Minireview Article

Emergent new anti PD-1/PD-L1 small molecules for cancer treatment

Abstract

Currently all approved PD-1/PD-L1 inhibitors are monoclonal antibodies. Along with that, compounds from other chemical classes are being investigated as well. Among those are small molecules which demonstrate commensurable therapeutic effect in preclinical and early clinical development. In comparison with antibodies, small molecules have certain advantages such as shorter blood half-times and possibility for oral intake. If clinical trials will confirm acceptable therapeutic and safety profile in forthcoming years, these agents may become good alternatives to the monoclonal antibodies for using in treatment regimens implementing immune checkpoint inhibition via PD-1/PD-L1 pathway.

Keywords: small molecules, anti-PD-1/PD-L1, cancer immunotherapy, cancer treatment

Introduction

In the recent decade, the PD-1/PD-L1 immune checkpoint pathway inhibition has become one of the most promising approaches in cancer therapy. Its attractiveness lies with "unblocking" the immune system to fight against cancer, thus overcoming death escape mechanisms of tumour cells. Most clinically used anti-PD-1/PD-L1 immune checkpoint inhibitors are recombinant monoclonal antibodies (mAbs). Indicative of the interest towards cancer immunotherapy is the number of cancer clinical trials being conducted as per the ClinicalTrials.gov register – about 307 worldwide as a single investigational drug or in combinations with other therapeutics for cancer [1]. They have been approved for first- and second-line treatment options in several malignancies, thanks to the encouraging efficacy. At present, mAbs targeting PD-1 (e.g., Cemiplimab, Nivolumab, Pembrolizumab and Dostarlimab) or PD-L1 (e.g., Durvalumab, Avelumab, and Atezolizumab) are approved by the United States FDA and by other Regulatory Agencies for the treatment of series of locally advanced and metastatic solid tumours like Melanoma, Non-Small Cell Lung Cancer (NSCLC), Malignant Pleural Mesothelioma, and Lymphomas [2].

Discussion

In contrast to all these approved anti-PD-1/PD-L1 mAbs, several other-agents against PD-1/PD-L1 are being investigated, such as peptides/peptidomimetics, macrocycles, and small molecules [3]. Pursuing the same therapeutic immunologic objective anti-PD-1/PD-L1 small molecules

have different biophysical and biochemical properties, resulting from and dependent on the structural classes to which they belong. Most essential among those from the clinical perspective are tumour penetration, ability to cross physiological barriers, oral bioavailability, accessibility to intracellular targets, immunogenicity, and receptor affinity [4,5]. Table 1 shows a polar difference between the antibodies and small molecules properties, whereas peptides and macrocycles' properties fall between them.

Table 1: Comparison of biophysical and biochemical properties between mAbs and small molecules.

	Small Molecules	**Antibodies / Biologics**
Size	Small, less than 600 Daltons	Large, ~150.000 Daltons
Structure	Simple	Complex
Stability	Stable	Unstable
Permeability	High	Low
Target	Intra or Extracellular	Extracellular
Delivery	Multiple (oral, injection, inhaled, etc.)	Parenteral only (infusion, injection)
Production	Chemical synthesis	From living cells
Specificity	Variable specificity	Very specific
Dosing	Usually once or twice a day	Usually once every 1-4 weeks
Immunogenicity	No	Yes
Blood half-times	Hours	Days/weeks
Receptor affinity	Comparably low	High

Although these anti-PD-1/PD-L1 ICI mAbs exhibited promising therapeutic effects in clinical studies, restrictions including toxicity, immunogenicity, and high costs are imposed for their clinical utilization of them. The immune-related adverse events (irAEs) of anti-PD-1/PD-L1 mAbs are well described in clinical study reports and scientific medical literature [6]. The spectrum of organ systems affected by irAEs is vast; toxicities can affect almost any organ with varying frequencies and severities. Frequently observed irAEs include dermatitis, colitis, and thyroiditis, while especially rare irAEs, such as myocarditis, myositis, and encephalitis, have a high fatality rate [7,8]. The class-specific properties of anti-PD-1/PD-L1 mAbs and small molecules contribute to the safety profile of these compounds. For example, the longer blood half-lives of anti-PD-1/PD-L1 mAbs, which increase the difficulty in drug elimination, predetermine the intensity and duration of immune-related adverse events (irAEs). While mAbs inflict the toxic effects throughout days/weeks after discontinuing administration, small molecules may stop their toxic effect in hours. Expectedly, treatment compliance is essentially affected due to toxicities of anti-PD-1/PD-L1 mAbs and may result in treatment delays or discontinuations impacting their efficacy. In addition, the use of steroids, which may inactivate the mAbs, in their management could compromise even more their efficacy [9, 10].

