Oncology Advances **2024** vol. 2(3) | 148–157
DOI: 10.14218/OnA.2024.00019

Mini Review

Small Molecules as Immune Checkpoint Inhibitors in Cancer Therapeutics

Nitin Srivastava[1], Aaruni Saxena[2] and Anil K. Saxena[3*]

[1]Department of Chemistry, Amity University, Uttar Pradesh Lucknow Campus, Lucknow, Uttar Pradesh, India; [2]Department of Medical Oncology, University of Nottingham, Nottingham, UK; [3]Department of Pharmaceutical Chemistry, Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand, India

Received: July 05, 2024 | **Revised:** September 08, 2024 | **Accepted:** September 12, 2024 | **Published online:** September 20, 2024

Abstract

Despite the large number of cancer chemotherapeutics, cancer treatment is still not very satisfactory. Immune checkpoint inhibition has emerged as a new ray of hope in the immunotherapy approach for cancer treatment. Immune checkpoint inhibitors are molecules located on the surface of immune cells that regulate unnecessary immune responses and keep autoimmune reactions in check. Immune checkpoint inhibitors (ICIs), such as anti-programmed cell death protein-1 and anti-programmed cell death ligand-1, have been employed to activate receptors on immune cells like T-cells, which can deactivate the immune checkpoint and thus reactivate them against cancer cells. However, ICI therapy has limitations, including resistance development in patients, its suitability for all patients, multiple organ disorders, and hyper-progression. Therefore, understanding the chemical structures of small molecule ICIs may aid in designing and developing novel ICIs with improved efficacy and efficiency for cancer chemotherapy. This review's novelty lies in its summary of the U.S. Food and Drug Administration-approved drugs, repurposed drugs, candidate drugs used alone or in combination with monoclonal antibodies, and novel potential lead molecules under preclinical investigation, which may be useful for designing new chemical entities as ICIs. The review describes 10 different drugs approved by the U.S. Food and Drug Administration that have demonstrated immune checkpoint inhibition targeting the programmed cell death ligand-1/programmed cell death protein-1 signaling, CTLA-4/CD28, TIGIT/PVR, and CD47/SIRPα pathways, as well as three repurposed drugs, 11 candidate drugs, and nine drugs in combination with monoclonal antibodies that are in various phases of clinical trials.

Introduction

Cancer is among the leading causes of morbidity and mortality in humans. The International Agency for Research on Cancer projects 27.5 million new cancer cases and an alarming mortality rate of 16.3 million by 2040. Cancer treatment requires expensive procedures and follow-ups, necessitating the development of advanced, cost-effective therapies. Current cancer treatments involve various approaches, including radiotherapy, chemotherapy using protein kinase inhibitors and epigenetic modulators, interleukin therapy, and anti-angiogenic therapy targeting vascular endothelial growth factor, which have been found to enhance the body's anti-tumor immunity. Among these therapies, cancer immunotherapy has gained significant importance, with enormous market growth.[1] The 2018 Nobel Prize in Physiology or Medicine was awarded for immunotherapy with immune checkpoint inhibition, as it has revolutionized cancer treatment. The U.S. Food and Drug Administration (FDA) has approved programmed cell death protein-1 (PD-1) and programmed cell death ligand-1 (PD-L1) antibodies, such as Dostarlimab, Avelumab, Atezolizumab, and Nivolumab, for renal, prostate, breast, and lung carcinomas. Immune checkpoint inhibitors or modulators, which fall under the category of immunotherapy, have revolutionized oncology.

Various immunoreceptors, such as V-domain Ig suppressor of T cell activation (VISTA), B and T cell attenuator, T cell immunoglobulin and ITIM domain (TIGIT), T cell immunoglobulin and mucin-domain containing-3 (TIM3), lymphocyte activation gene-3, Cytotoxic T-lymphocyte antigen 4 (CTLA-4), PD-1, and PD-L1,[2] have been employed to inhibit cancer proliferation by acting as immune checkpoints that regulate immune responses. These checkpoints are significant because correcting their aber-

Keywords: Cancer immunotherapy; Immune checkpoint inhibitors; Small molecule ICIs; PD-1; PD-L1; CTLA-4/CD28; TIGIT/PVR; irAEs; circRNAs.

***Correspondence to**: Anil K. Saxena, Department of Pharmaceutical Chemistry, Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand 244713, India. ORCID: https://orcid.org/0000-0002-0212-7246. Tel: +91-9839012951, E-mail: anilsak@gmail.com

How to cite this article: Srivastava N, Saxena A, Saxena AK. Small Molecules as Immune Checkpoint Inhibitors in Cancer Therapeutics. *Oncol Adv* 2024;2(3):148–157. doi: 10.14218/OnA.2024.00019.

© 2024 The Author(s). This article has been published under the terms of Creative Commons Attribution-Noncommercial 4.0 International License (CC BY-NC 4.0), which permits noncommercial unrestricted use, distribution, and reproduction in any medium, provided that the following statement is provided. "This article has been published in *Oncology Advances* at https://doi.org/10.14218/OnA.2024.00019 and can also be viewed on the Journal's website at https://www.xiahepublishing.com/journal/oncoladv".

rant behavior may strengthen the immune system's ability to combat cancer cell proliferation. Immune cells, such as T cells, are equipped with checkpoints that function as receptors. The interaction between immune checkpoint receptors and complementary receptors on cancer cells protects cancer cells from T cells, allowing the cancer cells to become immortal and evade T cells. Immune checkpoint inhibitors (ICIs) prevent these immune checkpoint receptors from interacting with complementary receptors on cancer cells, helping T cells destroy cancerous cells. Anti-PD-L1 or PD-1 and anti-CTLA4 antibodies are ICIs that have been successfully employed as cancer therapeutics.[3] Ipilimumab, which has significantly improved the quality of life in patients with metastatic melanoma, targets CTLA-4, mediating T cell antitumor immune responses.[4–7] It was the first FDA-approved immune checkpoint inhibitor. Later, the FDA approved nivolumab for the inhibition of PD-1 in the treatment of advanced melanoma, improving the quality of life.[8,9] Following this research, blocking PD-1 or its ligand PD-L1 with monoclonal antibody drugs has gained importance and development potential. However, current ICIs have benefitted only a few patients,[10,11] while others develop resistance and adverse side-effects.[12,13] Moreover, they can lead to immune-related adverse events (irAEs), causing multiple organ disorders, hyper-progression,[14–16] or overactive immune responses.[17–19] Monoclonal antibody treatment for inhibiting immune checkpoints has gained momentum as a cancer therapy, but it also suffers from toxicities or irAEs, which are different from the toxicities linked to traditional chemotherapy. These irAEs may affect several organs, including the skin, gastrointestinal tract, liver, lungs, and endocrine systems, due to the nature of the immune system's response.

The other side effects include neurotoxicity, myocarditis, hematological toxicities, and nephritis.[3,20] Identifying these adverse events and managing them is necessary to prevent morbidity in patients undergoing immunotherapy. Thus, it is evident that there is a need for rational design and in-depth clinical and biological phenotyping of ICIs to improve the therapeutic outcomes of next-generation ICIs.

Recently, circular RNAs (circRNAs), which are stable, loop-structured molecules with both coding and non-coding properties, have been reported. They help control cell signaling pathways and regulate tumors.[21–25] circRNAs modulate immune checkpoint interactions to influence ICI resistance; however, the other adverse reactions and resistance to ICIs need further exploration in the case of circRNAs. Moreover, the role of circRNA-mediated epigenomics, its control over immune checkpoints, and resistance to cancer immunotherapy are yet to be explained.

Among several checkpoint proteins/receptors, PD-1 and CTLA-4 play important roles in immune function.[26–28] Monoclonal antibodies (mAbs) sometimes have low response rates due to poor tissue permeability, inhibition of a single target, long half-life, and inherent immunogenicity, which is responsible for their irAEs. Additionally, they are expensive and involve high costs in clinical applications because of their intravenous or subcutaneous route of administration. These challenges are major constraints to their widespread use in cancer immunotherapy. Thus, an alternative strategy is necessary to improve the clinical efficacy of cancer immunotherapy. To this end, small molecule checkpoint inhibitors are gaining importance, as they target tumor immunity, have good oral bioavailability, short half-life, lower molecular weights, extensive penetration into cells and tissues, lower immunogenicity, and are cost-effective compared to mAbs.[29–33] Small molecules also offer easy pharmacokinetic optimization for flexible dosing, which may help avoid mAb-associated irAEs. Furthermore, optimizing checkpoint inhibitory activity, pharmacokinetic parameters, and unwanted toxicity through structural modifications, guided by state-of-the-art computational structural and ligand-based approaches, can be more easily applied to small molecules than to mAbs. These approaches now involve virtual screening to identify new lead drug-like molecules for further clinical trials. The virtual screening protocols include two major approaches: structure-based and ligand-based. The former works on a similarity approach, considering physicochemical properties, chemical functionality, and ligand shape similarity, while the latter is based on the complementarity of the ligand with the target protein's binding sites. Predictive models developed using these approaches may be useful for virtual screening of large databases or focused libraries for selecting lead molecules for lead optimization.[34–38] Hence, the major limitations of mAbs in terms of irAEs may be overcome with chemical entities under/for preclinical studies, and these may also provide insights for optimization and the design of novel chemical entities for cancer immunotherapy. Such small chemical molecules may have the potential to develop more effective immune checkpoint inhibitors, offering a better alternative to mAbs. Therefore, this review is limited to describing small molecules that have shown checkpoint inhibitory activity, including FDA-approved drugs, repurposed drugs, candidate drugs used alone or in combination with mAbs, and novel potential lead molecules under preclinical investigation.

