

OTX015 PROTACs: Emerging Novel Therapeutic Agents in Cancer Treatment

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Abstract. Cancer is a wide-spreading disease. Its count goes on increasing and became the second leading cause of death in respect of diseases. New cancer-targeting molecules are explored. In this study, we tried to collect information about one such molecule, OTX015. Articles were searched across reputed search engines and publishers such as Cochrane, EMBASE, The Lancet, PubMed, GoogleScholar, ScienceDirect, Wiley Online, Springer and Bentham Science by using different keywords: “OTX015”, “Cancer”, “Small molecule PROTACs”, “BRD/BET” and “BET inhibitors”. The quality papers were retrieved, studied, categorized into different sections, analyzed, and used for article writing. OTX015 is a novel molecule in clinical trials. It showed some promising results in various cancers as well as other diseases like latent-HIV with the least side-effects. This article will give an insight into Small Molecules as PROTACs, their advantages and disadvantages, OTX015 and its PROTAC ARV-825. It is advised that more research/studies are required to be carried out to know more about OTX015 and other PROTACs, their advancements, receptors, and mechanism/ mode of action to know their abilities to work against proteins involving diseases.

1 Introduction

Cancer is a serious life-threatening illness [1]. It affects both developed and developing nations [2]. Cancer ranked second in causing mortality in the United States, approximately 606,500 US patients died due to cancer (in 2020) [3]. The US spends money on Cancer study and treatment more than any other nation [3]. Of all cancers, lung cancer is most common, almost 10 lakh deaths occur every year [4,5]. Other forms of cancers include Breast, Colorectal, Liver, Stomach, Cervix uteri, Oesophagus, Pancreas, Ovary, Leukemia, etc. [5-7]. Cancer pathogenesis is complex and it involves various factors [2].

Rather than inhibiting, protein degradation is more effective in the treatment of cancer, so, protein-protein interactions become the new trend for cell degradation in the field of science, especially in cancer therapy [8]. Two main ways for the breakdown of protein are the Ubiquitin-Proteasome System (UPS) and Autophagy [9]. PROTACs i.e. Proteolysis Targeting Chimeric molecules make use of the cell's destructive mechanism for protein breakdown by controlling E3 ubiquitin ligases [10-14]. In general, UPS washout the denatured, mutated, or harmful proteins from the cell [14]. So PROTACs can be used in a variety of disorders that occur due to the expression of proteins [14]. PROTAC is synthesized by joining two ligands with the help of a linker [9]. One ligand is protein-specific while the other binds to E3 ligase [10]. PROTAC aim different transcription regulating proteins like nuclear receptors, Histone deacetylases, and other transcription regulators such as Bromodomain containing protein-7/9 (BRD7/9), P300/CBP-associated factor and General Control Nonderepressible5 (PCAF/GCN5), Signal transducer and activator of transcription 3 (STAT3), Mothers against decapentaplegic homolog 3 (SMAD3), Ikaros family zinc finger protein 1 and 3 (IKZF1/3) [14,15] and BET proteins are one of them [14].

2 Small Molecule PROTACs

In 2008, the first small molecule PROTAC (SMP) was announced [16]. SMPs act on some E3 ubiquitin ligands including Mouse double minute 2 (MDM2), cellular inhibitor of apoptosis protein-1 (cIAP1), Von Hippel-Lindau syndrome (VHL), and Cereblon (CRBN)[17]. After the success of peptide PROTACs (that use small molecules to act) over simple peptides, SMPs were prepared [8]. SMPs have a strong affinity for the BET family [8]. There is a total of 61 human genomic encoded Bromodomains (BRDs) [18,19]. BRD is 8-structural left-handed alpha-helical fold family [18,20]. A protein of BRD/BET plays a crucial part in many biological processes, cancer, and other disorders [11,18,20,21]. BD-1 and BD-2 are two bromodomains of BET (Bromodomain and extra-terminal family) protein [22-24] but in pre-clinical models of inflammation and autoimmune diseases, BD-2 inhibitors had greater therapeutic activity as compared to BD-1 inhibitors [23]. Members of BET:BRD-2, BRD-3, BRD-4 and BRD4 [21,22,25-29] are the primary aim for treatment of various hematologic and solid tumors [18,21,25,26]. The BRD4 plays an important role in transcription initiation, elongation, regulation, telomere regulation, and repairing of damaged DNA, in the regulation of crucial oncogenes like Myc proto-oncogene protein (c-myc), B-cell lymphoma-extra large (bcl-x1) and B-cell lymphoma 6 protein (bcl-6) [19,20,25,30,31], but dysfunction of BET-protein develops cancer [26]. Inhibiting BET is a sound approach for the treatment of cancer [24]. Selective BET-inhibitors are more effective in different pediatric cancer cell-lines with the least toxicity [24]. Inhibition of BRD4 causes size reduction, differentiation, along with phosphorylation of H2A histone family member X (H2AX) and apoptosis in acute myeloid leukemia cells [30,32]. JQ1, I-BET762, OTX015, MS417, CPI203, BET-BAY-002, XD14, RVX-208, PFI-1, Olinone, BIC1, MS436, I-BET726, and I-BET151 are some BET-inhibitors [21]. According to Yang *et al.*, 13 small molecule BET-inhibitors are in clinical trials [11]. BET-inhibitors alone showed effective activity against many cancers but moderate against advanced cancers [11,21]. JQ1 and OTX015 have reflected impressive results in many preclinical models of cancers [27].

