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EVOLVING THERAPIES (RM BUKOWSKI, SECTION EDITOR)

Indoleamine Dioxygenase Inhibitors: Clinical Rationale and Current Development

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Abstract

Purpose of Review This review focuses on the recent clinical development of indolamine-2,3-dioxygenase-1 (IDO-1) inhibitors.

Recent Findings IDO-1 alters tryptophan metabolism in a manner enhancing T-regulatory cell activity, but pre-clinical data show that its role in tumorigenesis is context-dependent on host and tumor interaction, highlighting some challenges in understanding the molecular oncology of this enzymatic drug target. Because results from phase I/II trials of IDO-1 inhibitor monotherapy have been disappointing, current clinical trials employ IDO-1 inhibitors in combination strategies with other immunotherapy agents or with chemotherapy ± radiation. Combinations with anti-PD-1/PD-L1 antibodies are already showing promise, and related strategies are under active evaluation.

Summary While further research is needed to elucidate the precise role of IDO-1 in tumor development, its mechanisms of action appear sufficiently distinct from other immunotherapy targets to warrant inclusion in combination immunotherapy regimens, an approach where multiple clinical trials are currently underway.

Keywords Immune checkpoint blockade · Immuno-oncology · Combination therapy · Epacadostat · Indoximod · BMS-986205

Introduction

With increasing recognition of immune evasion as a hallmark of cancer [1], immunotherapy has emerged as a novel branch of oncological treatment. More targeted and usually less toxic than conventional chemotherapy drugs, immunotherapy enhances endogenous antitumor activity through one of the several modalities, including cytokine therapy, cancer vaccines, engineered T cell therapy, and immune checkpoint blockade [2, 3]. In particular, the field has seen substantive progress with immune checkpoint inhibitors, especially with antibody therapies targeting programmed cell death protein (PD-1/PD-L1) and cytotoxic T lymphocyte–associated protein-4 (CTLA-4). Physiologically, immune checkpoints regulate balance in the immune system to prevent autoimmunity [4]. Malignant tumors can co-opt this system by modifying the expression of immune checkpoint receptors and ligands, leading to downregulation of anti-tumoral immune responses. Therapeutic blockade of immune checkpoints can restore host immunity [4], and the US Food and Drug Administration has approved the use of PD-1/PD-L1 and CTLA-4 targeted therapies for the treatment of many cancers including metastatic melanoma, non-small cell lung carcinoma, renal cell carcinoma, and squamous cell carcinoma of the head and neck. However, limited responses [5, 6] and serious adverse effects [7, 8] call for a need to identify other immunotherapy options that could be used alone or in combination with existing treatments.

Indolamine-2,3-dioxygenase 1 (IDO-1), a metalloprotein enzyme that catalyzes the rate-limiting step of tryptophan metabolism to kynurenine [9], is a checkpoint blockade target that has undergone considerable investigation due to promising pre-clinical data [10–12]. IDO-1 oxidizes tryptophan (Trp) to *N*-formylkynurenine, which is then converted into catabolites collectively known as kynurenine (Kyn) [13]. The antiproliferative activity of IDO-1 was first established by Ozaki et al. [14], and subsequent work identified its immunosuppressive functions on T lymphocytes [15, 16]. IDO-1 activation

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causes concurrent depletion of co-localized tryptophan and the production of Kyn and Kyn metabolites, triggering several pathways that suppress T cell proliferation and promote differentiation into regulatory T cells (Tregs). Tryptophan depletion has two key consequences: (1) activation of metabolic stress-sensing kinase GCN2 to induce T cell antigen-specific anergy [17], and (2) inhibition of energy sensor kinase mTORC1 to downregulate T cell activation kinase PKC-θ activity, with a net consequence of shifting the T cell population from effector to regulatory [18]. Tryptophan catabolites Kyn, 3-hydroxy-Kyn, and kynurenic acid all contribute to immunosuppression by binding to aryl hydrocarbon receptor (AhR) [19], which promotes CD4+ T cell differentiation to Tregs while limiting their differentiation to Th17 cells [20, 21]. A more extensive coverage of the mechanism of action of IDO-1 has been discussed in detail [9, 22, 23]; this review will focus on the recent clinical development of IDO-1 inhibitors involving various novel combination therapies from a pre-clinical rationale.

Clinical Rationale

IDO-1 is expressed physiologically in placenta, myeloid cells of lymphoid organs, and endothelium of the lungs, prostate, and uterus [24••]. Its expression is constitutively driven by cyclooxygenase-2 through the production of prostaglandin E2 [25, 26]. Alternatively, it can be induced by various immune signals, including type I and II interferon (IFN) [13, 27], pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) [9], and transforming growth factor-β (TGF-β) [28].

