, or both, by shaping tumour immunogenicity or attenuating immune responses to cancer [17]. The process is closely regulated by immune checkpoints, which are surface receptors that control the activation or inhibition of immune responses of the immune cells [18] .The activation of the immune system is, on the one hand, the desired result for controlling The discovery and development of monoclonal antibodies against ctla-4 and PD-1 inhibitory immune checkpoints have led to dramatic antitumor responses by increasing immune activation at various stages of the immune cycle[17,18] .

THE CANCER IMMUNITY CYCLE - The model of the cancer immune cycle, which summarizes our scientific knowledge on each step of an effective immune response against cancer, begins with the recognition of tumor antibodies by the immune system [19]. Genetic instability or mutation is one of the characteristics of cancer [20] .All cancers, regardless of their tissue origin, have genetic mutations ranging from small mutations in paediatric tumors to dozens or hundreds in adult cancers [21] .These non-synonymous DNA mutations may produce proteins different from the proteins expressed in normal cells, i.e. tumor antigens, As a second enabler, some cancers express non-mutation-related tumor antigens, such as proteins normally expressed in immune-privileged sites, viral proteins, or proteins encoded by retroviral endogene genes. When these antigens are collected and processed by professional antigen-presenting cells (APCs), APCs migrate to secondary lymph organs and activate nave T cells together with highly coordinated co-stimulating signals, such as the CD28/B7-1/2-mediated signal. In order to achieve homeostasis and avoid excessive reactions to non-self-antigens, the immune system also developed highly coordinated negative feedback circuits. CTLA-4 is one of the most important negative regulators of immune responses through T cells. The expression of CTLA-4 is rapidly regulated in the engagement of T cell receptors (TCRs)[22], allowing it to outperform CD28 in ligation by B7-1/2, thus negatively regulating T cell activation and effector function[22].



. Fig. 1 .The cancer immunity cycle

Once activated, T-cells act in a systemic way, infiltrate the cancer site, recognize cancer cells expressing tumor antigen peptides presented by the Major Histocompatibility Complex (MHC) and kill target cancer cells. In turn, cancer cells release the neoantigens transposed by APC, leading to further expansion of the anticancer immune response, allowing more T cells to be detected and activated, and allowing the end stage of the anticancer response to be controlled by a complex network of stimulation and inhibitory pathways. The PD-1/PD-L1 pathway is one of the main inhibitory pathways. The involvement of the TCR with its known antigen-MHC. combination, together with cytokine stimulation (e.g. IL-2 stimulation), induces PD-1 expression. The binding of PD-1 with PD-L1 on target cells inhibits T cell proliferation and IL-2 production, the immune response. Thus, rational combination immunotherapy must aim to coordinate the activation and function of T cells and the suppression of the inhibitory mechanisms of T cells [23].

IMMUNE -RELATED ADVERSE EVENTS - Although there are several possible irAEs that may appear after the introduction of IO therapy, it is important to have clear and solid guidelines about when to refer to other medical professionals who can contribute to the management of individual patients. To perform this function in practice, it is essential to develop good relationships with other specialties, perhaps most importantly gastroenterology, endocrinology and dermatology. The Clinical Practice Guidelines of the European Society for Medical Oncology (ESMO) "Management of Toxicity from Immunotherapy" contain comprehensive guidelines for the use of IO in the clinic[24].