Interestingly, preclinical studies have demonstrated that small molecule inhibitors are potent immunomodulators that can induce cytokine production (IL-2 and IFN-γ) and T cell proliferation, at levels comparable to pembrolizumab [11]. Therefore, small molecules with better management of AEs and treatment compliance may be meaningful for the survival of cancer patients than mAbs. Another essential disadvantage of anti-PD-1/PD-L1 mAbs s is the need for parenteral (intravenous infusion)

administration, which means the additional need for medical/nursing care to the patient, additional manipulations related to the storage and preparation of the IV infusion, infusion-related reactions, and discomfort for the patient related to the length infusion itself. Small-molecule-based compounds offer the potential to address these shortcomings of antibody-based therapies as they are easier self-administered [12]. In table 2 and 3 is outlined the most relevant small molecule compounds under research and development in preclinical and clinical studies based on open-source literature and drug databases.

Table 2: List of relevant anti-PD1 and/or anti-PD-L1 small molecule compounds under most advanced preclinical development for cancer treatment

Comound	Comments
CCX 559, CCX 4503 and others	Orally available, small molecule compounds inhibiting programmed death-ligand 1 (PD-L1) are being developed by ChemoCentryx for the treatment of various types of cancers, including colon cancer. Preclinical development is underway in the US [13, 14].
ABSK043	Orally available small molecule inhibitors of programmed-cell-death-1-ligand-1 (PD-L1) are being developed by Abbisko Therapeutics to treat cancer and have demonstrated robust T-cell activating ability and potent anti-tumour activity in various preclinical models [15].
JBI-426 and others	Small molecule PD-L1 inhibitors are being developed by Jubilant Life Science subsidiary companies to treat cancer. Three chemical series of inhibitors, including lead molecule JBI-426, showed good in vitro ADME properties in terms of aqueous solubility, metabolic stability, permeability and excellent oral bioavailability in a preclinical setting along with a potent tumour growth inhibition, comparable (or better) than the PD-L1 mAb, and was well tolerated. Preclinical development is underway in India and the US [16].
CS 17938 and others	Chipscreen Biosciences is developing a series of small molecule therapeutics to treat multiple indications with cancer amongst them [3].
SB-415286 and SB-216763	SB415286 and SB-216763 developed by GlaxoSmithKline are investigated for their ability to inhibit the serine/threonine kinase GSK-3, which downregulates the LAG-3 and PD-1 expression in T—cells and can be as effective as anti-PD-1 and PD-L1 blocking antibodies in the control of tumour growth [5, 17, 18].
BMS-8, BMS-37, BMS-202, BMS-1166 and others	Molecules from Bristol-Myers Squibb block the post-translational processing of PD-L1, preventing it from directly interacting with PD-1 via different mechanisms such as inhibition of PD-L1 glycosylation [19, 20, 21].

Table 3: List of anti-PD1 and/or anti-PD-L1 small molecule compounds under clinical development for cancer treatment

Compund	Therapeutic indications	Highest Phase	Comments	www.clinicaltrials.gov
CA-170	Solid tumours and Lymphoma	Phase II/III	CA 170 is being jointly developed by Aurigene and Curis. Along with PD-L1 inhibition, the drug candidate is also a V-domain Immunoglobulin suppressor of T cell activation (VISTA) antagonist, both of which function as negative checkpoint regulators of immune activation. Phase I study completed in 2020 showing acceptable safety profile, and phase II study (in patients with Head & Neck Cancer, Squamous-NSCLC, Non-Squamous-NSCLC, MSI-H positive solid tumours and Hodgkin Lymphoma) investigating two dosages (400mg versus 800mg) is underway [22, 23].	NCT02812875
INCB086550	Solid tumours	Phase I/II	INCB086550 is being developed by Incyte Corporation for solid tumours, Non-Small Cell Lung Cancer, Urothelial Cancer, Renal Cell Carcinoma, Hepatocellular Carcinoma and Melanoma. Three clinical trials (two-phase I and one phase II) are currently underway, targeting to complete in 2022/2023 [24].	NCT03762447 NCT04674748 NCT04629339

