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REVIEW

Trial watch: IDO inhibitors in cancer therapy

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ABSTRACT

Indoleamine 2,3-dioxygenase 1 (IDO1) catalyzes the first, rate-limiting step of the so-called "kynurenine pathway", which converts the essential amino acid *L*-tryptophan (Trp) into the immunosuppressive metabolite *L*-kynurenine (Kyn). While expressed constitutively by some tissues, IDO1 can also be induced in specific subsets of antigen-presenting cells that ultimately favor the establishment of immune tolerance to tumor antigens. At least in part, the immunomodulatory functions of IDO1 can be explained by depletion of Trp and accumulation of Kyn and its derivatives. In animal tumor models, genetic or pharmacological IDO1 inhibition can cause the (re)activation of anticancer immune responses. Similarly, neoplasms expressing high levels of IDO1 may elude anticancer immunosurveillance. Therefore, IDO1 inhibitors represent promising therapeutic candidates for cancer therapy, and some of them have already entered clinical evaluation. Here, we summarize preclinical and clinical studies testing IDO1-targeting interventions for oncologic indications.

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Introduction

L-tryptophan (Trp), one of the essential amino acids, is indispensable for protein synthesis and cell survival. The kynurenine pathway catabolizes Trp to active metabolites such as *L*-kynurenine (Kyn), kynurenic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, picolinic acid and quinolinic acid. This metabolic cascade can be catalyzed by three enzymes, namely, indoleamine 2,3- dioxygenase 1 (IDO1), IDO2, and tryptophan 2,3-dioxygenase (TDO2).[1–4] IDO1 is by far the best-studied among these enzymes, as it was the first interferon (IFN)-activated gene to be described as early as in the late 1970s.[5] The differential distribution and activity of IDO2 and TDO2 calls for further investigation to elucidate to which extent IDO2 and TDO2 contribute to Trp catabolism *in vivo*.[1,5–7]

In 1998 Munn, Mellor and colleagues demonstrated for the first time that IDO1 exerts immunosuppressive functions, as it prevents rejection of allogenic fetuses by the maternal immune system.[6,8] This conceptual breakthrough initiated an intense wave of research aimed at understanding the molecular and cellular circuitries implicated in the immunomodulatory functions of IDO1.

Subsequent studies revealed that IDO1 is a central driver of cancer development and progression. In particular, IDO1 mediates pathogenic inflammatory processes in malignant, stromal and immune cells that ultimately lead to immune tolerance to tumor antigens.[9,10] According to current knowledge, the pleiotropic role of IDO in cancer includes the suppression of cytotoxic T lymphocytes (CTL)[10–13] and natural killer (NK) cells,[14,15] the generation and activation of regulatory T (T_{REG}) cells[16,17] and myeloid-derived suppressor cells (MDSCs)[17–20] as well as the promotion of tumor angiogenesis.[10,17] The immunomodulatory functions of IDO1 can be attributed to Trp starvation and increased Kyn levels.[21,22] More specifically, Trp depletion induces cell cycle arrest of T cells and apoptosis through inhibition of the mechanistic target of rapamycin complex 1 (mTORC1),[10,23,24] while inducing a stress response that activates the general control nondepressible 2 (GCN2).[25–27] Increased levels of Trp metabolites, especially Kyn, activate the transcription factor aryl hydrocarbon receptor (AHR), which in return induces differentiation of $CD4^+$ T cells into immunosuppressive T_{REG} cells.[28–30] Alongside, IDO1-epxressing dendritic cells (DCs) have been shown to mediate immunosuppressive functions independent of Trp depletion and Kyn accumulation.[31–35] Moreover, IDO1 has been recently implicated in the microbiota-dependent control of obesity by shifting Trp metabolism from indole derivatives and interleukin 22 (IL-22) synthesis toward kynurenine production.[28,36]

IDO1 is widely overexpressed in tumor cells, which has been predominantly associated with poor prognosis.[8,37–39] Similarly, increased circulating levels of Trp metabolites, such