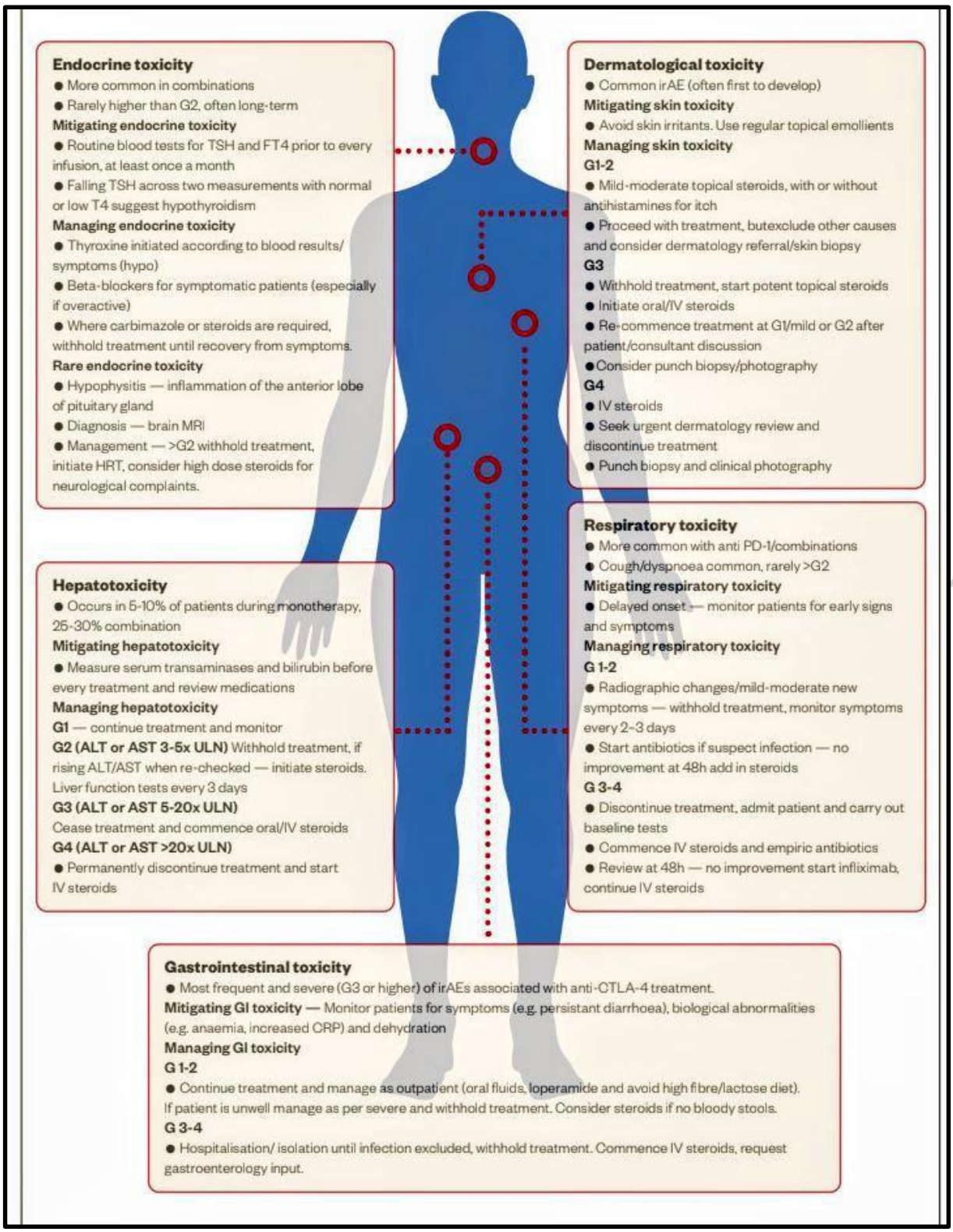


Fig. 2-The most common immune-related adverse events associated with the use of immune checkpoint inhibitors(Abx: Antibiotics; CRP: C-reactive protein; G: grade; irAE: immune-related adverse event)[24]

COMMON IMMUNOTHERAPY SIDE EFFECTS - The most common side effects of immunotherapy include:

1)Skin reactions -Skin redness, blistering, and dryness are common reactions to immunotherapy. Skin on the fingertips may crack. Skin may also become more sensitive to sunlight. A lot of scratching can break the skin, making it more prone to infections. Inflammation around the nails can make grooming, dressing, and other activities painful or difficult. Read more about managing and treating skin irritations and reactions [25].

2)Flu-like symptoms-Fatigue (feeling tired), fever, chills, weakness, nausea (feeling sick to your stomach), vomiting (throwing up), dizziness, body aches, and high or low blood pressure are all possible side effects of immunotherapy[26].