IDO-1 protein expression has been characterized in a variety of cancers [29], including acute myeloid leukemia [30], melanoma [12•, 27], and in carcinomas of the thyroid [31], lung [32, 33], breast [34–36], endometrium [37], esophagus [38], stomach [39], and colon [40]. IDO-1 can be expressed by tumor or host cells [24••], the latter largely comprising endothelial and myeloid cells [16, 41]. IDO-1-expressing myeloid cells are of particular importance in oncogenesis, as they influence tumor-infiltrating lymphocyte (TIL) activities [42•, 43], which are associated with tumor immunogenicity and prognosis [44–47]. Tumoral IDO-1 expression in breast [36], thyroid [31], and esophageal squamous cell cancers [38] has been associated with greater tumor-infiltrating regulatory T cells. IDO-1 expression and activity by myeloid-derived suppressor cells (MDSCs) correlate with lymph node metastasis and advanced clinical stage in breast cancer [36].

Numerous recent studies have reported an association between high IDO-1 expression and worsened clinical outcomes. Elevated IDO-1 protein expression in tumor cells correlates with poor overall survival in breast cancer [35] and esophageal squamous cell cancer [38], and poor relapse-free survival in colorectal cancer [40]. The presence of IDO-1-expressing leukemia cells in patients with childhood acute myeloid leukemia is associated with worse event-free and overall survival [30]. Elevated serum Kyn concentration reflecting IDO metabolic activity, correlates with poor overall survival in lung cancer [48] and shorter disease-specific survival in cervical cancer [49].

Nonetheless, some groups report contradictory trends with regard to the clinicopathological correlations of IDO-1 expression. No association was observed between tumoral IDO-1 expression and patient survival in non-small cell lung cancer [32]. Increased IDO-positive non-neoplastic cells in primary diffuse large B cell lymphoma correlates with longer progression-free survival [50]. Protein expression of IDO-1 in gastric cancer tumor cells has been linked to clinical characteristics of better prognosis, including lower stage, lack of vascular invasion, and greater differentiation [39].

These conflicting results concerning the prognostic value of IDO-1 expression may be explained by contextual heterogeneity across tumors and tumor microenvironments. A study by Lemos et al. [42•] showed that the immunosuppressive role of IDO-1 on TILs and MDSCs is highly dependent on tumor antigenicity. IDO-1 activation through STimulator of INterferon Genes (STING) and IFN-I signaling is promoted in low-antigenicity tumors, such as native Lewis lung carcinoma, but not in melanoma or Lewis lung carcinomas with enhanced antigenicity [42•]. Furthermore, the effect of tumor and non-tumor IDO-1 expressions on survival and therapy response in vivo has been inconsistent. Tumoral IDO-1 expression correlates with worse median survival in mouse glioma [51], enhanced tumor growth and resistance to immunotherapy in a mouse xenograft model of human melanoma [12•]. In a glioblastoma model, host IDO-1 activity is necessary for response to immunotherapy [51, 52], and yet in a melanoma model, host IDO-1 deficiency was optimal for immunotherapy [43]. Evidently, the role of IDO-1 in cancer is context-dependent, and further work is needed to understand the complexities of this immune checkpoint.

Newer studies have also begun to elucidate mechanisms of IDO-1 independent from those mediating adaptive immunity. The tryptophan metabolites Kyn and quinolinic acid can directly activate β-catenin signaling and epithelial proliferation in colon tumorigenesis [53, 54]. Liu et al. [55•] recently characterized IDO-1's role in inducing tumor dormancy of tumor-repopulating cells through the IDO-Kyn-AhRp27 pathway. This discovery supports a novel combination therapy strategy, as the combination of INF-γ and IDO inhibitors was effective in disrupting dormancy in tumor cells and reducing tumor growth in vitro and in vivo [55•]. These discoveries suggest that the potential for wider involvement of IDO-1 in immune-oncology is worthy of further investigation, and that while its mechanisms of action can be complex, it is distinct from other immunotherapy targets, implying that its inhibition could have effects that complement other immunotherapy approaches.

Other IDO Enzymes

Included in the Trp-catabolic family are two other enzymes, IDO-2 and TDO (tryptophan 2,3-dioxygenase). While similar in function, the three enzymes differ in sequence and distribution. The human IDO-2 protein has 43% amino acid homology with human IDO-1, whereas TDO has minimal sequence homology with IDO-1 or IDO-2 [56, 57]. Although IDO-2 has been shown to have negligible catalytic activity, its regulatory activity on IDO-1 through competitive heme-binding may be of significance [58]. Furthermore, gene silencing of IDO-2 in murine melanoma models delayed tumor onset and slowed tumor growth, demonstrating a potential role of IDO-2 in immunotherapy [59]. TDO is constitutively expressed in the liver and the brain [22], and has been correlated with reduced overall survival in glioma patients [19]. Injection of IDO-competent tumor cells into IDO-deficient mice leads to increased IDO-2 and decreased TDO activity in immunodeficient mice [51]. Therefore, although the focus in immunotherapy has been largely on IDO-1, these two related Trp enzymes may also be important in addressing tumor immune evasion.