Small molecules immune checkpoint inhibitors

Drugs

There are some FDA-approved drugs that work as immune checkpoint inhibitors, as shown in Figure 1, along with repurposed drugs. FDA-approved drug 1 (Gefitinib) activates the anti-tumor activity of immune cells by inhibiting EGF signaling and destabilizing PD-L1. It has been used to treat metastatic non-small cell lung cancer patients with abnormal epidermal growth factor receptor and no history of medical treatment for cancer.[39]

Drugs 2 (Fedratinib) and 3 (Ruxolitinib) downregulated PD-L1 expression in non-small cell lung cancer (NSCLC) and breast cancer cells by targeting Janus kinase/signal transducer and activator of transcription pathways.[40] These two drugs were approved by the FDA in 2019 and 2022 for myelofibrosis and relapsed/refractory multiple myeloma, respectively.[41]

The mitogen-activated protein kinase (MEK1/2) inhibitor, drug 4 (Selumetinib), approved by the FDA, inhibited PD-L1 in lung adenocarcinoma cells and is used for the treatment of neurofibromatosis type 1 in children around the age of 2 years with plexiform neurofibromas.[42,43]

In view of the role of histone acetylation at the PD-L1 promoter region in regulating PD-L1 expression, the histone deacetylase inhibitor drugs 5 (Belinostat), 6 (Panobinostat), 7 (Vorinostat), and 8 (Romidepsin) increased PD-L1 expression and enhanced *in vivo* proliferation of cancer cells by inducing cell cycle arrest and promoting apoptosis.[44–46] FDA-approved drug 5 is used for treating peripheral T-cell lymphoma.[47] Drug 6 is an oral deacetylase inhibitor used for treating multiple myeloma.

Injections of drug 8 are employed for the treatment of cutaneous T-cell lymphoma in people with a history of prior treatment with other medications. Drug 8 is a histone deacetylase inhibitor.[48] Further, it is in a Phase I pharmacokinetic study in patients with cancer and hepatic dysfunctions.

Drug 9 (Etoposide), also an FDA-approved drug used in can-

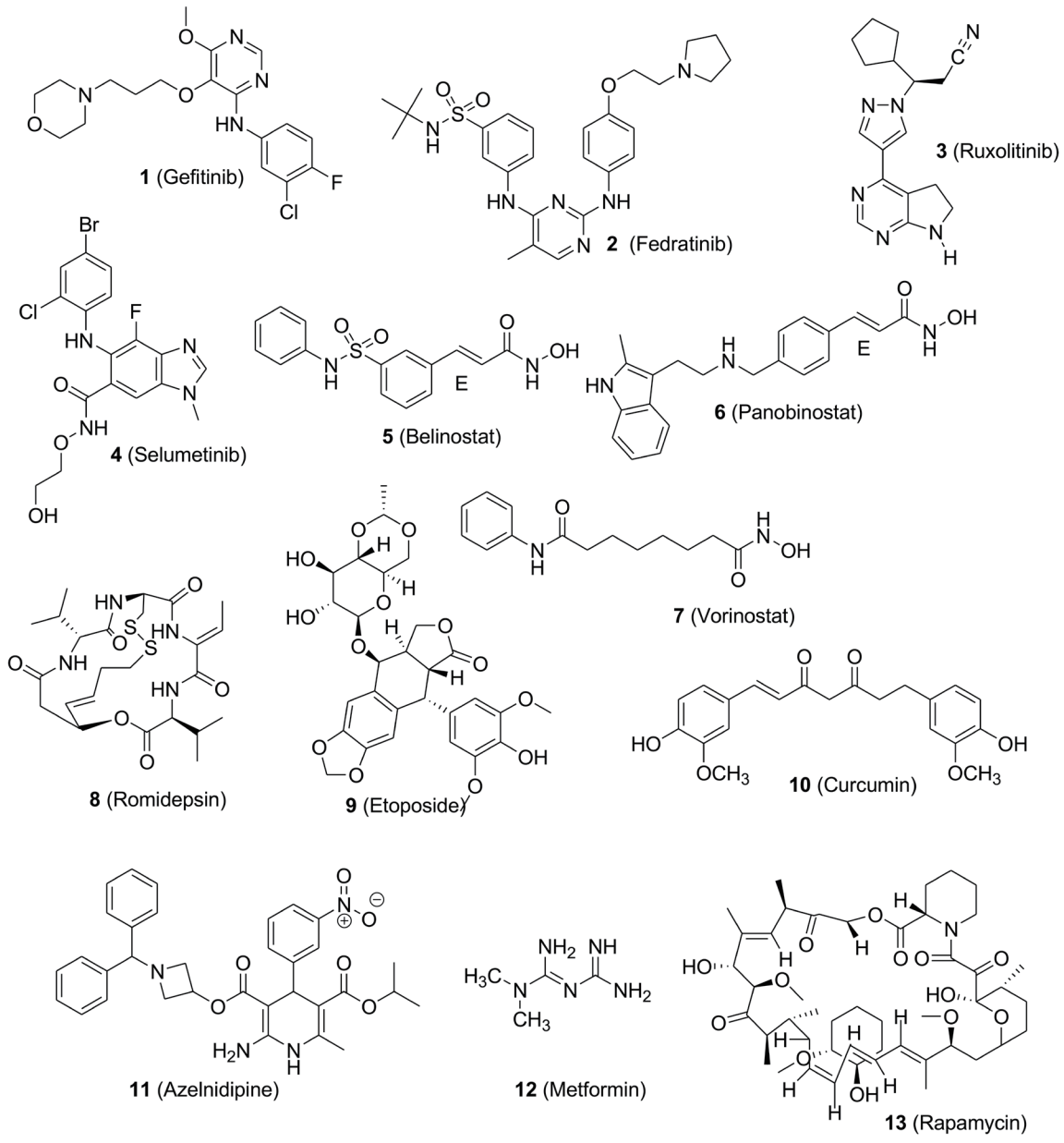

Fig. 1. Immune checkpoint inhibitors (ICIs): Drugs (1–10) and repurposed drugs (11–13).

cer chemotherapy, interferes with PD-L1 glycosylation induced by epithelial-to-mesenchymal transition and disrupts surface PD-L1 in tumor cells. The drug, along with metformin, is reported to improve the effectiveness of anti-TIM-3 and anti-CTLA-4 therapies. The well-known natural drug 10 (Curcumin) also destabilizes PD-L1, inhibits the deubiquitylation of the CSN5 protein, and supports the development of anti-CTLA-4 therapy.[49]

Repurposed drugs

Several drugs used for diseases other than cancer have also been investigated under the novel approach of accelerated drug discovery and development, as it overcomes steps *viz*. general toxicity, pharmacokinetics, and human tolerance. In this context, the following repurposed drugs (Fig. 1, drugs 11–13) showing potential in checkpoint inhibition are described below:

The antihypertensive FDA-approved drug 11 (Azelnidipine) has been found to inhibit CD47/SIRPα and TIGIT/poliovirus receptor (PVR) through molecular docking studies using Molecular Operating Environment software. It has been demonstrated to inhibit the growth of CT26 tumors *in vivo* due to enhanced penetration and improved functioning of $CD8^+$ T cells in tumors.[50] Drug 12 (Metformin), a well-known anti-diabetic drug, activated T-cells by triggering AMP-activated protein kinase to influence the phosphorylation of PD-L1, preventing PD-L1 glycosylation and promoting antitumor immunity.[51]

Drug 13 (Rapamycin/Sirolimus), a well-known FDA-approved immunosuppressant (mTOR inhibitor) used after organ trans-

