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Beyond Checkpoints: OX40 Agonists as Pioneers in Immune System Activation Against Cancer: Review

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A B S T R A C T

Cancer cells differ significantly from normal cells in the body, evading natural cell death processes, multiplying uncontrollably, frequently mutating, and often bypassing the immune system's defense mechanisms. Treatment strategies for cancer vary according to the disease stage; in some instances, the goal is a complete cure, while in others, it is to prevent further progression. Certain therapies also aim to alleviate symptoms and enhance patient quality of life. Immunotherapy has recently gained traction as a novel cancer treatment approach. This method involves modulating the immune system to enhance its ability to target and eliminate cancer cells. Numerous clinical trials have demonstrated that immunotherapy is effective in treating a variety of cancers with good patient tolerance. A notable focus in immunotherapy research is the OX40 (CD134) pathway, which involves OX40 and its ligand, OX40L. These costimulatory molecules are expressed on specific immune cells and, when activated, facilitate T cell expansion and proliferation while reducing the immunosuppressive activity of regulatory T (Treg) cells, thereby strengthening the immune response against cancer-specific antigens. Chemotherapy and immunotherapy may be administered individually or in combination, sometimes along with other treatments such as surgery or radiation. While chemotherapy generally produces immediate effects by shrinking tumors and directly targeting cancer cells, immunotherapy fosters a more sustained immune response over time. This literature review analyzed clinical studies on OX40 agonists, sourcing articles from global journal databases such as PubMed, focusing specifically on clinical research assessing the efficacy of OX40 agonists in cancer treatment. Findings from these studies support the advancement of OX40 agonists as valuable agents in cancer immunotherapy, though further research is essential to fully understand how the OX40/OX40L pathway might synergize with other immune checkpoints to maximize therapeutic effectiveness.

Keywords: Cancer, OX40/OX40L, Immunotherapy, Chemotherapy

I. Introduction

Cancer is a chronic inflammatory disease that impacts the entire body. Whether this inflammation initiates cancer development (carcinogenesis) or stimulates tumor growth is influenced by the surrounding environment, but over time, tumor progression significantly reshapes the immune system on a global level. Over the past decade, immunotherapy—specifically targeting the immune system—has revolutionized cancer treatment. Immune checkpoint inhibitors (ICIs), such as anti-CTLA4, anti-PD1, and anti-PDL1, modify the patient's own immune responses and have led to sustained remissions in various tumor types. Furthermore, leukemia patients have benefited from the infusion of expanded, autologous tumor-specific T cells or chimeric antigen receptor (CAR) T cells. However, despite these successes, immunotherapy remains ineffective for most cancer patients [1,2]. As a tumor expands quickly, the immune system initially keeps pace by targeting and destroying tumor cells. However, when the tumor's growth outpaces the immune response, it enlarges and becomes malignant. During this process, tumors develop numerous mechanisms to evade immune detection. They may express "self-receptors" on their cell surfaces—like those found on normal cells—or conceal these receptors altogether. Some tumors even release signals that inhibit immune cell function, effectively telling them to halt their defensive activities. Consequently, this suppression allows cancer to progress and spread. Tumor cells release molecules that not only promote their own proliferation and activity but also hinder the mobility and effectiveness of immune cells, allowing the tumor to thrive at the expense of healthy cells while avoiding immune detection [3,4,5].

OX40 is a type I transmembrane glycoprotein composed of approximately 275 amino acids, containing three complete cysteine-rich domains (CRDs) and a partial C-terminal CRD. Upon TCR engagement following antigen recognition, OX40 expression transiently increases on activated T cells, including CD4+ and CD8+ T cells, as well as neutrophils, natural killer (NK) cells, and natural killer T (NKT) cells, peaking around 48-72 hours later [6,7,8]. The level of OX40 expression is influenced by several factors, including the cytokine environment, antigen persistence, the inflammatory milieu, and other co-stimulatory pathways. OX40's ligand, OX40L (also known as CD252), is a member of the TNFR superfamily and is a type II glycoprotein with a 133-amino-acid extracellular domain and a 23-amino-acid cytoplasmic tail. Activated antigen-presenting cells (APCs)—such as dendritic cells (DCs), activated B cells, and macrophages—are the primary sources of OX40L. However, OX40L expression can be induced on a broader range of cells. Besides APCs, OX40L is also found on non-hematopoietic cells, such as endothelial and smooth muscle cells, as well as hematopoietic cells, including activated NK cells, mast cells, and responding CD4+ T cells [9,10,11]. OX40/OX40L signaling is essential for T cell function and can also promote the