Current Development

There are numerous IDO-1 inhibitors in clinical development, including indoximod (D-1-methyl-tryptophan, 1-D-MT, NLG-8189), epacadostat (INCB024360), BMS-986205, and navoximod (GDC-0919): pharmaceuticals which are currently in phase I/II trials (Table 1). Newer IDO-1 inhibitors, such as PF-06840003, NLG802, SHR9146, KHK2455, LY3381916, and MK-7162 have just begun in clinical evaluation, and may yield promising results in upcoming years. The pharmacology of various clinical development candidates has been reviewed extensively [60]; this review will focus on what is known to date about their clinical effects.

IDO-1 Inhibitor Monotherapy

The in vivo antitumor effects of IDO-1 inhibitors administered as single agents were first reported by Muller et al. [10] using the competitive IDO-1 inhibitor indoximod. Since then, several in vivo studies have demonstrated inhibition of tumor growth in melanoma [12•], breast cancer [61], and colitis-associated tumorigenesis [54]. The loss of IDO-1-dependent immunosuppressive activity through IDO-1 inhibitors was shown through an increase in infiltrating lymphocytes [43], accompanied by a decrease in the T regulatory cell fraction [43, 62]. Administration of 1-D-MT in a murine melanoma reduces intratumoral MDSCs [12•]. Similarly in an ex vivo breast cancer model, 1-MT inhibits MDSC activity to result in reduced upregulation of IL-10 and TGF-beta, and diminished apoptosis of T-cells [36].

Disappointingly, the pronounced tumor reduction observed in pre-clinical work was not confirmed in phase I and II trials of IDO-1 inhibitor monotherapies (Table 1). In a phase I study using indoximod to treat 48 patients with advanced malignancies (NCT00567931), the best response observed at 6 months was stable disease (SD) in five patients (melanoma, colon cancer, sarcoma) [63•]. No changes in T cell population were detected by flow cytometry, but in 12 patients there was an increase in auto-antibody titers after 5 weeks of treatment

Table 1 Clinical trials of IDO-1 inhibitors as a single agent

Agent	Identifier	Phase	Status	Participants	Disease(s)
Indoximod (1-D-MT)	NCT00567931	I	Completed	52	Unspecified adult solid tumors
	NCT00739609	I	Terminated (lack of enrollment)	17	Breast cancer, lung cancer, melanoma, pancreatic cancer, solid tumors
Epacadostat (INCB024360)	NCT01195311	I	Completed	52	Solid tumors and hematologic malignancy
	NCT01685255	II	Terminated	83	Biochemical-recurrent-only epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer
	NCT01822691	II	Completed	15	Myelodysplastic syndromes
	NCT02042430	pilot	Active, not recruiting	17	Newly diagnosed epithelial ovarian, fallopian tube, primary peritoneal cancer
GDC-0919 (NLG919)	NCT02048709	I	Completed	22	Solid tumor
PF-06840003	NCT02764151	I	Active, not recruiting	17	Oligodendroglioma, astrocytoma, malignant glioma
NLG802	NCT03164603	I	Recruiting	36	Advanced solid tumors
SHR9146 (HTI-1090)	NCT03208959	I	Recruiting	30	Advanced solid tumors
IDO peptide vaccine	NCT01219348	I	Completed	14	Non-small cell lung cancer

[63•]. A phase I trial using epacadostat to treat 52 patients with advanced solid malignancies (NCT01195311) showed a dose-dependent decrease in plasma Kyn and Kyn/Trp ratio in all patients [64•]. While seven patients had SD lasting more than 16 weeks, no objective responses were detected [64•]. Similarly, in a phase Ia study of navoximod for 22 patients with solid tumors (NCT02048709), the IDO-1 inhibitor-induced SD in eight patients, but again there were no objective responses [65•].

Phase II trials have produced comparable results. In myelodysplastic syndrome, a phase II study of epacadostat in 15 patients reported SD in 12 (NCT01822691) but no significant clinical activity [66]. When treating epithelial ovarian/fallopian tube cancers with peritoneal spread in a phase II study of 22 patients (NCT01685255), no superior efficacy of epacadostat relative to tamoxifen was demonstrable [67].

As of mid-2018, the majority of clinical trials testing IDO-1 inhibitors as single agents have been completed (NCT00567931, NCT01195311, NCT01219348, NCT01822691, NCT02048709) or terminated (NCT00739609, NCT01685255). In contradistinction to preclinical in vivo results, no monotherapy trials reported objective responses. Consequently, pharmaceutical companies have reprioritized the design of clinical trials to test combination therapies.