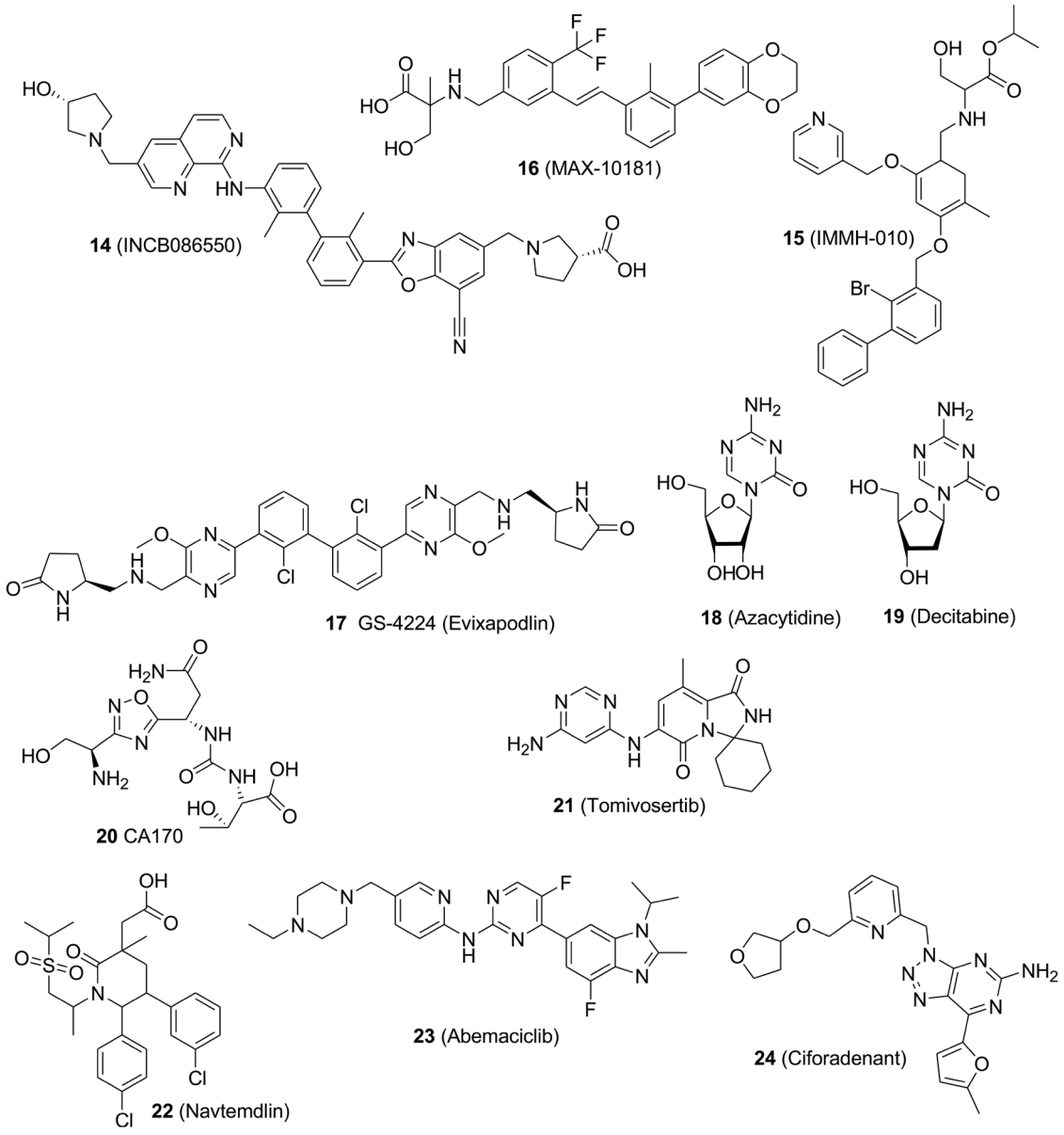

Fig. 2. Immune checkpoint inhibitors (ICIs) under clinical trials.

plants, enhances lysosomal protein degradation and decreases protein synthesis.[52] Its combination with anti-PD-1 significantly reduced tumor growth in a mouse model of lung cancer, where an increase in $CD3^+$ T cells and a decrease in $FoxP3^+$ Tregs were observed.[52]

Molecules in clinical trials

The potential drug molecules in various stages of clinical trials are shown in Figure 2. Molecule 14 (INCB086550), a PD-L1 inhibitor,[53,54] reduced tumor growth in mice by activating T cells and blocking PD-1/PD-L1 pathways in peripheral blood mononuclear cells, representing the activation of the immune system. It is in phase 2 clinical trials for solid tumors and may provide alternatives to antibody therapies.[55]

An oral PD-L1 inhibitor, compound 15 (IMMH-010), quickly metabolizes into YPD-29B. It exhibits notable antitumor efficacy in colon cancer xenograft mouse models and melanoma.[56] It is in phase 1 clinical trials for malignant neoplasms in advanced malignant solid tumors.[57]

Compound 16 (MAX-10181) is under phase 1 study, where its safety, tolerability, and pharmacokinetic characteristics are being evaluated in patients with advanced solid tumors. It interferes with the interaction of PD-L1 and PD-1, inhibiting immunosuppressive signals.[58]

ASC61 (NCT05287399), a small-molecule PD-L1 inhibitor, is under phase 1 clinical study for its safety in treating solid tumors. It is an oral prodrug whose active metabolite, ASC61-A, blocks the PD-1/PD-L1 interaction *via* PD-L1 internalization and dimerization. It displayed remarkable antitumor efficacy in multiple animal

Table 1. Small molecules in clinical trials in combination with mAbs

S.N	Small molecule	Synergistic mAbs	Cancer	The phase of clinical trials	Reference
1	25 (Pexidartinib) (MW = 417.09)	Sirolimus	Unresectable sarcoma and malignant peripheral nerve tumors	Phase 1	77
2	26 (6-Thio-2′-deoxyguanosine) (MW = 283.309)	Cemiplimab	Advanced NSCLC	Phase 2	78
3	27 (Vismodegib) (MW = 420.01)	Atezolizumab	Platinum-resistant ovarian, fallopian tube, and primary peritoneal cancer	Phase 2	79
4	28 (Cabozantinib) (MW = 501.50)	Nivolumab and Ipilimumab	Renal-cell carcinoma	Phase 3	80
5	29 (Itacitinib) (MW = 552.52)	Pembrolizumab	Metastatic NSCLC	Phase 3	81
6	30 (SF1126) (MW = 865.86)	Nivolumab	Advanced hepatocellular carcinoma	Phase 1	82
7	31 (Sitravatinib) (MW = 629.19)	Nivolumab	Nonsquamous NSCLC progressing	Phase 2	83
8	32 (Talazoparib) (MW = 380.35)	Avelumab	Repair proficient endometrial cancer	Phase 1	84
9	33 (Apatinib) (MW = 397.19)	Camrelizumab	First-line platinum-resistant or PD-1 inhibitor resistant recurrent/metastatic nasopharyngeal carcinoma	Phase 2	85

mAbs, monoclonal antibodies; MW, molecular weight; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein-1.

models and humanized mouse models. Preclinical examinations revealed significant safety and pharmacokinetic properties in animal models.[59,60]

Compound 17, GS-4224, an antiviral drug and PD-L1 inhibitor for treating advanced solid tumors, was under phase 1 studies, but the studies have been terminated for unknown reasons.[61]

DNA hypomethylating agents have also been explored for their checkpoint inhibition. Among these, compounds 18 (Azacytidine, NCT02447666) and 19 (Decitabine) upregulated PD-L1 expression and potentiated anti-PD-L1 antibody efficacy in different cancer mouse models for colorectal cancer, gastric cancer, and NSCLC.[62,63] They are in phase 2 clinical trials for myelodysplastic syndrome and leukemia.[64]

The combination of decitabine and the poly (ADP-ribose) polymerase inhibitor Talazoparib is in a phase 1 clinical trial for therapy in relapsed/refractory acute myeloid leukemia.[65]

An orally available small molecule 20 (CA170), containing L-threonine, D-asparagine, and L-serine partially linked to urea and diacylhydrazine linker moieties, targets both VISTA and PD-L1.[66] A single daily dose suppressed metastasis and tumor growth in mouse models of melanoma cells (B16F10) and colorectal cells (MC38).[67] It rescued interferon gamma release from human peripheral blood mononuclear cells blocked by recombinant VISTA, PD-L1, and PD-L2. In a phase 1 study, it was found to be well-tolerated at an oral dose of 50–1,200 mg, with a plasma half-life of 4–9.5 h depending on the dosage.[68] In phase 2 studies, it showed remarkable clinical activity, with a 30% overall response rate in Hodgkin lymphoma and a more than 85% clinical benefit rate at 400 mg daily, with progression-free survival of up to 19.6 weeks in advanced non-squamous NSCLC.[69] It is also currently in a phase 1 trial for advanced solid tumors or lymphomas.[70]

Additionally, several other PD-L1 inhibitors, such as BPI-371153, are progressing through phase 1 clinical trials for advanced solid tumors or relapsed/refractory lymphoma[71]; compound 21 (Tomivosertib) is in phase 2 clinical trials for solid tumors[72]; compound 22 (Navtemadlin) is in phase 1 clinical trials for Merkel cell carcinoma[73]; compound 23 (Abemaciclib) is in phase 2 clinical trials for head and neck neoplasms[74]; compound 24 (Ciforadenant) is in phase 1 clinical trials for the treatment of renal cell cancers[75]; and recently developed small molecules like ABSK043 are in phase 1 clinical trials for neoplasms and advanced solid tumors.[76]

Small molecules have been explored for cancer treatment to overcome the limitations of mAbs. The following molecules, PD-1 and PD-L1 checkpoint inhibitors, are in various stages of clinical trials and have been investigated in combination with different mAbs, as shown in Table 1 and Figure 3.[77–85] Small molecules are used in combination with mAbs to address issues such as lack of oral bioavailability and immune-related side effects.