development and maturation of DCs. Human immature DCs do not naturally express OX40L, but stimulation by sCD40L rapidly induces its expression. In this induced phase, OX40L binding upregulates the expression of CD80, CD86, CD54, and CD40 on monocyte-derived DCs, enhancing the production of cytokines like IL-4, IL-6, IL-12, TNF-α, and IL-1 by four to thirty-five-fold [12,13,14]. This indicates that OX40L signaling facilitates DC maturation. In germinal center formation, B cells serve as essential APCs expressing OX40L. OX40L engagement enhances B cell proliferation and immunoglobulin production. Morimoto et al. observed that, rather than increasing the number of plasma cells, CD134L interaction on human B cells elevated the IgG production rate per cell. Therefore, the OX40/OX40L bidirectional signaling pathway is vital for the differentiation and maturation of APCs, particularly DCs and B cells, as well as for modulating T cell responses [15,16,17]

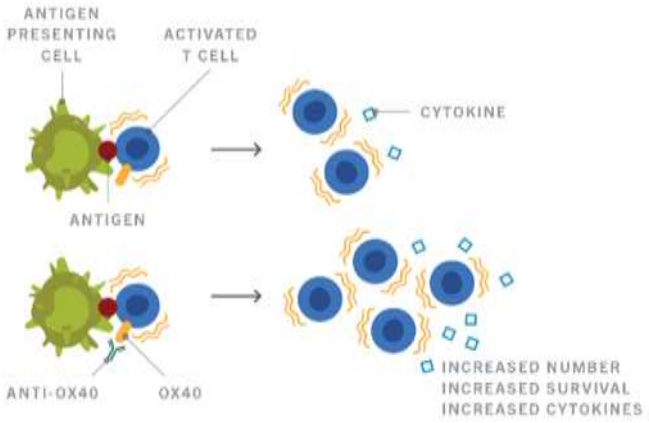

Fig. 1: Anti-OX40 appears to work like a T cell 'power boost' that may enhance different properties to make them more effective at fighting cancer.

II. Methods

Researchers conducted a thorough examination of articles relevant to the topic under study. To guide the literature search, they determined keywords based on the PICO(T) framework: P (Patient/Problem), I/E (Intervention/Exposure), C (Control/Comparison), O (Outcome), and T (Time). This structured approach ensures that the research question effectively defines the scope of the review and aids in developing a targeted search strategy. For the literature review, articles were sourced from PubMed, focusing on clinical trials published between 2013 and 2023. Researchers used Medical Subject Headings (MeSH) keywords, specifically "OX40" and "Cancer," and filtered the search to include only full-text articles. Inclusion Criteria: Population or sample consists of cancer patients. Exclusion Criteria: Population or sample includes individuals other than cancer patients. The selection process was designed to identify studies that align closely with the topic and provide insights into the role of OX40 in cancer treatment.

III. Results and Discussion

OX40 is a type I transmembrane glycoprotein predominantly expressed on T cells. It is constitutively present on regulatory T cells and, upon activation, is also expressed on effector T cells. OX40 is involved in upregulating proteins linked to anti-apoptotic functions (such as Bcl-2, Bcl-xl, and Bfl-1) and those related to cell-cycle progression (such as Survivin). It plays a role in counteracting the suppression of immune cells—including CD4+ and CD8+ T lymphocytes, NK cells, and B lymphocytes—while directly activating effector T cells. Due to OX40's capacity to modulate immune responses and its expression on CD4+ and CD8+ T cells within tumors and tumor-draining lymph nodes in both murine models and human patients, OX40 agonists have been investigated as a potential therapeutic strategy for cancer treatment [18,19,20,21].