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as Kyn, have been detected in patients with various cancers and have been attributed a poor predictive value in some cohorts.[40–42] Also, IDO1 expression in tumor cells has been linked to the status of the oncosuppressor gene bridging integrator 1 (BIN1).[43,44] BIN1 is one of the most frequently downregulated genes in human cancer,[45] due to either abnormal RNA splicing patterns compromising its tumor suppressor function,[46–48] or increased gene methylation abolishing its expression.[49,50] In particular, BIN1 is absent or underexpressed in various human neoplasms, such as neuroblastoma,[51] melanoma,[46] as well as breast, lung, colorectal and prostate carcinoma.[46,52,53] The loss of BIN1 triggers the interferon gamma (IFNγ)-induced expression of IDO1, ultimately favoring tumor growth in immunocompetent, but not in immunodeficient, mice.[43] High levels of IDO not only correlate with poor outcome in some malignancies but they may also be implicated in drug resistance, as this has been reported for IDO1-expressing ovarian cancer patients.[54] Likewise, higher Kyn/Trp ratio have been shown to predict resistance to programmed cell death 1 (PDCD1, best known as PD-1) blockade in patients with non-small cell lung carcinoma (NSCLC).[55,56] At last, profiling of advanced melanoma and renal cell carcinoma (RCC) patients showed that Kyn/Trp alterations correlated with overall survival upon administration of nivolumab (a PD-1 blocker).[57]

Thus, IDO inhibition stands out as a promising strategy to (re)instance cancer immunosurveillance. Indeed, IDO inhibitors demonstrated their ability to successfully cooperate with immunotherapy, radiotherapy or chemotherapy even in tumors that are normally resistant to conventional treatments.[10,58,59] In this setting, preclinical studies have revealed an interesting paradox: while IDO inhibitors have a negligible effect on established tumors as single-agent, combination of IDO inhibitors and immunotherapies including checkpoint blockers targeting cytotoxic T lymphocyte-associated protein 4 (CTLA4) or PD-1 yields a synergistic effect to control cancer burden and favor survival.[17,60–63] Here, we discuss recent progresses on the use of IDO1 agonists in preclinical and clinical settings as a strategy for the (re)activation of antitumor immune responses.

Preclinical advances

In this section we summarize the findings of key preclinical studies on the ability of IDO1 inhibitors to (re)instate anticancer immunosurveillance since the publication by Hornyák *et al*. dealing with this topic.[64]

Indoximod

The simple racemic compound 1-methyl-tryptophan (1MT) was first described as a competitive inhibitor of the IDO1 enzyme in the early 1990s.[65] It is by far the most employed IDO inhibitor in the preclinical literature. Unlike its *L* isomer, which has shown weak inhibitory activity, *D*-1MT isomer neither binds nor inhibits the purified IDO1 enzyme while demonstrating anticancer activity.[66–68] Therefore, clinical development focused on *D*-1MT (best known as indoximod or NLG8189).[69] In contrast to direct enzymatic inhibitors of IDO1, indoximod acts downstream of IDO1 to stimulate mTORC1, possibly lowering risks of drug resistance.[69,70] Several combinatorial regimens have been developed to increase the antineoplastic effects of indoximod, some of which demonstrated pronounced therapeutic activity in preclinical models of hepatocellular carcinoma (HCC),[71] advanced prostate[72] and lung cancer.[73] Indeed, IDO1 inhibition with 1MT, synergized with radiotherapy to downregulate T_{REG} cells, reduce expression of PD-1 or its ligand CD274 (best known as PD-L1), and to prevent T cell exhaustion in Lewis lung cancer (LLC)-bearing mice.[73] *D*-1MT and CTLA4 blockers administration mediated improved therapeutic effects in treatment resistant IDO1-overexpressing HCCs in both subcutaneous and hepatic orthotopic models.[71] Additionally, CTLA4 blockade induced the IFNγ-dependent upregulation of IDO1 in chemoresistant (but not sensitive) HCCs in mice.[71] At last, IDO activity positively correlates with disease stage in prostate cancer patients,[72] and both a DNA vaccine encoding the tumor-associated antigen acid phosphatase 3 (ACP3, best known as PAP) and PD-1 blockade with pembrolizumab promotes IDO expression and activity in these individuals.[72] Consistent with the immunosuppressive activity of IDO in this setting, *ex vivo* stimulation of peripheral blood cells with 1-MT increased T cell responses to vaccination.[72] Recently, Hu *et al.* also demonstrated that a methyltryptophan-paclitaxel (MP) albumin-bound drug conjugate (that links indoximod to the microtubular poison paclitaxel[74-77] through an ester bond) not only significantly elevates the tumor levels of indoximod and local $CD8^+$ T populations, but reduces granulocyte-like myeloid derived suppressor cells (G-MDSCs) and T_{REG} cells.[78]