IDO-1 Inhibitors in Combination with Checkpoint Inhibitors

PD-1/PD-L1

Co-expression of IDO-1 and PD-1/PD-L1, along with preclinical data combining IDO-1 inhibitors with anti-PD-1/PD-L1 therapies, suggests the presence of a synergistic relationship between these two immune checkpoints. Although one study reported limited co-expression of PD-L1 and IDO-1 in non-small cell lung cancer [33], other studies have found high concordance between tumoral IDO-1 and PD-L1 expression in melanoma [68] and in breast [34], endometrial, [37] and non-small cell lung carcinomas [32]. IDO-1 mRNA in breast tumors also significantly correlates with mRNA expression of the PD-1 and PD-L1 genes [69]. The same trend was found during a phase II trial of sarcomas using the anti-PD-L1 antibody drug pembrolizumab, in which PD-L1 in immune cells was positively associated with IDO-1 expression [70]. Coupled with the observation that the Kyn:Trp ratio increases during pembrolizumab treatment [70], IDO-1 activation could explain the limited efficacy of PD-1/PD-L1 in clinical use, as it represents a potential mechanism of resistance. Indeed, in vivo studies have demonstrated that IDO-1 expression increases with anti-PD-1/PD-L1 treatments [11]. The combination of 1-D-MT or epacadostat with an anti-PD-1 antibody enhanced the reduction in tumor volume in a murine hepatocellular carcinoma model [71], strengthening the rationale for combination therapy.

Most clinical trials combining IDO-1 inhibitors with anti-PD-1/PD-L1 therapies are currently in phase I or II (Table 2). In a phase Ib dose-escalation trial treating 52 solid tumor patients with navoximod and the anti-PD-L1 antibody drug atezolizumab (NCT02471846), four patients developed partial response (PR), and 11 patients had SD [72]. A phase I/IIa trial using the IDO inhibitor BMS-986205 in combination with the anti-PD-1 antibody nivolumab (NCT02658890) reported a disease control rate of 48% among 28 patients with advanced bladder cancer [73]. A phase II trial of indoximod and pembrolizumab (NCT02073123) reported an overall response rate (ORR) of 55.7% among 70 advanced melanoma patients compared to an ORR of 33% for pembrolizumab alone [74]. In a phase I/II 3 + 3 dose-escalation study of epacadostat plus the anti-PD-L1 antibody durvalumab (NCT02318277; ECHO-203), four out of 34 patients with advanced solid tumors achieved SD [75].

The varied responses observed in these clinical trials are underscored by the ECHO-202/KEYNOTE-037 (NCT02178722) study, which reported very different response rates depending on cancer type. This phase I/II study treating 444 patients with epacadostat and pembrolizumab found that this combination therapy was effective for urothelial carcinoma [76], renal cell carcinoma [77], melanoma [78], and non-small cell lung cancer [79], with ORRs ranging from 35 to 58%. Contrastingly, this combination, when administered to ovarian and triple-negative breast cancer, showed ORR comparable to that of pembrolizumab on its own [80]. Similarly, the phase II ECHO-204 study (NCT02327078) showed a wide range of responses among 241 patients with respect to cancer types treated with indoximod and nivolumab. Advanced melanoma [81] and squamous cell carcinoma of the head and neck [82] demonstrated the most promising responses. Most impressively, the ORR was 62% (31/50) among melanoma patients, among whom nine patients achieved a complete response [81].

In contrast, phase III results from ECHO-301/KEYNOTE-252 (NCT02752074) presented at the ASCO 2018 reported minimal response [83]. The 706 randomized patients with stage III or IV melanoma did not demonstrate a survival benefit from using epacadostat and pembrolizumab in combination when compared to the pembrolizumab monotherapy control arm [83]. Although more trials are in development that would combine PD-1/PD-L1 and IDO-1 inhibitors, the ECHO-301/KEYNOTE-252 results have dampened the earlier enthusiasm for this combination strategy [84].

CTLA-4

CTLA-4 is another central immune checkpoint target based on its critical functions in regulating T cell activation. Holmgaard