Table 1: Clinical trials using anti-OX40 in cancer treatment

Authors	Name	Type of Study	Methods	Results and conclusion
Duhen et al. [22]	Neoadjuvant anti-OX40 (MEDI6469) therapy in patients with head and neck squamous cell carcinoma activates and expands antigen-specific tumor-infiltrating T cells	Clinical Trial 2021	17 patients with locally advanced head and neck squamous cell carcinoma (HNSCC) received a murine anti-human OX40 agonist antibody (MEDI6469) prior to definitive surgical resection. The primary endpoint was to determine safety and feasibility of the anti-OX40 neoadjuvant treatment. The secondary	Peripheral blood phenotyping data show increases in CD4+ and CD8+ T cell proliferation two weeks after anti-OX40 administration. Comparison of tumor biopsies before and after treatment reveals an increase of activated, conventional CD4+ tumor-infiltrating lymphocytes (TIL) in most patients and higher clonality by TCRβ sequencing. Analyses of CD8+ TIL

			objective was to assess the effect of anti-OX40 on lymphocyte subsets in the tumor and blood	show increases in tumor-antigen reactive, proliferating CD103+ CD39+ cells in 25% of patients with evaluable tumor tissue (N = 4/16), all of whom remain disease-free.
Wang et al. [23]	A novel adoptive synthetic TCR and antigen receptor (STAR) T-Cell therapy for B-Cell acute lymphoblastic leukemia	Clinical Trial 2022	Eighteen patients with R/R B-ALL were enrolled into the clinical trial. In a xenograft mouse model, STAR-T-cells exhibited superior tumor-specific cytotoxicity compared with conventional CAR-T cells.	In our clinical trial, 100% of patients achieved complete remission 4 weeks post-STAR-OX40 T-cell infusion and 16/18 (88.9%) patients pursued consolidative allogeneic hematopoietic stem cell transplantation (allo-HSCT). Twelve of 16 patients (75%) remained leukemia-free after a median follow-up of 545 (433-665) days. The two patients without consolidative allo-HSCT relapsed on Day 58 and Day 186. Mild cytokine release syndrome occurred in 10/18 (55.6%) patients, and 2 patients experienced grade III neurotoxicity.
Hamid et al. [24]	First-in-human study of an OX40 (ivuxolimab) and 4-1BB (utomilumab) agonistic antibody combination in patients with advanced solid tumors	Clinical Trial 2022	patients with advanced bladder, gastric, or cervical cancer, melanoma, head and neck squamous cell carcinoma, or non-small cell lung cancer (NSCLC) who were unresponsive to available therapies, had no standard therapy available or declined standard therapy were enrolled into five dose cohorts	Ivuxolimab+utomilumab was found to be well tolerated and demonstrated preliminary antitumor activity in selected groups of patients.
Kim et al. [25]	First-In-Human Phase I Study of the OX40 Agonist MOXR0916 in Patients with Advanced Solid Tumors	Clinical Trial 2022	Eligible patients with locally advanced or metastatic refractory solid tumors were treated with MOXR0916 intravenously once every 3 weeks (Q3W). A 3+3 dose-escalation stage (0.2-1,200 mg; n = 34) was followed by expansion cohorts at 300 mg (n = 138) for patients with melanoma, renal cell carcinoma, non-small cell lung carcinoma, urothelial carcinoma, and triple-negative breast cancer.	MOXR0916 was well tolerated with no dose-limiting toxicities observed. An MTD was not reached. Most patients (95%) experienced at least one adverse event (AE); 56% of AEs, mostly grade 1-2, were related to MOXR0916. Most common treatment-related AEs included fatigue (17%), diarrhea (8%), myalgia (7%), nausea (6%), decreased appetite (6%), and infusion-related reaction (5%). Pharmacokinetic (PK) parameters were dose proportional between 80 and 1,200 mg and supported Q3W administration.
Curti et al. [26]	OX40 is a potent immune-stimulating target in late-stage cancer patients	Clinical Trial 2013	a phase I clinical trial using a mouse monoclonal antibody (mAb) that agonizes human OX40 signaling in patients with advanced cancer	Patients treated with one course of the anti-OX40 mAb showed an acceptable toxicity profile and regression of at least one metastatic lesion in 12 of 30 patients. Mechanistically, this treatment increased T and B cell responses to