Lead molecules

Apart from the drugs, repurposed drugs, and checkpoint inhibitors under different stages of clinical trials discussed above, novel lead molecules with the potential to serve as checkpoint inhibitors are explored in this section and shown in Figure 4.

Virtual screening using Molecular Operating Environment software led to the development of PVR binder compound 34 (Liothyronine), which interferes with interactions between the ITIM domain (TIGIT) and PVR, as well as T cell immunoglobulin. Its *in vivo* administration increased $CD8^+$ T cell infiltration and immune responses in tumor-bearing mice, leading to tumor growth arrest.[86] Homology modeling of VISTA, coupled with virtual screening, identified compound 35 as a VISTA binder with potent immunomodulatory activity in coculture cellular assays.[87]

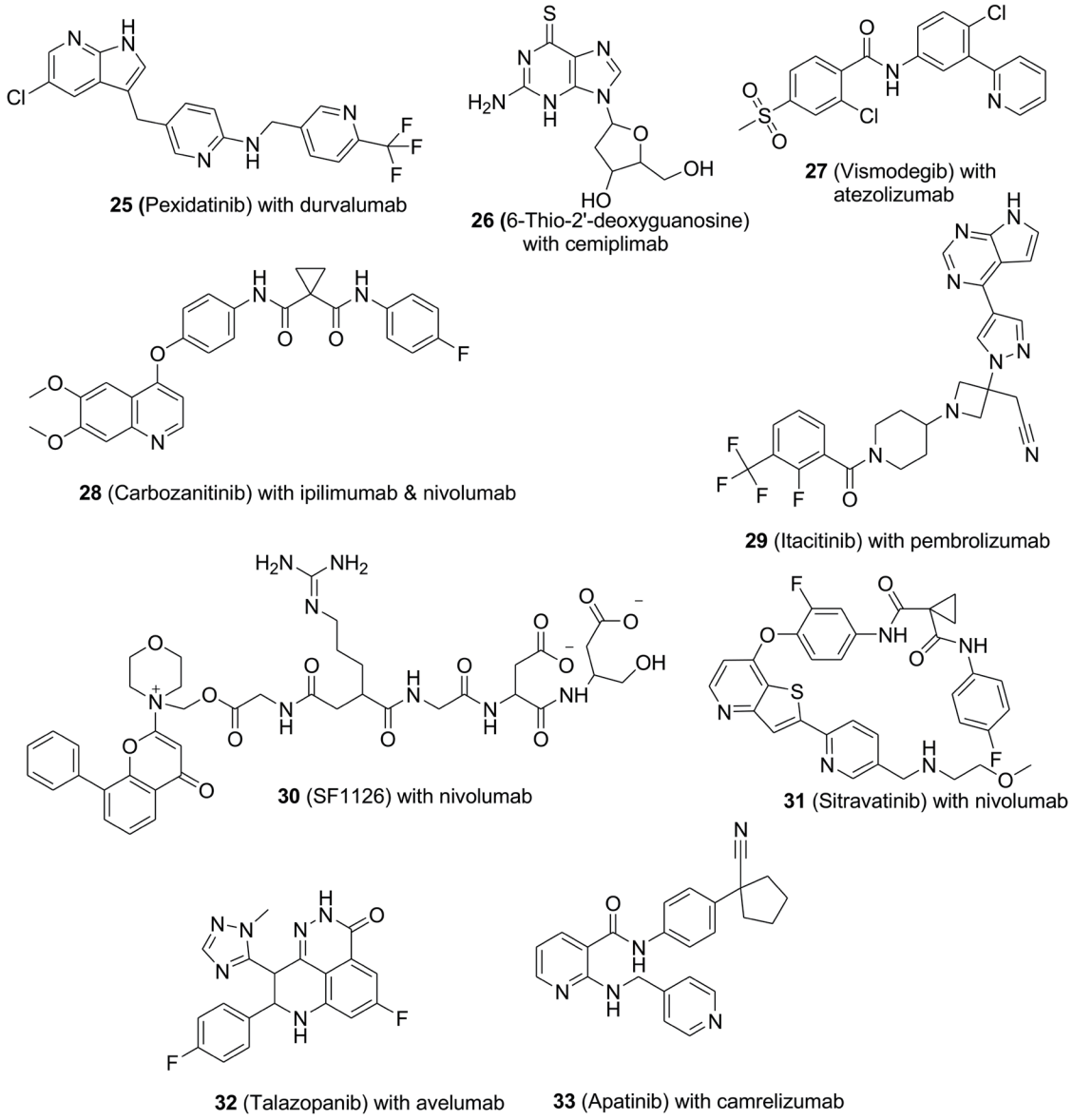

Fig. 3. Small molecules as checkpoint inhibitors in clinical trials in combination with monoclonal antibodies (mAbs).

Compound 36, incorporating a benzimidazole moiety with substituted phenyls, is a VISTA inhibitor with submicromolar binding affinity. It promoted VISTA degradation and enhanced the expression of lipidated MAP1LC3, an autophagosome membrane marker in HepG2 cancer cells.[88] It also exhibited promising activity in the CT26 mouse model by suppressing tumor growth.[89]

Compound 37 [2-Fluoro-L-fucose (2F-Fuc)] reduced checkpoint glycosylation (fucosylation) and PD-1 levels on the surface of activated T-cells.[90] It increased T-cell activity by inhibiting Fut8 and reducing PD-1 expression. Its combination with anti-PD-L1 ameliorated B7-H3 expression and enhanced efficacy in triple-negative breast cancer.

In addition to the molecules discussed above, other small molecules reported as ICIs interacting with PD-1 and PD-L1 include substituted biphenyls (38–41),[30] compound 42 (2-bromopalmitate),[49,91] compound 43 (BMS1166) (in preclinical phase),[92] and compound 44 (NGI-1) (in preclinical phase).[93] NGI-1 inhibited the activity of STT3A and STT3B, with higher specificity to the latter.[94,95] The migration, invasion, and proliferation of lung adenocarcinoma cells were well inhibited by the compound.[96] NGI-1 was also found to inhibit triple-negative breast tumors, which tend to be "cold" with low T-cell infiltration.[93]

Conclusions

It is evident from the above discussion that ICIs are substantially used clinically for various cancers. ICIs appear to be revolutionizing cancer therapeutics as an alternative to traditional chemotherapeutics for treating diverse malignancies. Despite several recent advancements in this field, it may still be considered in its infancy. Hence, more research is needed to overcome major shortcomings such as irAEs and heterogeneity. It is well known that each pa-