MAX-10181	Solid tumours	Phase I	MAX-10181 able to penetrate the blood-brain barrier is being developed by Maxinovel Pharmaceuticals. Phase I trial given to patients with advanced solid tumour is underway in Australia estimated to complete in June 2021.	NCT04122339
GS-4224	Solid tumours	Phase I/II	GS-4224 is being developed by Gilead Sciences. A phase I/II study is underway in the US and New Zealand for advanced solid tumours aiming to complete in 2023.	NCT04049617

Conclusion

Summarizing all the above, anti-PD-1/PD-L1 small molecule compounds can guide the development of next-generation drug-like inhibitors. If proven successful in clinical trials, these small molecules may represent a better therapeutic option from an efficacy and safety point of view. Treatment costs may be reduced essentially because of cheaper production and less complicated storage, maintenance, and administration than the mAbs. Oral administration will be a significant advantage, especially from the patients' perspective, ensuring better treatment compliance in an outpatient setting.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References:

1. ClinicalTrials.gov [Internet]. Web resource provided by the U.S. National Library of Medicine (NLM). Available from: https://clinicaltrials.gov.
2. Twomey, J.D., Zhang, B. Cancer Immunotherapy Update: FDA-Approved Checkpoint Inhibitors and Companion Diagnostics. *AAPS J* **23,** 39 (2021). https://doi.org/10.1208/s12248-021-00574-0
3. Ai L et al. Research Status and Outlook of PD-1/PD-L1 Inhibitors for Cancer Therapy. Drug Des Devel Ther. 2020;14:3625-3649 Available from: https://doi.org/10.2147/DDDT.S267433
4. Jiao P et al. Small Molecules as PD-1/PD-L1 Pathway Modulators for Cancer Immunotherapy. Curr Pharm Des. 2018;24(41):4911-4920. doi: 10.2174/1381612824666181112114958. PMID: 30417781 Review. Available from: https://pubmed.ncbi.nlm.nih.gov/30417781/ Subscription required.
5. Taylor A, Rudd CE. Commentary: Small Molecule Inhibition of PD-1 Transcription is an Effective Alternative to Antibody Blockade in Cancer Therapy. J Immunological Sci. (2019); 3(1): 9-12. Available from:

https://www.immunologyresearchjournal.com/articles/commentary-small-molecule-inhibition-of-pd1-transcription-is-an-effective-alternative-to-antibody-blockade-in-cancer-therapy.html
6. Bajwa R et al. Adverse Effects of Immune Checkpoint Inhibitors (Programmed Death-1 Inhibitors and Cytotoxic T-Lymphocyte-Associated Protein-4 Inhibitors): Results of a Retrospective Study. J Clin Med Res. 2019;11(4):225-236. doi:10.14740/jocmr3750. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6436564/
7. Spiers L et al. Toxicities associated with checkpoint inhibitors-an overview. Rheumatology (Oxford). 2019;58(Suppl 7):vii7-vii16. doi:10.1093/rheumatology/kez418. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6900917/
8. Su Chaoyue et al. Adverse Effects of Anti-PD-1/PD-L1 Therapy in Non-small Cell Lung Cancer. Front. Oncol., 17 September 2020. Available from: https://doi.org/10.3389/fonc.2020.554313
9. Su C et al. Adverse Effects of Anti-PD-1/PD-L1 Therapy in Non-small Cell Lung Cancer. Front Oncol. 2020;10:554313. Published 2020 Sep 17. doi:10.3389/fonc.2020.554313. Available from: https://www.frontiersin.org/articles/10.3389/fonc.2020.554313/full
10. Guo L et al. Clinical and Recent Patents Applications of PD-1/PD-L1 Targeting Immunotherapy in Cancer Treatment—Current Progress, Strategy, and Future Perspective. Frontiers in Immunology, V 11, 2020, page 1508. DOI=10.3389/fimmu.2020.01508. ISSN=1664-3224. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2020.01508/full
11. Ganesan A et al. Comprehensive in vitro characterization of PD-L1 small molecule inhibitors. *Sci Rep*. 2019;9(1):12392. Published 2019 Aug 27 doi:10.1038/s41598-019-48826-6. Available from: https://pubmed.ncbi.nlm.nih.gov/31455818/
12. Sasikumar PG, Ramachandra M. Small-Molecule Immune Checkpoint Inhibitors Targeting PD-1/PD-L1 and Other Emerging Checkpoint Pathways. BioDrugs. 2018 Oct;32(5):481-497. doi: 10.1007/s40259-018-0303-4. PMID: 30168070 Review. Available from: https://pubmed.ncbi.nlm.nih.gov/30168070/ Subscription required.
13. Li S"C" et al. Abstract 5693: Anti-tumor effect of orally available small molecule PD-L1 inhibitors in a murine model of colon adenocarcinoma. DOI 10.1158/1538-7445.AM2020-5693, 2020 Aug 15, Cancer Research, 5693, 80, Supplement. Available from: https://cancerres.aacrjournals.org/content/80/16_Supplement/5693
14. Guzik K 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 May 30;24(11):2071. doi: 10.3390/molecules24112071. PMID: 31151293; PMCID: PMC6600339. Available from: https://pubmed.ncbi.nlm.nih.gov/31151293/ Subscription required.
15. Ying H et al. Discovery and characterization of a novel small molecule antagonist of PD-L1. AACR-NCI-EORTC-2019 2019; abstr. LB-A17. Available from: URL: https://eventpilotadmin.com/web/page.php?page=IntHtml&project=AACR19MT&id=613
16. Dhanalakshmi S et al. Novel, heterocyclic small molecule inhibitors of PD-1 and PD-L1 pathway. AACR-2018 2018; abstr. 5552 / 8. Available from: http://link.adisinsight.com/k2S4D
17. Rudd CE et al. Small Molecule Inhibition of GSK-3 Specifically Inhibits the Transcription of Inhibitory Co-receptor LAG-3 for Enhanced Anti-tumor Immunity. Cell Reports, Volume 30, Issue 7, 2020, Pages 2075-2082.e4. ISSN 2211-1247, doi: 10.1016/j.celrep.2020.01.076. Available from: https://www.sciencedirect.com/science/article/pii/S2211124720301017?via%3Dihub
18. Coghlan MP et al. Selective small molecule inhibitors of glycogen synthase kinase-3 modulate glycogen metabolism and gene transcription, Chemistry & Biology, Volume 7, Issue 10, 2000, Pages 793-803, ISSN 1074-5521, doi: 10.1016/S1074-5521(00)00025-9. Available from: https://www.sciencedirect.com/science/article/pii/S1074552100000259?via%3Dihub
19. Zak KM et al. Structural basis for small molecule targeting of the programmed death ligand 1 (PD-L1). Oncotarget 2016 May 24;7(21):30323-30335. Available from: https://www.oncotarget.com/article/8730/text/

20. Bojadzic D, Buchwald P. Toward Small-Molecule Inhibition of Protein-Protein Interactions: General Aspects and Recent Progress in Targeting Costimulatory and Coinhibitory (Immune Checkpoint) Interactions. Curr Top Med Chem. 2018;18(8):674-699. doi: 10.2174/1568026618666180531092503. PMID: 29848279; PMCID: PMC6067980. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6067980/
21. Chen FF et al. Small-molecule PD-L1 inhibitor BMS1166 abrogates the function of PD-L1 by blocking its ER export. Oncoimmunology. 2020 Oct 14;9(1):1831153. doi: 10.1080/2162402X.2020.1831153. PMID: 33110706; PMCID: PMC7567511. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7567511/
22. Zauderer M et al. P2.06-07 Phase 1 Study of CA-170: First-in-Class Small Molecule Targeting VISTA/PD-L1 in Patients with Malignant Pleural Mesothelioma, Journal of Thoracic Oncology, Volume 14, Issue 10, Supplement, 2019, Pages S757-S758.
23. Radhakrishnan VS et al. Phase 2 trial of CA-170, a novel oral small molecule dual inhibitor of immune checkpoints VISTA and PD-1, in patients (pts) with advanced solid tumor and Hodgkin lymphoma. Journal for ImmunoTherapy of Cancer 2018, 6(Suppl 2):P714, Abstract P714. Available from: https://www.researchgate.net/publication/335601752_Abstract_P714_Phase_2_trial_of_CA-170_a_novel_oral_small_molecule_dual_inhibitor_of_immune_checkpoints_VISTA_and_PD-1_in_patients_pts_with_advanced_solid_tumor_and_Hodgkin_lymphoma#fullTextFileContent
24. Cutsem EV et al. 529 Phase 1 study of INCB086550, an oral PD-L1 inhibitor, in immune-checkpoint naive patients with advanced solid tumors. Journal for ImmunoTherapy of Cancer 2021; 9: doi: 10.1136/jitc-2021-SITC2021.529. Available from: https://jitc.bmj.com/content/9/Suppl_2/A559