				reporter antigen immunizations, led to preferential upregulation of OX40 on CD4(+) FoxP3(+) regulatory T cells in tumor-infiltrating lymphocytes, and increased the antitumor reactivity of T and B cells in patients with melanoma. Our findings clinically validate OX40 as a potent immune-stimulating target for treatment in patients with cancer, providing a generalizable tool to favorably influence the antitumor properties of circulating T cells, B cells, and intratumoral regulatory T cells.
Davis et al. [27]	First-in-human phase I/II, open-label study of the anti-OX40 agonist INCAGN01949 in patients with advanced solid tumors	Clinical Trial 2022	Phase I/II, open-label, non-randomized, dose-escalation and dose-expansion study conducted in patients with advanced or metastatic solid tumors. Patients received INCAGN01949 monotherapy (7-1400 mg) in 14-day cycles while deriving benefit. Safety measures, clinical activity, pharmacokinetics, and pharmacodynamic effects were assessed and summarized with descriptive statistics.	Eighty-seven patients were enrolled; most common tumor types were colorectal (17.2%), ovarian (8.0%), and non-small cell lung (6.9%) cancers. Patients received a median three (range 1-9) prior therapies, including immunotherapy in 24 patients (27.6%). Maximum tolerated dose was not reached; one patient (1.1%) receiving 350 mg dose reported dose-limiting toxicity of grade 3 colitis. Treatment-related adverse events were reported in 45 patients (51.7%), with fatigue (16 (18.4%)), rash (6 (6.9%)), and diarrhea (6 (6.9%)) being most frequent. One patient (1.1%) with metastatic gallbladder cancer achieved a partial response (duration of 6.3 months), and 23 patients (26.4%) achieved stable disease (lasting >6 months in one patient).
Short et al. [28]	A multi-arm phase Ib/II study designed for rapid, parallel evaluation of novel immunotherapy combinations in relapsed/refractory acute myeloid leukemia	Clinical Trial 2022	conducted a phase Ib/II multi-arm, parallel cohort study to simultaneously evaluate various immunotherapeutic agents and combinations in relapsed/refractory acute myeloid leukemia (AML). Overall, 50 patients were enrolled into one of 6 arms: (A) single agent PF-04518600 (OX40 agonist monoclonal antibody), (B) azacitidine + venetoclax + gemtuzumab ozogamicin (GO), (C) azacitidine + avelumab (anti-PD-L1 monoclonal antibody) + GO, (D) azacitidine + venetoclax + avelumab, (E)	In this arm, the CR/CRi rates among venetoclax-naïve and prior venetoclax-exposed patients were 50% and 22%, respectively, and the 1-year OS rate was 31%. This study shows the feasibility of a conducting a multi-arm trial to efficiently and simultaneously evaluate novel therapies in AML, a needed strategy in light of the plethora of emerging therapies.

			azacitidine + avelumab + PF-04518600, and (F) glasdegib + GO. Among all regimens evaluated, azacitidine + venetoclax + GO appeared most promising.	
Wang et al. [29]	An Integrative Approach to Inform Optimal Administration of OX40 Agonist Antibodies in Patients with Advanced Solid Tumors	Clinical Trial 2019	integrated both preclinical and clinical biomarker data sets centered on dose, exposure, receptor occupancy, receptor engagement, and downstream pharmacodynamic changes to model the optimal dose and schedule for the OX40 agonist antibody BMS-986178 alone and in combination with checkpoint blockade.	Administration of the ligand-blocking anti-mouse surrogate antibody OX40.23 or BMS-986178 as monotherapy or in combination with checkpoint blockade led to increased peripheral CD4+ and CD8+ T-cell activation in tumor-bearing mice and patients with solid tumors, respectively. OX40 receptor occupancy between 20% and 50% both in vitro and in vivo was associated with maximal enhancement of T-cell effector function by anti-OX40 treatment, whereas a receptor occupancy > 40% led to a profound loss in OX40 receptor expression, with clear implications for availability for repeat dosing.