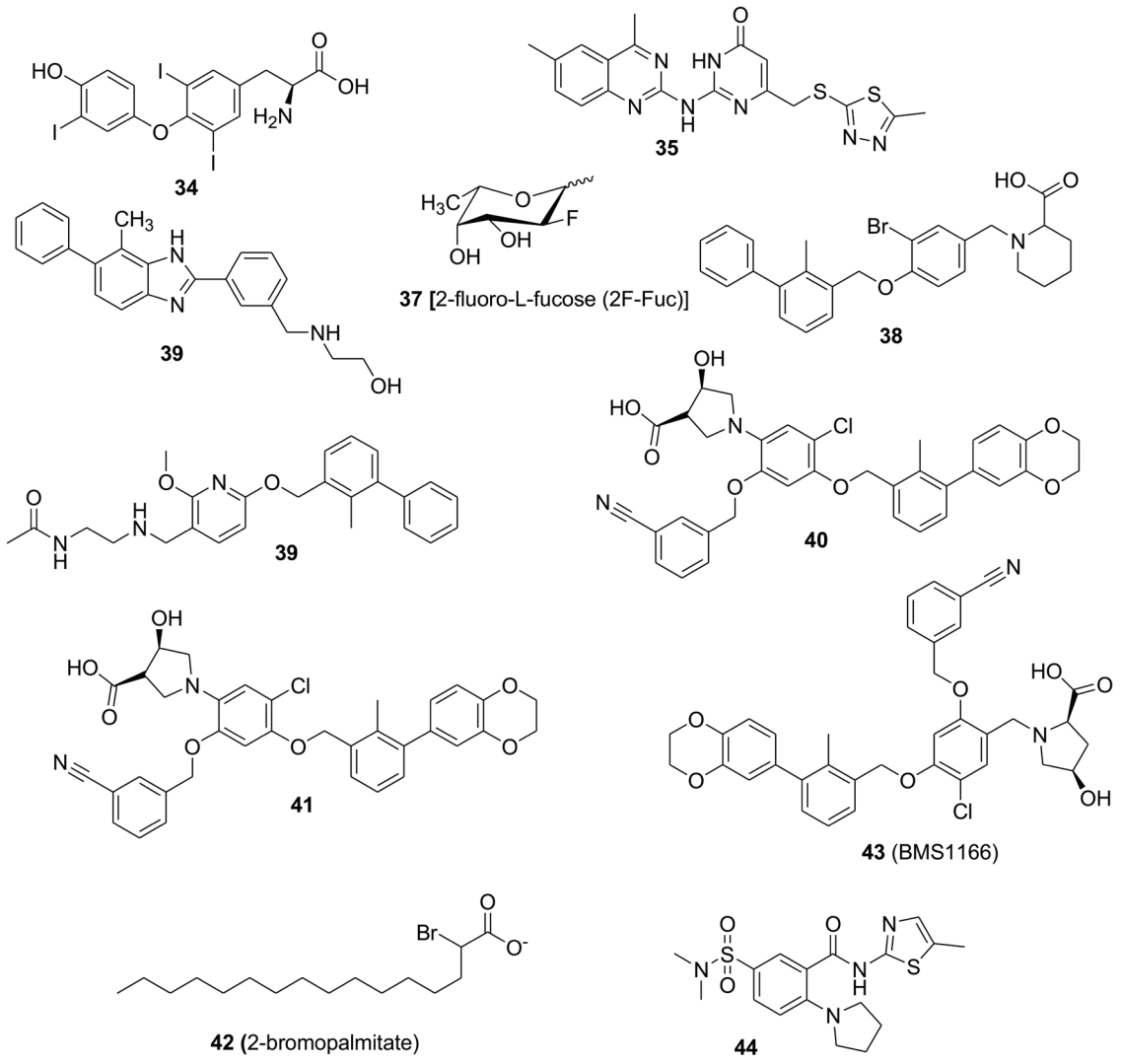

Fig. 4. Promising lead molecules as checkpoint inhibitors.

tient's response to ICIs and the onset of irAEs can differ, so a careful understanding of these factors may help in devising strategies for personalized treatment.

Compared to widely used mAbs, small molecules offer advantages such as improved drug penetration into tumors or organs, enhanced stability, and better movement across cell membranes. Although the use of mAbs has been optimistic, they have not shown significant clinical improvements in patients with different types of cancer at various stages in several clinical trials. The efficacy of immunomodulators depends on the cancer type and its microenvironment. The therapeutic efficacy of these molecules is greatly influenced by mutations and specific molecular changes. Thus, identifying the relevant proteins or genes and understanding their molecular mechanisms may help enhance the efficacy of current immunomodulators. Another major drawback to consider is off-target toxicity or "cytokine storm", which needs to be addressed for successful treatment with ICIs. Given these limitations, small molecules as immuno-oncology drugs have been explored as potential immune checkpoint inhibitors. However, these developments are still in the early stages and require further exploration to improve efficacy, reduce toxicity, increase bioavailability, and ensure specific action for their selection as candidate molecules for clinical development. Despite some disadvantages, small molecule ICIs have shown potential, and some are in various stages of clinical trials as immuno-oncology drugs. In this review, we summarized FDA-approved drugs, repurposed drugs, candidate drugs alone or in combination with mAbs, and novel potential lead molecules under preclinical investigation. The review described ten FDA-approved drugs that target PD-L1/PD-1 signaling, CTLA-4/CD28, TIGIT/PVR, and CD47/SIRPα pathways, as well as three repurposed drugs, eleven candidate drugs alone, and nine in combination with mAbs that are in different phases of clinical trials. Additionally, eleven novel chemical entities under pre-clinical studies may provide insights for optimization and the design of novel chemical entities for cancer immunotherapy.

Acknowledgments

None.

Funding

No funding was received for this research.

Conflict of interest

One of the authors, AKS, has been an editorial board member of the *Oncology Advances* journal since May 2021. The authors have no other conflicts of interest to declare.

Author contributions

Literature search and compilation (NS), topic conception and design (AS), intellectual input, manuscript writing, and critical revision of the manuscript (AKS). All authors have made significant contributions to this study and have approved the final manuscript.

References

[1] Dhasmana A, Dhasmana S, Kotnala S, Anukriti A, Kashyap VK, Shaji PD, *et al*. A topography of immunotherapies against gastrointestinal malignancies. Panminerva Med 2022;64(1):56–71. doi:10.23736/S0031-0808.21.04541-9, PMID:34664484.

[2] Shibru B, Fey K, Fricke S, Blaudszun AR, Fürst F, Weise M, *et al*. Detection of Immune Checkpoint Receptors - A Current Challenge in Clinical Flow Cytometry. Front Immunol 2021;12:694055. doi:10.3389/fimmu.2021.694055, PMID:34276685.

[3] He X, Xu C. Immune checkpoint signaling and cancer immunotherapy. Cell Res 2020;30(8):660–669. doi:10.1038/s41422-020-0343-4, PMID:32467592.

[4] Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271(5256):1734–1736. doi:10.1126/science.271.5256.1734, PMID:8596936.

[5] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, *et al*. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363(8):711–723. doi:10.1056/NEJMoa1003466, PMID:20525992.

[6] Ledford H. Melanoma drug wins US approval. Nature 2011 ;471(7340):561. doi:10.1038/471561a, PMID:21455150.

[7] Korman AJ, Garrett-Thomson SC, Lonberg N. The foundations of immune checkpoint blockade and the ipilimumab approval decennial. Nat Rev Drug Discov 2022;21(7):509–528. doi:10.1038/s41573-021-00345-8, PMID:34937915.

[8] Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, *et al*. Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab. J Clin Oncol 2023;41(5):943–954. doi:10.1200/JCO.22.02272, PMID:36750016.

[9] O'Sullivan Coyne G, Madan RA, Gulley JL. Nivolumab: promising survival signal coupled with limited toxicity raises expectations. J Clin Oncol 2014;32(10):986–988. doi:10.1200/JCO.2013.54.5996, PMID:24590655.

[10] Doroshow DB, Bhalla S, Beasley MB, Sholl LM, Kerr KM, Gnjatic S, *et al*. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. Nat Rev Clin Oncol 2021;18(6):345–362. doi:10.1038/s41571-021-00473-5, PMID:33580222.

[11] Wang DR, Wu XL, Sun YL. Therapeutic targets and biomarkers of tumor immunotherapy: response versus non-response. Signal Transduct Target Ther 2022;7(1):331. doi:10.1038/s41392-022-01136-2, PMID:36123348.

[12] Syn NL, Teng MWL, Mok TSK, Soo RA. De-novo and acquired resistance to immune checkpoint targeting. Lancet Oncol 2017;18(12):e731–e741. doi:10.1016/S1470-2045(17)30607-1, PMID:29208439.

[13] Dougan M, Luoma AM, Dougan SK, Wucherpfennig KW. Understanding and treating the inflammatory adverse events of cancer immunotherapy. Cell 2021;184(6):1575–1588. doi:10.1016/j.cell.2021.02.011, PMID:33675691.

[14] Sullivan RJ, Weber JS. Immune-related toxicities of checkpoint inhibitors: mechanisms and mitigation strategies. Nat Rev Drug Discov 2022;21(7):495–508. doi:10.1038/s41573-021-00259-5, PMID:34316029.

[15] Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. Nat Rev Clin Oncol 2022;19(4):254–267. doi:10.1038/s41571-022-00600-w, PMID:35082367.

[16] de Miguel M, Calvo E. Clinical Challenges of Immune Checkpoint Inhibitors. Cancer Cell 2020;38(3):326–333. doi:10.1016/j.ccell.2020.07.004, PMID:32750319.

[17] Sharma P, Allison JP. Immune checkpoint therapy: Forging ahead. Sci Transl Med 2022;14(670):eadf2947. doi:10.1126/scitranslmed.adf2947, PMID:36350993.