2.1 Advantages of PROTAC and SMPs

- SMPs are easy to absorb and to develop into the drug as compared to peptide PROTACs [8].
- PROTAC acts as a catalyst to breakdown protein of interest more effectively as compared to small molecule inhibitors [10].
- PROTAC targets undruggable proteins, rapid protein breakdown, better cell permeability, better in-vitro stability, and biodistribution [10,30].
- SMPs and other PROTACs can be administered orally [31] and exhibit less drug resistance [14].

2.2 Disadvantages of PROTACs

- As activity depends on the presence of E3 ubiquitin ligase drug resistance may occur due to mutation in UPS [17].
- *In-vivo* poor stability, biodistribution, and cell penetration [30].

3 OTX015

OTX015 is thienotriazolodiazepine compound with a molecular weight of 492 g/mol and molecular formula $C_{25}H_{22}ClN_5O_2S$ [33,34]. Other names for OTX015 are: Birabresib, MK-8628, OTX-015, OTX 015 [34]. It is a potent oral small molecule inhibitor which binds and inhibits BRD2, BRD3, and BRD4 proteins, especially BRD2 and BRD4 of BET family [33,35-40]. (-)-OTX015 of OTX015 is an active enantiomer [35]. OTX015 shows both *in-vivo* and *in-vitro* activity against many tumors like leukemia, prostate, lung carcinoma, lung cancer, lymphoma, myeloma, neuroblastoma, triple-negative breast cancer, glioblastoma multiforme, and mature B-cell tumors, etc [36,37] by reducing expression of many oncogenes such as c-myc, homeobox protein NANOG (Nanog mRNA), cancer stem cells (CSC), etc [33,36-38,41,42]. It suppresses different nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), Toll-like receptors (TLR) and Janus kinases, signal transducer and activator of transcription proteins (JAK/STAT) pathways for suppression of B-cell malignancies [43]. and in a pre-clinical study affects the cell-cycle by causing derangement in S- and G0/G1-phase [33,36,40].

OTX015 retards tumor in various leukemic, lymphoid, myeloma, Malignant pleural mesothelioma (MPM) (epithelioid, biphasic, and sarcomatoid), and Glioblastoma multiforme (GBM) cell-lines [35-37]. It acts more potently against Non-small cell lung carcinoma (NSCLC) type of lung cancers than small cell lung carcinoma (SCLC) type of lung cancers [44]. It is a potent, well-tolerated drug [36] with some side-effects like diarrhea, weakness, paresthesia, anemia, neutropenia, thrombocytopenia, fatigue, and bilirubin elevation [39,40].

OTX015's activity increases with dose and time [36,45]. It can show anti-cancer activity alone or in combinations [43,45-47] with broad spectrum standard anti-leukemic drugs including Azacytine, Decitabine, Cytarabine, Daunorubicin, and Methotrexate and some other drugs like Dexamethasone, Everolimus, and Panobinostat (*in-vitro* studies) [46]. OTX015 is combined with Everolimus for the treatment of triple-breast cancer [47] and with Everolimus,

Ibrutinib, Idelalisib, Vorinostat, Rituximab, Decitabine, Lenalidomide, and all-trans retinoic acids fortreating B-cell tumors [43].

OTX015 is also known as M-8628. Severe trials were started on this molecule but only two were completed, others were either terminated or withdrawn (Table 1).

3.1 ARV-825

OTX015 is linked to pomalidomide, an immunomodulator which can take over the control on E3-ubiquitin ligase cereblon through polyethyleneglycol linkers to form PROTAC ARV-825 [8, 10]. ARV-825, because of the presence of phenyl-ring, acts more potently on different immune cells, causing anti-proliferation and apoptosis in various tumor celllines [8, 10]. Compared to BRD4-inhibitors, ARV-825 decrease c-myc levels more potently and shows impressive activity in Burkitt’s lymphoma [27,48].According to Lu, *et al.* OTX015 is active against latent-HIV-1 and can be used in its treatment [45]. It increases the number of cyclin-dependent kinase 9 (CDK9) and phosphorylates the RNA polymerase II carboxy-terminal domain (RNAP II CTD) [45]. OTX015 is a novel drug under the clinical trials for various cancer treatments like hematologic, solid, prostate cancer, etc. and Merck has acquired OTX015 molecule to carry out the clinical trials [41].