Table 2 Clinical trials of IDO-1 inhibitors in combination with other therapies

Agent	Other agents	Identifier	Phase	Status	Participants	Disease(s)
IDO-1 inhibitor in combination anti-PD-1/PD-L1 therapy						
Indoximod (1-D-MT)	Pembrolizumab and nivolumab	NCT03301636	II/III	Recruiting	624	Metastatic melanoma
	Ipilimumab (anti-CTLA-4 antibody), pembrolizumab (anti-PD-1 antibody), and nivolumab (anti-PD-1 antibody)	NCT02073123	II	Unknown	102	Advance melanoma
Epacadostat	Pembrolizumab	NCT02178722 (ECHO-202/KEYNOT-E-037)	I/II	Active, not recruiting	444	Colorectal cancer, endometrial cancer, head and neck cancer, hepatocellular carcinoma, gastric cancer, lung cancer, lymphoma, renal cell carcinoma, ovarian cancer, solid tumors, urothelial cancer, breast cancer, melanoma
	Pembrolizumab	NCT02752074 (ECHO-301/KEYNOT-E-252)	III	Active, not recruiting	706	Metastatic melanoma
	Pembrolizumab	NCT03260894 (ECHO-302)	III	Active, not recruiting	630	Metastatic renal cell carcinoma
	Pembrolizumab	NCT03291054	II	Recruiting	23	Gastrointestinal stromal tumors
	Pembrolizumab	NCT03310567	II	Not yet recruiting	49	Recurrent/metastatic endometrial carcinoma
	Pembrolizumab	NCT03322540 (ECHO-305/KEYNOT-E-654)	III	Recruiting	588	Non-small cell lung cancer
	Pembrolizumab	NCT03325465	II	Not yet recruiting	44	Squamous cell carcinoma of the head and neck
	Pembrolizumab	NCT03358472 (ECHO-304/KEYNOT-E-669)	III	Active, not recruiting	625	Head and neck squamous cell carcinoma
	Pembrolizumab	NCT03361865 (ECHO-307/KEYNOT-E-672)	III	Active, not recruiting	650	Urothelial cancer
	Pembrolizumab	NCT03374488 (ECHO-303/KEYNOT-E-698)	III	Active, not recruiting	648	Urothelial cancer
	Pembrolizumab	NCT03414229	II	Recruiting	30	Sarcoma
	Pembrolizumab	NCT03432676	II	Not yet recruiting	21	Pancreatic adenocarcinoma
	Nivolumab	NCT02327078 (ECHO-204)	I/II	Active, not recruiting	209	Advanced cancer
	MEDI4736 (anti-PD-L1 antibody)	NCT02318277 (ECHO-203)	I/II	Recruiting	192	Advanced solid tumors
	Ipilimumab	NCT01604889	I/II	Terminated	136	Melanoma
BMS-986205	Nivolumab	NCT03192943	I	Active, not recruiting	18	Advanced cancers
	Nivolumab	NCT03329846 (CA017-055)	III	Active, not recruiting	72	Advanced melanoma
	Nivolumab	NCT03335540	I	Recruiting	50	Advanced cancer
	Nivolumab	NCT03386838 (CA017-063)	III	Terminated (business objectives have changed)	1	Head and neck cancer
	Nivolumab and ipilimumab	NCT02658890	I/IIa	Recruiting	434	Advanced bladder cancer
	Relatlimab (anti-LAG-3 antibody) and nivolumab	NCT03459222	I/II	Recruiting	230	Advanced cancer
GDC-0919	Atezolizumab (anti-PD-L1 antibody)	NCT02471846	I	Active, not recruiting	158	Solid tumor
LY3381916	LY3300054 (anti-PD-L1-antibody)	NCT03343613	I	Recruiting	290	

Table 2 (continued)

Agent	Other agents	Identifier	Phase	Status	Participants	Disease(s)
						Solid tumor, non-small cell lung cancer, squamous cell carcinoma of the head and neck, urothelial carcinoma, brain metastasis
MK-7162	Pembrolizumab	NCT03364049	I	Recruiting	40	Advanced solid tumors
IDO peptide vaccine	Nivolumab	NCT03047928	I/II	Recruiting	6/24	Metastatic melanoma
	Ipilimumab or vemurafenib (B-Raf enzyme inhibitor)	NCT02077114	I	Completed	10	Malignant melanoma with metastasis
IDO-1 inhibitor in combination with immune checkpoint inhibitor and another agent						
Epacadostat	Pembrolizumab and CRS-207	NCT02575807	I/II	Active, not recruiting	126	Platinum-resistant ovarian, fallopian tube, or peritoneal cancer
	Pembrolizumab with azacitidine, INCB057643 (BET inhibitor), or INCB059872 (LSD1 inhibitor)	NCT02959437	I/II	Active, not recruiting	70	Advanced/metastatic solid tumors
	Pembrolizumab, CRS-207, cyclophosphamide, and GVAX pancreas vaccine	NCT03006302	II	Recruiting	70	Metastatic pancreatic adenocarcinoma
	Nivolumab, ipilimumab, and lirilumab (anti-KIR antibody)	NCT03347123	I/II	Recruiting	141	Solid tumors
	M7824 (bifunction fusion protein) + BN-Brachyury (cancer vaccine) + ALT-803 (IL-15/IL-15R alpha superagonist complex)	NCT03493945	I/II	Recruiting	113	Prostate Cancer (± metastasis), prostate neoplasm, (advanced) solid tumors
SHR9146	SHR-1210 (PD-1 inhibitor) and apatinib (VEGFR inhibitor)	NCT03491631	I	Not yet recruiting	200	Solid tumor
IDO inhibitor in combination with other immunotherapy targets						
Indoximod	Adenovirus-p53–transduced dendritic cell (DC) vaccine	NCT01042535	I/II	Completed	44	Metastatic breast cancer
	Radiotherapy and adenovirus-p53–transduced dendritic cell vaccine	NCT01302821	n/a	Withdrawn	0	Breast cancer
	Sipuleucel-T	NCT01560923	II	Active, not recruiting	47	Metastatic prostate cancer
	Tergenpumatucel-L and docetaxel	NCT02460367	Ib/II	Unknown	115	Advanced previously treated non-small cell lung cancer
Epacadostat	MELITAC 12.1	NCT01961115	II	Completed	11	Stage III–IV melanoma
	ALVAC(2)-NY-ESO-1 (M)/TRICOM vaccine	NCT01982487	I/IIb	Withdrawn	0	Recurrent epithelial ovarian, recurrent fallopian tube, primary peritoneal cancer (NY-ESO-1 or LAGE-1 Antigen)
	DEC-205/NY-ESO-1 fusion protein CDX-1401 and poly ICLC	NCT02166905	I/IIb	Recruiting	62	Fallopian tube carcinoma, ovarian carcinoma, primary peritoneal carcinoma
	Itacitinib (JAK1 inhibitor)	NCT02559492	I	Recruiting	159	Solid tumors
	DPX-Survivac, and cyclophosphamide	NCT02785250	Ib	Recruiting	14	Advanced ovarian cancer
	INCAGN01876 (anti-GITR agonistic antibody) and pembrolizumab	NCT03277352	I	Active, not recruiting	10	Advanced malignancies
KHK2455	Mogamulizumab (anti-CCR4 antibody)	NCT02867007	I	Recruiting	50	Solid tumors
IDO5 peptide vaccine	Survivin peptide, montanide, GM-CSF, imiquimod, and temozolomide	NCT01543464	II	Terminated (diminished recruitment)	41	Malignant melanoma