[18] Kalaora S, Nagler A, Wargo JA, Samuels Y. Mechanisms of immune activation and regulation: lessons from melanoma. Nat Rev Cancer 2022;22(4):195–207. doi:10.1038/s41568-022-00442-9, PMID:35105962.

[19] Fessas P, Possamai LA, Clark J, Daniels E, Gudd C, Mullish BH, *et al*. Immunotoxicity from checkpoint inhibitor therapy: clinical features and underlying mechanisms. Immunology 2020;159(2):167–177. doi:10.1111/imm.13141, PMID:31646612.

[20] Axelrod ML, Meijers WC, Screever EM, Qin J, Carroll MG, Sun X, *et al*. T cells specific for α-myosin drive immunotherapy-related myocarditis. Nature 2022;611(7937):818–826. doi:10.1038/s41586-022-05432-3, PMID:36385524.

[21] Kristensen LS, Jakobsen T, Hager H, Kjems J. The emerging roles of circRNAs in cancer and oncology. Nat Rev Clin Oncol 2022;19(3):188–206. doi:10.1038/s41571-021-00585-y, PMID:34912049.

[22] Misir S, Wu N, Yang BB. Specific expression and functions of circular RNAs. Cell Death Differ 2022;29(3):481–491. doi:10.1038/s41418-022-00948-7, PMID:35169296.

[23] Liu J, Li D, Luo H, Zhu X. Circular RNAs: The star molecules in cancer. Mol Aspects Med 2019;70:141–152. doi:10.1016/j.mam.2019.10.006, PMID:31676107.

[24] Chen L, Shan G. CircRNA in cancer: Fundamental mechanism and clinical potential. Cancer Lett 2021;505:49–57. doi:10.1016/j.canlet.2021.02.004, PMID:33609610.

[25] Almouh M, Razmara E, Bitaraf A, Ghazimoradi MH, Hassan ZM, Babashah S. Circular RNAs play roles in regulatory networks of cell signaling pathways in human cancers. Life Sci 2022;309:120975. doi:10.1016/j.lfs.2022.120975, PMID:36126723.

[26] Zhang Y, Zheng J. Functions of Immune Checkpoint Molecules Beyond Immune Evasion. Adv Exp Med Biol 2020;1248:201–226. doi:10.1007/978-981-15-3266-5_9, PMID:32185712.

[27] Wang Y, Yang S, Wan L, Ling W, Chen H, Wang J. New developments in the mechanism and application of immune checkpoint inhibitors in cancer therapy (Review). Int J Oncol 2023;63(1):86. doi:10.3892/ijo.2023.5534, PMID:37326100.

[28] Weinmann H. Cancer Immunotherapy: Selected Targets and Small-Molecule Modulators. ChemMedChem 2016;11(5):450–466. doi:10.1002/cmdc.201500566, PMID:26836578.

[29] Smith WM, Purvis IJ, Bomstad CN, Labak CM, Velpula KK, Tsung AJ, *et al*. Therapeutic targeting of immune checkpoints with small molecule inhibitors. Am J Transl Res 2019;11(2):529–541. PMID:30899360.

[30] Sasikumar PG, Ramachandra M. Small Molecule Agents Targeting PD-1 Checkpoint Pathway for Cancer Immunotherapy: Mechanisms of Action and Other Considerations for Their Advanced Development. Front Immunol 2022;13:752065. doi:10.3389/fimmu.2022.752065, PMID:35585982.

[31] Park JJ, Thi EP, Carpio VH, Bi Y, Cole AG, Dorsey BD, *et al*. Checkpoint inhibition through small molecule-induced internalization of programmed death-ligand 1. Nat Commun 2021;12(1):1222. doi:10.1038/s41467-021-21410-1, PMID:33619272.

[32] Kerr WG, Chisholm JD. The Next Generation of Immunotherapy for Cancer: Small Molecules Could Make Big Waves. J Immunol 2019;202(1):11–19. doi:10.4049/jimmunol.1800991, PMID:30587569.

[33] Bhunia SS, Saxena M, Saxena AK. Ligand- and Structure-Based Virtual Screening in Drug Discovery. In: Saxena AK (ed). Biophysical and Computational Tools in Drug Discovery. Cham: Springer; 2021:281–340. doi:10.1007/7355_2021_130.