Table 1 presents clinical studies investigating anti-OX40 therapy in cancer. In a study by Duhen [22], CD4+ and CD8+ T cell proliferation significantly increased two weeks after administering anti-OX40. A comparative analysis of tumor biopsies before and after treatment revealed an elevated presence of activated, conventional CD4+ tumor-infiltrating lymphocytes (TILs) in most patients, with increased clonality observed via TCRβ sequencing. Analysis of CD8+ TILs indicated a rise in tumor-antigen-reactive, proliferating CD103+ CD39+ cells in 25% of patients with evaluable tumor tissue (N = 4/16), all of whom remained disease-free. In another study, Wang [23] reported that integrating OX40 into the STAR platform enhanced both the proliferation and persistence of tumor-targeted T cells. In this clinical trial, all patients (100%) achieved complete remission four weeks after receiving STAR-OX40 T cell infusion. Of the 18 patients, 16 (88.9%) proceeded with consolidative allogeneic hematopoietic stem cell transplantation (allo-HSCT), with 75% (12 out of 16) remaining leukemia-free after a median follow-up of 545 days (range 433-665). Among those who did not undergo allo-HSCT, two patients experienced relapse on Days 58 and 186, respectively. Mild cytokine release syndrome was reported in 10 of 18 patients (55.6%), while two patients experienced grade III neurotoxicity. Hamid [24] found that the combination of Ivuxolimab and Utomilumab was well tolerated and showed preliminary antitumor activity in selected patient groups. In a separate study, Kim [25] reported that MOXR0916 was generally well tolerated, with no dose-limiting toxicities observed, and the maximum tolerated dose (MTD) was not reached. Nearly all patients (95%) reported at least one adverse event (AE), with 56% of AEs, primarily grades 1-2, attributed to MOXR0916. The most common treatment-related AEs included fatigue (17%), diarrhea (8%), myalgia (7%), nausea (6%), decreased appetite (6%), and infusion reactions (5%). Pharmacokinetic (PK) analysis showed dose proportionality between 80 and 1,200 mg, supporting administration every three weeks (Q3W). Curti's study demonstrated that patients receiving a single course of anti-OX40 mAb experienced a manageable toxicity profile, with regression in at least one metastatic lesion in 12 out of 30 patients. Mechanistically, the treatment enhanced T and B cell responses to reporter antigens, preferentially upregulated OX40 on CD4(+) FoxP3(+) regulatory T cells within TILs and increased antitumor reactivity of T and B cells in patients with melanoma. These findings validate OX40 as a promising immune-stimulatory target in cancer treatment, offering a broad approach to enhance antitumor functions of circulating T cells, B cells, and intratumoral regulatory T cells. In Davis's study, 87 patients were enrolled, with the most common tumor types being colorectal (17.2%), ovarian (8.0%), and non-small cell lung (6.9%) cancers. Patients received a median of three prior therapies (range 1-9), including immunotherapy in 24 cases (27.6%). The maximum tolerated dose was not reached; one patient (1.1%) at the 350 mg dose level experienced a dose-limiting toxicity of grade 3 colitis. Treatment-related adverse events were reported in 45 patients (51.7%), with the most common being fatigue (16 patients, 18.4%), rash (6 patients, 6.9%), and diarrhea (6 patients, 6.9%). One patient (1.1%) with metastatic gallbladder cancer achieved a partial response lasting 6.3 months, while 23 patients (26.4%) achieved stable disease, with one patient's stability lasting over six months.

Short found that CR/CRi rates among venetoclax-naïve and prior venetoclax-exposed patients were 50% and 22%, respectively, and the 1-year OS rate was 31%. This study shows the feasibility of conducting a multi-arm trial to efficiently and simultaneously evaluate novel therapies in AML, a needed strategy considering the plethora of emerging therapies. Wang found that Administration of the ligand-blocking anti-mouse surrogate antibody OX40.23 or BMS-986178 as monotherapy or in combination with checkpoint blockade led to increased peripheral CD4+ and CD8+ T-cell activation in tumor-bearing mice and patients with solid tumors, respectively. OX40 receptor occupancy between 20% and 50% both in vitro and in vivo was associated with

maximal enhancement of T-cell effector function by anti-OX40 treatment, whereas a receptor occupancy > 40% led to a profound loss in OX40 receptor expression, with clear implications for availability for repeat dosing.

IV. Conclusion

Immunotherapy has become foundational in cancer treatment due to its ability to induce durable anti-tumor immune responses capable of eliminating both primary tumors and metastatic lesions. A significant advancement in this area is the development of immune checkpoint inhibitors, including CTLA-4 and PD-1 blockers, which alleviate inhibition on anti-tumor T cell responses through antibody-mediated antagonism. These immune checkpoints are vital components of cancer therapy. Recent studies have shown that the activation of the OX40/OX40L pathway via agonists can further potentiate the anti-tumor immune response by enhancing immune cell activity. As a result, the OX40/OX40L pathway has attracted considerable interest as a target in cancer immunotherapy. Nevertheless, the current therapeutic efficacy of OX40/OX40L-targeted treatments remains limited. The combination of OX40/OX40L agonists with other immune checkpoints has yielded promising outcomes, suggesting a potential synergistic effect; however, the underlying mechanisms of this synergy remain unclear and require further study. Agonistic anti-OX40 monoclonal antibodies (mAbs) have demonstrated the capacity to enhance T cell expansion and cytotoxic functions, thereby strengthening anti-tumor immunity across multiple cancer types. Nonetheless, additional research is needed to fully elucidate the interactions between OX40/OX40L and other immune checkpoints to maximize its therapeutic efficacy in cancer treatment.

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