Table 2 (continued)

Agent	Other agents	Identifier	Phase	Status	Participants	Disease(s)
IDO inhibitor in combination with chemotherapy or chemoradiation						
Indoximod	Docetaxel	NCT01191216	I	Completed	27	Metastatic solid tumors
	Docetaxel or paclitaxel	NCT01792050	II	Unknown	169	Metastatic breast cancer
	temozolomide, bevacizumab and stereotactic radiation	NCT02052648	I/II	Recruiting	144	Glioblastoma multiforme, glioma, gliosarcoma, malignant brain tumor
	Nab-paclitaxel and gemcitabine	NCT02077881	I/II	Recruiting	135	Metastatic pancreatic cancer
	Temozolomide, conformal radiation, cyclophosphamide, and etoposide	NCT02502708	I	Recruiting	66	Glioblastoma multiforme, glioma, gliosarcoma, malignant brain tumor, ependymoma, medulloblastoma, diffuse intrinsic pontine glioma, primary CNS tumor
	Idarubicin and cytarabine	NCT02835729	Ib/IIa	Recruiting	138	Acute myeloid leukemia
Epacadostat	Fludarabine, cyclophosphamide, NK cells, and IL-2	NCT02118285	I	Completed	2	Ovarian cancer, fallopian tube carcinoma, primary peritoneal carcinoma
IDO inhibitor in combination with immune checkpoint inhibitor and chemotherapy						
Epacadostat	Pembrolizumab and cyclophosphamide	NCT02406781	II	Recruiting	163	Sarcoma
	Pembrolizumab, cisplatin, carboplatin, pemetrexed, and paclitaxel	NCT02862457	I	Recruiting	60	Advanced solid tumors
	Pembrolizumab, oxaliplatin, leucovorin, 5-fluorouracil, gemcitabine, nab-paclitaxel, carboplatin, paclitaxel, pemetrexed, and cyclophosphamide	NCT03085914	I/II	Recruiting	421	Solid tumors, colorectal cancer, adenocarcinoma, non-small cell lung cancer, urothelial cancer, head and neck cancer
	Pembrolizumab and platinum-based chemotherapy	NCT03322566 (ECHO-306/KEYNOT-E-715)	II	Recruiting	148	Non-small cell lung cancer
	Nivolumab, carboplatin, cisplatin, and 5-fluorouracil	NCT03342352 (ECHO-310)	III	Withdrawn (canceled prior to enrollment)	550	Head and neck cancer
	Nivolumab, carboplatin, cisplatin, gemcitabine, paclitaxel, and pemetrexed	NCT03348904 (ECHO-309)	III	Active, not recruiting	2	Non-small cell lung cancer
BMS-986205	Nivolumab and platinum-based doublet chemotherapy	NCT03417037 (CA017-062)	III	Withdrawn (business objectives have changed)	0	Non-small cell lung cancer

et al. [43] was the first to report a survival benefit and tumor growth delay in vivo from combining an anti-CTLA-4 antibody and 1-D-MT in a murine melanoma model, in a context when the same dose of 1-D-MT alone did not elicit any response. Likewise, Brown et al. [71] showed that anti-CTLA-4 antibody treatment induced IDO-1 expression and caused tumor inhibition when combined with 1-D-MT in a murine model of hepatocellular carcinoma, a response that was not observed with either agent as monotherapy. The combination of epacadostat and anti-CTLA-4 antibody treatment also produced complete responses in a murine melanoma model, with increased production of IL-2 and functional antigen-specific T cells demonstrable in the spleen [11]. However, the same study found that the combination of anti-CTLA-4 and anti-PD-L1 therapy induced more complete responders than doublet therapies with epacadostat plus either anti-CTLA-4 or anti-PD-L1, undermining the relative value of IDO-1 inhibitors in combination therapies [11].