[34] Deore AB, Dhumane JR, Wagh R, Sonawane R. The Stages of Drug

Discovery and Development Process. Asian J Pharm Res Dev 2019; 7(6):62–67. doi:10.22270/ajprd.v7i6.616.
[35] Roy KK, Tota S, Tripathi T, Chander S, Nath C, Saxena AK. Lead optimization studies towards the discovery of novel carbamates as potent AChE inhibitors for the potential treatment of Alzheimer's disease. Bioorg Med Chem 2012;20(21):6313–6320. doi:10.1016/j.bmc.2012.09.005, PMID:23026084.
[36] Chaudhaery SS, Roy KK, Shakya N, Saxena G, Sammi SR, Nazir A, *et al*. Novel carbamates as orally active acetylcholinesterase inhibitors found to improve scopolamine-induced cognition impairment: pharmacophore-based virtual screening, synthesis, and pharmacology. J Med Chem 2010;53(17):6490–6505. doi:10.1021/jm100573q, PMID:20684567.
[37] Ahmed S, Prabahar AE, Saxena AK. Molecular docking-based interaction studies on imidazo[1,2-a] pyridine ethers and squaramides as anti-tubercular agents. SAR QSAR Environ Res 2023;34(6):435–457. doi:10.1080/1062936X.2023.2225872, PMID:37365919.
[38] Bhatia KS, Gupta AK, Saxena AK. Physicochemical Significance of Topological Indices: Importance in Drug Discovery Research. Curr Top Med Chem 2023;23(29):2735–2742. doi:10.2174/1568026623666230731103309, PMID:37519204.
[39] Kazandjian D, Blumenthal GM, Yuan W, He K, Keegan P, Pazdur R. FDA Approval of Gefitinib for the Treatment of Patients with Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer. Clin Cancer Res 2016;22(6):1307–1312. doi:10.1158/1078-0432.CCR-15-2266, PMID:26980062.
[40] Ikeda S, Okamoto T, Okano S, Umemoto Y, Tagawa T, Morodomi Y, *et al*. PD-L1 Is Upregulated by Simultaneous Amplification of the PD-L1 and JAK2 Genes in Non-Small Cell Lung Cancer. J Thorac Oncol 2016;11(1):62–71. doi:10.1016/j.jtho.2015.09.010, PMID:26762740.
[41] Talpaz M, Kiladjian JJ. Fedratinib, a newly approved treatment for patients with myeloproliferative neoplasm-associated myelofibrosis. Leukemia 2021;35(1):1–17. doi:10.1038/s41375-020-0954-2, PMID:32647323.
[42] Stutvoet TS, Kol A, de Vries EG, de Bruyn M, Fehrmann RS, Terwisscha van Scheltinga AG, *et al*. MAPK pathway activity plays a key role in PD-L1 expression of lung adenocarcinoma cells. J Pathol 2019;249(1):52–64. doi:10.1002/path.5280, PMID:30972766.
[43] Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, *et al*. Selumetinib in Children with Inoperable Plexiform Neurofibromas. N Engl J Med 2020;382(15):1430–1442. doi:10.1056/NEJMoa1912735, PMID:32187457.
[44] Woods DM, Sodré AL, Villagra A, Sarnaik A, Sotomayor EM, Weber J. HDAC Inhibition Upregulates PD-1 Ligands in Melanoma and Augments Immunotherapy with PD-1 Blockade. Cancer Immunol Res 2015;3(12):1375–1385. doi:10.1158/2326-6066.CIR-15-0077-T, PMID:26297712.
[45] Shi Y, Fu Y, Zhang X, Zhao G, Yao Y, Guo Y, *et al*. Romidepsin (FK228) regulates the expression of the immune checkpoint ligand PD-L1 and suppresses cellular immune functions in colon cancer. Cancer Immunol Immunother 2021;70(1):61–73. doi:10.1007/s00262-020-02653-1, PMID:32632663.
[46] Llopiz D, Ruiz M, Villanueva L, Iglesias T, Silva L, Egea J, *et al*. Enhanced anti-tumor efficacy of checkpoint inhibitors in combination with the histone deacetylase inhibitor Belinostat in a murine hepatocellular carcinoma model. Cancer Immunol Immunother 2019;68(3):379–393. doi:10.1007/s00262-018-2283-0, PMID:30547218.
[47] Lee HZ, Kwitkowski VE, Del Valle PL, Ricci MS, Saber H, Habtemariam BA, *et al*. FDA Approval: Belinostat for the Treatment of Patients with Relapsed or Refractory Peripheral T-cell Lymphoma. Clin Cancer Res 2015;21(12):2666–2670. doi:10.1158/1078-0432.CCR-14-3119, PMID:25802282.
[48] Connolly RM, Laille E, Vaishampayan U, Chung V, Kelly K, Dowlati A, *et al*. Phase I and Pharmacokinetic Study of Romidepsin in Patients with Cancer and Hepatic Dysfunction: A National Cancer Institute Organ Dysfunction Working Group Study. Clin Cancer Res 2020;26(20):5329–5337. doi:10.1158/1078-0432.CCR-20-1412, PMID:32816943.
[49] Dhasmana A, Dhasmana S, Haque S, Cobos E, Yallapu MM, Chauhan SC. Next-generation immune checkpoint inhibitors as promising functional molecules in cancer therapeutics. Cancer Metastasis Rev 2023;42(3):597–600. doi:10.1007/s10555-023-10139-6, PMID:37728815.
[50] Zhou X, Jiao L, Qian Y, Dong Q, Sun Y, Zheng WV, *et al*. Repositioning Azelnidipine as a Dual Inhibitor Targeting CD47/SIRPα and TIGIT/PVR Pathways for Cancer Immuno-Therapy. Biomolecules 2021;11(5):706. doi:10.3390/biom11050706, PMID:34068552.
[51] Cha JH, Yang WH, Xia W, Wei Y, Chan LC, Lim SO, *et al*. Metformin Promotes Antitumor Immunity via Endoplasmic-Reticulum-Associated Degradation of PD-L1. Mol Cell 2018;71(4):606–620.e7. doi:10.1016/j.molcel.2018.07.030, PMID:30118680.
[52] Lastwika KJ, Wilson W 3rd, Li QK, Norris J, Xu H, Ghazarian SR, *et al*. Control of PD-L1 Expression by Oncogenic Activation of the AKT-mTOR Pathway in Non-Small Cell Lung Cancer. Cancer Res 2016;76(2):227–238. doi:10.1158/0008-5472.CAN-14-3362, PMID:26637667.
[53] Guzik K, Tomala M, Muszak D, Konieczny M, Hec A, Błaszkiewicz U, *et al*. Development of the Inhibitors that Target the PD-1/PD-L1 Interaction-A Brief Look at Progress on Small Molecules, Peptides and Macrocycles. Molecules 2019;24(11):2071. doi:10.3390/molecules24112071, PMID:31151293.
[54] Javed SA, Najmi A, Ahsan W, Zoghebi K. Targeting PD-1/PD-L-1 immune checkpoint inhibition for cancer immunotherapy: success and challenges. Front Immunol 2024;15:1383456. doi:10.3389/fimmu.2024.1383456, PMID:38660299.
[55] Koblish HK, Wu L, Wang LS, Liu PCC, Wynn R, Rios-Doria J, *et al*. Characterization of INCB086550: A Potent and Novel Small-Molecule PD-L1 Inhibitor. Cancer Discov 2022;12(6):1482–1499. doi:10.1158/2159-8290.CD-21-1156, PMID:35254416.
[56] Wang Y, Liu X, Zou X, Wang S, Luo L, Liu Y, *et al*. Metabolism and Interspecies Variation of IMMH-010, a Programmed Cell Death Ligand 1 Inhibitor Prodrug. Pharmaceutics 2021;13(5):598. doi:10.3390/pharmaceutics13050598, PMID:33919384.
[57] Jiang J, Zou X, Liu Y, Liu X, Dong K, Yao X, *et al*. Simultaneous Determination of a Novel PD-L1 Inhibitor, IMMH-010, and Its Active Metabolite, YPD-29B, in Rat Biological Matrices by Polarity-Switching Liquid Chromatography-Tandem Mass Spectrometry: Application to ADME Studies. Front Pharmacol 2021;12:677120. doi:10.3389/fphar.2021.677120, PMID:34234673.
[58] Wang Y, Gao Y, Mao C, Xu N, Zhang Q, Wang J, *et al*. Abstract LB098: Combination of a PD-1/CTLA-4 bispecific antibody with orally active PD-L1 inhibitor MAX-10181 effectively increased the percentage of tumors inhibited in animal model study. Cancer Res 2023;83(8_Supplement):LB098. doi:10.1158/1538-7445.AM2023-LB098.
[59] Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ASC61in Subjects With Advanced Solid Tumors. ClinicalTrials.gov identifier: NCT05287399. Updated April 3, 2024. Accessed June 5, 2024. https://clinicaltrials.gov/study/NCT05287399.
[60] Wu JJ, He H. Abstract 5529: *In vivo* efficacy evaluation of ASC61, an oral PD-L1 inhibitor, in two tumor mouse models. Cancer Res 2022;82(12_Suppl):5529. doi:10.1158/1538-7445.AM2022-5529.
[61] Odegard JM, Othman AA, Lin KW, Wang AY, Nazareno J, Yoon OK, *et al*. Oral PD-L1 inhibitor GS-4224 selectively engages PD-L1 high cells and elicits pharmacodynamic responses in patients with advanced solid tumors. J Immunother Cancer 2024;12(4):e008547. doi:10.1136/jitc-2023-008547, PMID:38604815.
[62] Huang KC, Chiang SF, Chen WT, Chen TW, Hu CH, Yang PC, *et al*. Decitabine Augments Chemotherapy-Induced PD-L1 Upregulation for PD-L1 Blockade in Colorectal Cancer. Cancers (Basel) 2020;12(2):462. doi:10.3390/cancers12020462, PMID:32079180.
[63] Zhu T, Hu Z, Wang Z, Ding H, Li R, Sun J, *et al*. Epigenetically silenced PD-L1 confers drug resistance to anti-PD1 therapy in gastric cardia adenocarcinoma. Int Immunopharmacol 2020;82:106245. doi:10.1016/j.intimp.2020.106245, PMID:32088639.
[64] Zeidan AM, Boss I, Beach CL, Copeland WB, Thompson E, Fox BA, *et al*. A randomized phase 2 trial of azacitidine with or without durvalumab as first-line therapy for older patients with AML. Blood Adv 2022;6(7):2219–2229. doi:10.1182/bloodadvances.2021006138, PMID:34933333.
[65] Baer MR, Kogan AA, Bentzen SM, Mi T, Lapidus RG, Duong VH, *et al*. Phase I Clinical Trial of DNA Methyltransferase Inhibitor Decitabine and PARP Inhibitor Talazoparib Combination Therapy in Relapsed/Refractory Acute Myeloid Leukemia. Clin Cancer Res 2022;28(7):1313–