Epacadostat (INCB024360)

Epacadostat, also known as INCB024360, is an orally available reversible competitive IDO1 inhibitor. Wachowska and colleagues reported that photodynamic therapy (PDT)[79–82] induced IDO1 expression within neoplasms as well as in tumor draining lymph nodes in murine orthotopic breast cancer models.[83] Mechanistically, granulocytic $CD11b^+Ly6G^+$ myeloid cells were the major source of IDO1 and strongly infiltrated the tumor bed following PDT.[83] Although less abundant after PDT, monocytic $CD11b^+Ly6C^+$ myeloid cells, could also upregulate IDO1.[83] Interestingly, depending on the therapeutic scheme of PDT administration, IDO-induced immunosuppression can either be beneficial or lead to systemic toxicity.[83] Although IL-6 neutralization restored antitumor efficacy, it abolished the synergistic effect of epacadostat and PDT.[83] This might be explained by the fact that constitutive IDO expression in human cancer is sustained by an autocrine signaling loop involving IL-6, signal transducer and activator of transcription 3 (STAT3)[84–87] and the AHR.[88]

Navoximod (GDC-0919, NLG-919)

Navoximod (also known as GDC-0919 or NLG-919) was initially developed as an orally bioavailable IDO1/TDO inhibitor with an improved pharmacokinetic and toxicity profile, based on 4-phenylimidazole, a compound that binds the heme moiety within the catalytic site of IDO1.[89] IDO1 inhibition by navoximod has been shown to decrease plasmatic Kyn/Trp ratios and tumor Kyn levels.[90] In sarcoma-bearing mice, navoximod used

alone or combined with a PD-L1 blocker could neither efficiently control tumor growth nor affect the tumor immune cell infiltrate.[90] However, in the 4T1 murine breast tumor model, navoximod synergizes with doxorubicin[91-93] to elicit an antitumoral immune response and to control tumor growth.[94,95]

PF-06840003 and *BGS-5777*

PF-06840003 is a highly selective IDO1 inhibitor with favorable pharmacokinetic characteristics and a prolonged half-life in humans, which enable single-dose daily administration. Additionally, its ability to enter the central nervous system (CNS) allows for its use against brain metastases.[96] In several preclinical tumor models in mice, PF-06840003 strongly reduced intratumoral Kyn levels and inhibited tumor growth in both monotherapy and, with an increased efficacy, in combinatorial regimens with PD-L1 or CTLA4 blockers.[97] Recently, BGB-5777, a potent CNS-penetrating IDO1 inhibitor, enabled a durable survival benefit in a fraction of patients with advanced glioblastoma when combined with nivolumab and radiation therapy.[98,99]

BMS-986205

BMS-986205 is an orally available irreversible inhibitor of IDO1. Current clinical studies have shown its dose-dependent efficacy, coupled to better efficiency and pharmacokinetics than epacadostat.[10] Even at a low concentrations, BMS-986205 successfully inhibits IDO1 and lowers Kyn serum levels.[100]

Other IDO1 inhibitors

A few additional IDO1 inhibitors are in preclinical development, including Trp analogs,[1] imidazoles,[101] phenyl benzenesulfonylhydrazides,[102] *N*-hydroxyamidines[103] and LW106.[104] Other IDO1 inhibitors being developed by pharmaceutical groups in late preclinical settings, which include IOM2983 (Merck/IO-Met) and RG-70099 (Roche/CuraDev), have not yet publicly disclosed. In contrast, SHR9146 (also known as HTI-1090), an inhibitor of IDO1 and TDO, and KHK2455, an IDO1 inhibitor, have recently entered early clinical development.[1,105] Overall, these compounds offer abundant possibilities for exploring the effects of specific IDO1 inhibition in the clinics.

Translational and clinical progress

A number of translational and clinical results addressing the safety and therapeutic potential of IDO1 inhibitors have been published since the latest survey on this topic (January 2018).[64] Here, we discuss some of these recent studies to recapitulate the current state-of-the-art.