In 2014, Gibney et al. [85] presented the first phase I/II study results of epacadostat combined with the anti-CTLA-4 antibody ipilimumab in the treatment of metastatic melanoma (NCT01604889). They reported a confirmed disease control rate of 75%, in which six out of eight patients demonstrated tumor reduction [85]. Despite promising results, the study has been terminated and "further development of [epacadostat] with ipilimumab in the treatment of melanoma is no longer being pursued". Consequently, only one phase II trial (NCT02073123) is currently active for an IDO-1 inhibitor in combination with anti-CTLA-4 therapy (Table 2).

Meanwhile, two phase I/II trials are active and recruiting (NCT02658890, NCT03347123) employing triple therapy, combining IDO inhibitors with both anti-CTLA-4 and anti-PD-L1 antibodies. Triple immunotherapy showed decreased Treg infiltration in vivo, inducing T cell–dependent prolonged survival compared to monotherapies [51]. However, the study showed no difference in survival between CTLA-4/PD-L1 double therapy and triple therapies adding IDO inhibition [51].

IDO-1 Inhibitors in Combination with Other Immunotherapy Targets

Given the extensive involvement of IDO-1 in immunosuppression, therapies using IDO-1 inhibitors in combination with other immunotherapy targets are also under investigation (Table 2). Current active phase I/II trials combining IDO-1 inhibitors focus on monoclonal antibodies (NCT02867007) and cancer vaccines (NCT01982487, NCT02166905, NCT02575807, NCT02785250, NCT03493945). A new selective IDO-1 inhibitor, KHK2455, was used in a phase I dose-escalation study in combination with mogamulizumab, an anti-CCR4 monoclonal antibody [86] (NCT02867007). This combination induced disease stabilization in four out of 21 patients with advanced solid tumors [86]. In a phase I/II study using dendritic cell vaccine Ad.p53-DC with indoximod (NCT01042535), the best observed response was four SD among 39 patients with metastatic solid tumors [87]. There was no difference in progression-free or overall survival between the immunologic responders and nonresponding patients [87]. A pilot trial treating 11 patients with epacadostat and multipeptide melanoma vaccine MELITAC 12.1 (NCT01961115) was reported to be safe, demonstrating changes in IDO-1 activity through serum Kyn/Trp ratio reduction and CD8+ T cell infiltrate elevation [88]. Of the four patients with measurable disease after protocol biopsy, there was one PR and three with SDs [88]. The DeCidE Ib trial resulted in three PR out of ten evaluable patients with epithelial ovarian cancer [89] (NCT02785250), suggesting a benefit in using surviving antigen vaccine DPX-Survivac with low-dose cyclophosphamide and epacadostat.

IDO in Combination with Chemotherapy and Chemoradiation

Studies with non-small cell lung cancer patients have reported a correlation between IDO activity and survival after not only chemotherapy [90], but also radiation [48], indicating a potential role for IDO activity in chemoradiation responses. Serum Kyn concentration and Kyn/Trp ratios were observed to be higher post-radiation than before or during treatment, suggesting an induction of IDO activity by radiotherapy [48]. While one murine glioma study showed that 1-MT confers no additional survival benefit when combined with temozolomide [51], another group reported DL-1MT enhances survival in murine glioblastoma when used with cyclophosphamide-based chemotherapy and radiation [91]. More recently, a study treating induced mouse tumors and spontaneous canine malignancies showed that triple therapy combining radiation, 1MT, and the TLR-9 agonist CpG induced cytotoxic T cell-dependent tumor growth inhibition compared to double therapies [92].

Clinical trials combining IDO-1 inhibitors with chemotherapy or chemoradiation have shown mixed responses (Table 2). One of the first clinical trials combining an IDO inhibitor with chemotherapy was a phase Ib study using indoximod with docetaxel (NCT01191216). This trial treated 22 patients with metastatic solid tumors, among whom four reached PR and nine achieved SD [93]. Similar response rates were observed in another phase Ib/II study using indoximod with temozolomide on 30 patients with recurrent refractory malignant brain tumors (NCT02052648), in which one patient had PR and four achieved SD [94]. A trial of 29 pediatric patients with recurrent or progressive malignant brain tumors reported that the combination of indoximod with radiation and chemotherapy was well-tolerated [95]. More importantly, this combination therapy elicited symptomatic improvements and

radiographic responses in all three patients with newly diagnosed diffuse intrinsic pontine glioma [95]. A larger phase II trial involving 135 patients with metastatic pancreatic cancer used indoximod and gemcitabine/nab-paclitaxel (NCT02077881), and reported an ORR of 46.2%, with one patient having a complete response [96]. Although biochemically the biopsies showed an increase in intra-tumoral CD8+ T cell density after two cycles of therapy in responders compared to non-responders, clinically, the trial did not meet its primary endpoint [96].