1322. doi:10.1158/1078-0432.CCR-21-3729, PMID:35091444.
[66] Musielak B, Kocik J, Skalniak L, Magiera-Mularz K, Sala D, Czub M, *et al*. CA-170 - A Potent Small-Molecule PD-L1 Inhibitor or Not? Molecules 2019;24(15):2804. doi:10.3390/molecules24152804, PMID: 31374878.
[67] Sasikumar PG, Sudarshan NS, Adurthi S, Ramachandra RK, Samiulla DS, Lakshminarasimhan A, *et al*. PD-1 derived CA-170 is an oral immune checkpoint inhibitor that exhibits preclinical anti-tumor efficacy. Commun Biol 2021;4(1):699. doi:10.1038/s42003-021-02191-1, PMID:34103659.
[68] Powderly J, Patel MR, Lee JJ, Brody J, Meric-Bernstam F, Hamilton E, *et al*. CA-170, a first in class oral small molecule dual inhibitor of immune checkpoints PD-L1 and VISTA, demonstrates tumor growth inhibition in pre-clinical models and promotes T cell activation in Phase 1 study. Ann Oncol 2017;28(Suppl 5):v405–v406. doi:10.1093/annonc/mdx376.007.
[69] Wang F, Fu K, Wang Y, Pan C, Wang X, Liu Z, *et al*. Small-molecule agents for cancer immunotherapy. Acta Pharm Sin B 2024;14(3):905–952. doi:10.1016/j.apsb.2023.12.010, PMID:38486980.
[70] A Study of CA-170 (Oral PD-L1, PD-L2 and VISTA Checkpoint Antagonist) in Patients with Advanced Tumors and Lymphomas. ClinicalTrials.gov identifier: NCT02812875. Updated June 26, 2020. Accessed date June 05, 2024. https://clinicaltrials.gov/study/NCT02812875.
[71] A Phase 1 Study of BPI-371153 in Subjects With Advanced Solid Tumors or Relapsed/Refractory Lymphoma. ClinicalTrials.gov identifier: NCT05341557. Updated June 21, 2022. Accessed date June 05, 2024. https://clinicaltrials.gov/study/NCT05341557.
[72] Effector Therapeutics. Tomivosertib (eFT-508) in Combination With PD-1/PD-L1 Inhibitor Therapy. ClinicalTrials.gov identifier: NCT03616834. Updated March 22, 2023. Accessed date June 05, 2024. https://clinicaltrials.gov/study/NCT03616834.
[73] Wong MKK, Burgess MA, Chandra S, Fecher LA, Gaudy-Marqueste C, Silk AW, *et al*. A pivotal study of navtemadlin, a first-in-class mouse double minute 2 inhibitor (MDM2i), in patients (pts) with TP53 wild-type (TP53WT) Merkel cell carcinoma (MCC) for whom anti PD-1/L1 therapy has failed. J Clin Oncol 2023;41(16 Suppl):TPS9600–TPS9600. doi:10.1200/JCO.2023.41.16_suppl.TPS9600.
[74] Fayette J, Saada-Bouzid E, Cropet C, Daste A, Treilleux I, Pissaloux D, *et al*. Abemaciclib in recurrent/metastatic head and neck squamous cell carcinoma (RM-HNSCC) harboring CDKN2A loss, and/or CCND1 and/or CDK6 amplification: A phase II multicenter trial. J Clin Oncol 2023;41(16 Suppl):6044–6044. doi:10.1200/JCO.2023.41.16_suppl.6044.
[75] Beckermann K, Rini B, Haas N, George D, Jonasch E. Phase 1b/2 trial of Ipilimumab, Nivolumab, and Ciforadenant (INC) (adenosine A2a receptor antagonist) in first-line advanced renal cell carcinoma. Oncologist 2023;28(Suppl 1):S13–S14. doi:10.1093/oncolo/oyad216.022.
[76] Sobral PS, Luz VCC, Almeida JMGCF, Videira PA, Pereira F. Computational Approaches Drive Developments in Immune-Oncology Therapies for PD-1/PD-L1 Immune Checkpoint Inhibitors. Int J Mol Sci 2023;24(6):5908. doi:10.3390/ijms24065908, PMID:36982981.
[77] Manji GA, Van Tine BA, Lee SM, Raufi AG, Pellicciotta I, Hirbe AC, *et al*. A Phase I Study of the Combination of Pexidartinib and Sirolimus to Target Tumor-Associated Macrophages in Unresectable Sarcoma and Malignant Peripheral Nerve Sheath Tumors. Clin Cancer Res 2021;27(20):5519–5527. doi:10.1158/1078-0432.CCR-21-1779, PMID:34321280.
[78] Eglenen-Polat B, Kowash RR, Huang HC, Siteni S, Zhu M, Chen K, *et al*. A telomere-targeting drug depletes cancer initiating cells and promotes anti-tumor immunity in small cell lung cancer. Nat Commun 2024;15(1):672. doi:10.1038/s41467-024-44861-8, PMID:38253555.
[79] Kaye SB, Fehrenbacher L, Holloway R, Amit A, Karlan B, Slomovitz B, *et al*. A phase II, randomized, placebo-controlled study of vismodegib as maintenance therapy in patients with ovarian cancer in second or third complete remission. Clin Cancer Res 2012;18(23):6509–6518. doi:10.1158/1078-0432.CCR-12-1796, PMID:23032746.
[80] Choueiri TK , Powles T , Albiges L , Burotto M , Szczylik C, Zurawski B, *et al*. Cabozantinib plus Nivolumab and Ipilimumab in Renal-Cell Carcinoma. N Engl J Med 2023;388(19):1767–1778. doi:10.1056/NEJMoa2212851, PMID:37163623.
[81] Marmarelis ME, Mathew D, Bauml JM, Hwang WT, Zhang J, Singh A, *et al*. P1.15-07 Phase II Study of Pembrolizumab and Itacitinib for First Line Treatment of Metastatic NSCLC Expressing PD-L1. J Thorac Oncol 2022;17(9 Suppl):S122–S123. doi:10.1016/j.jtho.2022.07.203.
[82] Phase 1 Study of SF1126 in Combination With Nivolumab in Patients With Advanced Hepatocellular Carcinoma. ClinicalTrials.gov identifier: NCT03059147. Updated May 18, 2022. Accessed date June 05, 2024. https://clinicaltrials.gov/study/NCT03059147.
[83] He K, Berz D, Gadgeel SM, Iams WT, Bruno DS, Blakely CM, *et al*. MRTX-500 Phase 2 Trial: Sitravatinib With Nivolumab in Patients With Nonsquamous NSCLC Progressing On or After Checkpoint Inhibitor Therapy or Chemotherapy. J Thorac Oncol 2023;18(7):907–921. doi:10.1016/j.jtho.2023.02.016, PMID:36842467.
[84] Konstantinopoulos PA, Gockley AA, Xiong N, Krasner C, Horowitz N, Campos S, *et al*. Evaluation of Treatment With Talazoparib and Avelumab in Patients With Recurrent Mismatch Repair Proficient Endometrial Cancer. JAMA Oncol 2022;8(9):1317–1322. doi:10.1001/jamaoncol.2022.2181, PMID:35900726.
[85] Yuan L, Jia GD, Lv XF, Xie SY, Guo SS, Lin DF, *et al*. Camrelizumab combined with apatinib in patients with first-line platinum-resistant or PD-1 inhibitor resistant recurrent/metastatic nasopharyngeal carcinoma: a single-arm, phase 2 trial. Nat Commun 2023;14(1):4893. doi:10.1038/s41467-023-40402-x, PMID:37580352.
[86] Zhou X, Du J, Wang H, Chen C, Jiao L, Cheng X, *et al*. Repositioning liothyronine for cancer immunotherapy by blocking the interaction of immune checkpoint TIGIT/PVR. Cell Commun Signal 2020;18(1):142. doi:10.1186/s12964-020-00638-2, PMID:32894141.
[87] Li TT, Jiang JW, Qie CX, Xuan CX, Hu XL, Liu WM, *et al*. Identification of active small-molecule modulators targeting the novel immune checkpoint VISTA. BMC Immunol 2021;22(1):55. doi:10.1186/s12865-021-00446-4, PMID:34380434.
[88] Tanida I, Ueno T, Kominami E. LC3 and Autophagy. Methods Mol Biol 2008;445:77–88. doi:10.1007/978-1-59745-157-4_4, PMID:18425443.
[89] Wang T, Wang K, Zhang Y, Zhang K, Cai S, Jiang S, *et al*. Novel Benzimidazoles as Potent Small-Molecule Inhibitors and Degraders of V-Domain Ig Suppressor of T-Cell Activation (VISTA). J Med Chem 2023;66(17):11881–11892. doi:10.1021/acs.jmedchem.3c00484, PMID:37594853.
[90] Huang Y, Zhang HL, Li ZL, Du T, Chen YH, Wang Y, *et al*. FUT8-mediated aberrant N-glycosylation of B7H3 suppresses the immune response in triple-negative breast cancer. Nat Commun 2021;12(1):2672. doi:10.1038/s41467-021-22618-x, PMID:33976130.
[91] Mortezaee K, Majidpoor J, Najafi S, Tasa D. Bypassing anti-PD-(L)1 therapy: Mechanisms and management strategies. Biomed Pharmacother 2023;158:114150. doi:10.1016/j.biopha.2022.114150, PMID:36577330.
[92] Chen FF, Li Z, Ma D, Yu Q. Small-molecule PD-L1 inhibitor BMS1166 abrogates the function of PD-L1 by blocking its ER export. Oncoimmunology 2020;9(1):1831153. doi:10.1080/2162402X.2020.1831153, PMID:33110706.
[93] Song X, Zhou Z, Li H, Xue Y, Lu X, Bahar I, *et al*. Pharmacologic Suppression of B7-H4 Glycosylation Restores Antitumor Immunity in Immune-Cold Breast Cancers. Cancer Discov 2020;10(12):1872–1893. doi:10.1158/2159-8290.CD-20-0402, PMID:32938586.
[94] Lopez-Sambrooks C, Shrimal S, Khodier C, Flaherty DP, Rinis N, Charest JC, *et al*. Oligosaccharyltransferase inhibition induces senescence in RTK-driven tumor cells. Nat Chem Biol 2016;12(12):1023–1030. doi:10.1038/nchembio.2194, PMID:27694802.
[95] Rinis N, Golden JE, Marceau CD, Carette JE, Van Zandt MC, Gilmore R, *et al*. Editing N-Glycan Site Occupancy with Small-Molecule Oligosaccharyltransferase Inhibitors. Cell Chem Biol 2018;25(10):1231–1241.e4. doi:10.1016/j.chembiol.2018.07.005, PMID:30078634.
[96] Cheng J, Xia L, Hao X, Gan F, Bai Y, Zhang C, *et al*. Targeting STT3A produces an anti-tumor effect in lung adenocarcinoma by blocking the MAPK and PI3K/AKT signaling pathway. Transl Lung Cancer Res 2022;11(6):1089–1107. doi:10.21037/tlcr-22-396, PMID:35832442.