These are particularly common in non-specific immunotherapy and in oncolytic virus therapy. When experiencing these symptoms, it is very important to remain hydrated. If you cannot keep liquids, seek medical attention and talk to your doctor about how to manage these side effects. Many side effects will disappear by themselves, but others can be very serious and require immediate attention[27,28].

3)Other possible side effects -:

· Muscle aches
· Shortness of breath (trouble breathing)
· Swelling of legs (edema)
· Sinus congestion·
. Headaches
· Weight gain from retaining fluid
· Diarrhoea
· Hormone changes, including hypothyroidism, which is when the thyroid gland does not make enough thyroid hormones and can cause fatigue and weight gain [29].

FUTURE OF IMMUNOTHERAPY -

This area appears to be far from the development of selective agents for a particular type of cancer. IO agents are now rarely approved for specific types of cancers, but focus on pathways and expression of specific biomarkers in tumours, regardless of their origin or location (i.e., 'tissue-agnostic' therapies). This pan-cancer approach was demonstrated by the FDA's first tumor -agnostic approval of Keytruda in 2017, in patients with non- resectable or metastatic solid tumors based on their MSI-high and dMMR status, as opposed to the location or origin of the tumor. Merck, the company that developed Keytruda, is now seeking a second pancancer indicator for TMB biomarkers, with the aim of further expanding patient access[30].

ii) In the field of small molecule oncology, a similar trend has been to adopt a cancer-agnostic approach; for example, in the past two years, kinase inhibitors and entrectinib have been accelerated by the FDA for use in patients with any type of solid tumors that have NTRK fusion mutation[31].

iii)To date, two comprehensive studies of the global IO landscape have been carried out. Between September 2017 and August 2018, the global IO pipeline was estimated to have increased by 67%, and cell therapy was the most significant to increase the number of active substances by 113%, followed by other immunomodulatory therapies (e.g. aldeuterycin and interferon; 79%) and T cell targeted immunomodulatory therapies (76%) [32].

iv) The number of IO targets also increased by 50% between September 2017 and August 2018, indicating that the IO landscape could expand significantly in the future. Both studies concluded that of the many IOs in clinical development, a large percentage are concentrated on a few targets (e.g., PD-1, PD-L1, CTLA4). In addition to the five antibodies already approved by the FDA and EMA, the British Cancer Research Institute has identified 164 drugs for the development of PD-1 or PD-L1, of which 50 are in clinical development. This indicates significant overlaps in product development and raises concerns as to whether the current approach to focusing on a small number of biomarker objectives is restricting further innovation. It is remarkable that the number of agents developed against non-toxic antigens actually decreased over the same period, which explains that IO is increasingly focused on certain specific targets. However, interest and enthusiasm in the IO field has increased in the pharmaceutical industry and academia. In addition, clinical data indicate that I.O. drugs have significant potential in the future and may lead to some breakthrough treatments that improve the standard of care of many different types of cancer [33,34] .

CONCLUSION –

IO is a fundamentally different approach to cancer treatment and redefines the way solid and hematoid tumors are treated. However, this new treatment paradigm is still in the early stages, and the learning curve for optimising the use of these new therapies, minimizing toxicity, and integrating them into current care standards is far from complete. In addition, given their high cost, it will be difficult to incorporate them into the health system in a sustainable economic manner, while increasing the availability of patients. The development of cancer immunotherapy for ICI-resistant cancers is a challenge. ICI-based combined therapy strategies have achieved some success, although limited. A deep understanding of TIME biology in the field of IO is necessary to create next-generation immunooncology therapeutic strategies.ICI, CAR-T therapy, Adoptive Cell Therapy and other approaches to improving cancer immune suppression will continue to lead the way in the clinical field of IO. Research into new objectives and pathways in the field of IO is essential to develop new therapies; however, it is important to note that combinations of currently approved IO agents with existing chemotherapy or biological agents also generate significant interest. For example, a study evaluating a combination of an IO agent with an antibody-drug combination has reported positive results

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