Table.1Clinicalstatus of OTX015

-	OTX015/MK-8628-001 A Dose-finding Study in Hematologic Malignancies	OTX015/MK-8628-003 A Dose-Finding Study in Adults with Selected Advanced Solid Tumors	OTX015/MK-8628-002 A Phase IIa Trial With Dose Optimization of OTX015 in Recurrent Glioblastoma Multiforme (GBM) Patients: no of patients-12	Phase I/II Study A Phase Ib/II Study OTX015 in Combination With Azacitidine (AZA) or AZA Single Agent in Patients With Newly-diagnosed Acute Myeloid Leukemia (AML) Not Candidate for Standard Intensive Induction Therapy (SIIT)
Trial Phase	Phase-I	Phase-I	Phase-IIa	Phase-Ib/II
Sponsor	Oncoethix GmbH	Oncoethix GmbH	Oncoethix GmbH	Oncoethix GmbH
Purpose of the study	To find the recommended dose for Phase-II clinical trials in patients with Acute Leukemias (AML, ALL) or other hematologic malignancies (DLBCL and MM).	To find the recommended dose for Phase-II clinical trials in patients with selected advanced tumors.	To find effective OTX015 dose in relapsing GlioblastomaMultiforme.	To find maximum tolerance dose of OTX015 alone or in combination with Azacitidine for early new Acute Myeloid Leukemia cases.
Dose Range/ Early sign of drug activity	Dose Range: 10-160 mg once a day from 7/21 days to complete 21 days.	An early sign of drug action: Pain relief.	Dose range: 80-160 mg once a day for a continuous 28 days cycle.	—
Result	The recommended dose for Phase II is 80 mg once a day on 14 days on and 7 days off schedule i.e., 14/21 days.	The study reflects that the drug was well tolerated and activity was dose-dependent.	—	—
Status of Study	Completed	Completed	Terminated	Withdrawn
Reference	[49]	[50]	[49]	[49]

4 Future Perspectives

The small molecule PROTACs mediates the degradation of target proteins associated with cancer and its application in the treatment of cancer.[53] In comparison to traditional therapy of protein inhibition by small molecules, the PROTACs will demonstrate certain specific characteristics such as inducing a rapid, profound, and sustained degradation, inducing a robust inhibition of downstream signals, displaying enhanced target selectivity, and overcoming resistance to small molecule inhibitors.[54] Although PROTACs present a very promising and powerful approach for crossing the hurdles of present drug discovery and tool development in biology, more efforts are needed to gain to get a deeper insight into the efficacy and safety of PROTACs in the clinic.[55] More target binders and more E3 ligases applicable for developing PROTACs are waiting for exploration.

The SMP of BET inhibitor JQ1 *i.e.* MZ1 more potently causes apoptosis not only in BET-related TNBC (Triple-negative breast cancer) and ovarian cancer but also in JQ1 resistant TNBC and ovarian cancer cell lines [51]. Another PROTAC of small molecule inhibitor the BETd-260 degrades and causes cell-death both *in-vivo* and *in-vitro* HCC (hepatocellular carcinoma) lines more potently based on dose as compared to its small molecule inhibitor HJB-97 [52]. In the same way, PROTAC of OTX015 *i.e.* ARV-825 also shows better activity than OTX015 in Burkitt's lymphoma [27,48]. As the SMPs: MZ1, BETd-260, and ARV-825 are showing remarkable activities. In the same way, other PROTACs of OTX015 can also be used in the future for the treatment of these kinds of resistant and non-resistant tumors.[56]

OTX015 or Birabresib can be explored as a target inhibitor for the designing of some novel PROTACs against a variety of POIs (proteins of interest) for the management of diverse cancers. The specific selected bioactive PROTACs will be taken up for process development and validation for commercial utility. The OTX015 as a targeted protein inhibitor for ubiquitination will be linked to an E3 ubiquitin ligase ligand by a suitable linker molecule. Different OTX015 based PROTACs can be designed and synthesized by altering the linker. *In silico* studies can also be performed to validate the protein-protein interactions, ligand-protein interactions for the rational design of novel PROTACs. The specific selected bioactive PROTACs will be taken up for process development and validation for commercial utility.[57]

5 Conclusion

There is a rise in new treatment strategies for cancer with the widening of cancer types and patients. PROTACs, a new technique that targets two moieties at the same time due to the presence of a bifunctional compound joined by a linker, attracted the focus of healthcare researchers. SMPslike OTX015, which acts on various ligands especially BET-family show its efficacy in various diseases like latent-HIV, which are in the developing phase. Our study reveals that OTX015 is an excellent molecule, not only in cancer therapy but also in other diseases involving BET-proteins and its PROTACs ARV-825 showed better activity in Burkitt's lymphoma than OTX015. More research, clinical and pre-clinical trials are needed to be carried out to know more about OTX015 PROTACs, BRD/BET family, its structure, its role in other proteins involving diseases to get more benefit from SMPs as well as other PROTACs.

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