With these encouraging results from combination therapy using IDO inhibitors with chemotherapy or chemoradiation, more groups are continuing to pursue this strategy (NCT01792050, NCT02052648, NCT02077881, NCT02502708, NCT02835729). Meanwhile, other active trials are delving further into combination therapies to develop treatments that combine IDO inhibitors with both chemoradiation and other immunotherapy targets (NCT02406781, NCT02862457, NCT03085914, NCT03322566, NCT03348904).

IDO Peptide Vaccines

In addition to using IDO inhibitors, investigators have developed vaccines using an epitope derived from IDO. A phase I study treating patients with non-small cell lung cancer (NCT01219348) reported clinical benefit in seven out of 15 patients, among whom one had a PR [97]. The median survival of vaccinated patients was significantly longer than the vaccine-untreated patients: 25.9 months compared to 7.7 months [97]. Following treatment, there was a significant decrease in the number of Treg cells with no changes to other T cell populations [97], validating the role of IDO inhibition on the Treg population. The vaccination did not induce any grade 3–4 adverse events and was well-tolerated after 5 years of continued vaccination [98]. One patient with a solitary metastasis in a retroperitoneal gland had a complete response, suggesting a benefit of IDO vaccination for a select population [98]. Conversely, another study vaccinating metastatic melanoma patients (NCT02077114) with a peptide derived from IDO in combination with ipilimumab did not demonstrate any enhanced clinical response from the added vaccine [99]. Due to diminished recruitment, a phase II study (NCT01543464) for metastatic melanoma patients was terminated, with one I/II phase study (NCT03047928) remaining to study the IDO peptide vaccine in combination with nivolumab.

Conclusions

There are now many different IDO-1 inhibitors in development, encompassing both small-molecule drugs and peptide vaccines. Clinical trials are currently focused on combination strategies with a variety of agents, including immune checkpoint inhibitors, other immunotherapy agents, chemotherapy, and radiotherapy.

IDO-1 inhibitors represent a unique addition to the repertoire of immuno-oncology agents, because they are small-molecule drugs that target an intracellular enzyme, as opposed to other, more costly, cell receptor–targeting antibodies like those targeting PD-L1/PD-1 and CTLA-4. Targeting an enzyme means that IDO-1 inhibitors may elicit broad and potentially synergistic responses by the immune system, given the plethora of IDO-dependent pathways. In addition, IDO-1 inhibitors have generally been well-tolerated in monotherapy and in combination therapies, with fewer treatment-related adverse effects compared to combination strategies using anti-CTLA-4 therapy [60]. Thus, the unique mechanism of action and safe profile of IDO-1 inhibitors lend themselves well to roles in combination therapies.

However, it is concerning that IDO-1 inhibitors, as single agents, do not appear to elicit objective responses despite promising pre-clinical data. The broad downstream effect of IDO-dependent pathways may be a double-edged sword that does not induce selective, specific anti-tumor effects. Further contributing to the unpredictable pharmacological responses may be the differing mechanism of actions of each IDO-1 inhibitor. The mechanism of action of indoximod is unclear, as it appears to act only on the mTOR pathway, while navoximod does not show highly selective inhibition against IDO-1 compared with other Trp-metabolizing enzymes [23]. The extent to which these differences contribute to tumor response is unknown. It also remains debatable whether high selectivity of an IDO-1 inhibitor is desirable in immunotherapy, as targeting IDO-2 and TDO have also demonstrated antitumor potential.

IDO-1 inhibitors will likely be further developed as part of combination therapies, with response rates dependent on cancer types. Combining IDO-1 inhibitors with PD-1/PD-L1 therapy is effective for cancers with high immunogenicity such as melanoma, renal cell carcinoma, and non-small cell lung cancer, mirroring the cancer types that have been approved for treatment with pembrolizumab and nivolumab. On the other hand, combinatory regimens using IDO-1 inhibitors and chemoradiation have seen successes in patients with malignant brain tumors. Hence, future research may need to focus on developing predictive biomarkers to identify patient populations that would gain maximum benefit from a combination therapy with IDO-1 inhibitors. While studies have explored predictive biomarkers in the context of anti-PD-1/PD-L1 and CTLA-4 therapy response [100], little has been published on IDO-1 inhibitors.

In conclusion, IDO-1 inhibitors are still finding their place within the immuno-oncology armamentarium. These agents have a mechanism of action different from other drugs, with initial studies showing favorable toxicity but lower response rates than for more established checkpoint inhibitors. Thus, their place may be within combination strategies, an area which is under evaluation in many active clinical trials.

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Compliance with Ethical Standards

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