Translational studies

Recent immunohistochemical analyses demonstrate that patchy expression of IDO1 within cervical cancers is associated with an increased systemic Kyn/Trp ratio and poor disease outcome, whereas marginal IDO1 expression pattern in the tumor predicts favorable outcome.[106] At least in part, these observations could be related to T cell infiltration and IFNγ release in the cervical tumor microenvironment.[106] Along similar lines, analyses of 144 cervical tumor samples from The Cancer Genome Atlas (TCGA) revealed a strong and positive correlation between *IDO1* and *IFNG* mRNA expression levels, as well as significantly improved disease-free survival for patients with high *IDO1* and *IFNG* levels.[106]

Li and colleagues demonstrated that serum Kyn/Trp ratio increases as an adaptive resistance mechanism associated with worse overall survival in advanced melanoma and RCC patients treated with nivolumab.[57] They further established a correlation in melanoma samples between Kyn/Trp ratio and *IDO1* but not *TDO* mRNA levels 4 weeks after nivolumab administration,[57,107] suggesting that IDO1 may be the major source of Kyn in this setting. At last, two studies described synergistic effects of agents targeting erb-b2 receptor tyrosine kinase 2 (ERBB2, best known as HER2),[108,109] IDO1 and PD-1.[110,111] Upon antibody-dependent cellular phagocytosis (ADCP), macrophages inhibit NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and T cell-mediated cytotoxicity in breast cancers and lymphomas.[2–11,110,112] Mechanistically, following ADCP, absent in melanoma 2 (AIM2) is recruited to the phagosomes by FcγR signaling and activated by DNA from phagocytosed tumor cells.[111,113] Upon activation, AIM2 upregulates PD-L1 and IDO to cause immunosuppression. Combined treatment with anti-HER2 antibodies and inhibitors of PD-L1 and IDO enhances anti-tumor immunity and anti-HER2 therapeutic efficacy *in vitro*[111] as well as in mouse models of $HER2^+$ breast carcinoma.[110] Additionally, neoadjuvant trastuzumab[114-120] treatment significantly upregulates PD-L1 and IDO on tumor-associated macrophages (TAMs) from $HER2^+$ breast cancer patients, correlating with poor trastuzumab responses.[110] Collectively, these findings suggest that IDO inhibitors may provide synergistic effects with other targeted immunotherapies.

Published clinical trials

Komrokji *et al.* reported preliminary results for the sole published clinical trial monitoring the efficacy of epacadostat administered as standalone intervention.[121] In particular, this Phase II study aimed at evaluating the pharmacodynamics and activity of epacadostat in heavily pre-treated transfusion-dependent patients with myelodysplastic syndrome (MDS) after hypomethylating agent (HMA) failure.[122–124] The IDO1 inhibitor was well tolerated, as no Grade 3 or 4 treatment-related adverse events (TRAEs) were recorded. Only one patient (among the 15 included in the trial) developed grade 2 adrenal insufficiency and hypothyroidism, while another showed low testosterone levels. Eighty percent of individuals exhibited stable disease and 20% progressive disease, largely in line with the poor prognosis of this patient population (overall survival of ~18 months in low-risk disease and 4–6 months in high-risk disease). All these findings suggest that future studies should consider to test epacadostat earlier in the disease course, before HMA failure (since expansion of MDSCs probably contribute to myelosuppression).[121]

All other clinical studies recently published on IDO1 inhibitors tested these agents in combination with immune

checkpoint blockers. In particular, Gibney *et al.* reported the results for the Phase I/II clinical trial NCT01604889 enrolling patients with unresectable or metastatic melanoma and receiving epacadostat together with ipilimumab.[125–127] Among the 50 participants, 20 discontinued treatment due to disease progression and 48 experienced TRAEs including hypothyroidism (10%), pruritus (28%), alanine aminotransferase elevation (28%), rash (50%), and aspartate aminotransferase elevation (24%). Dose-limiting toxicities occurred in 11 patients, and doses ≥100 mg BID were not tested due to hepatotoxicity. Among immunotherapy-naive patients (n = 39), objective response rate was 23% by response evaluation criteria in solid tumors (RECIST) and 26% by immune-related response criteria (iRECIST). No objective response was observed in the 11 patients previously treated with immunotherapy. According to the authors, these preliminary findings support continuing the evaluation of epacadostat plus ipilimumab in patients with unresectable or metastatic melanoma.[128] Unfortunately the study was prematurely terminated due to the sponsor's decision, and only the Phase I portion of the trial was completed.

The NCT02298153 ECHO-11O Phase Ib trial evaluated the efficacy, tolerability and safety of the epacadostat administered together with the PD-L1 blocker atezolizumab,[129–131] to 29 patients with stage IIIB/IV NSCLC previously treated with platinum derivatives[132-136] chemotherapy in conjunction with a folic acid analogue.[137–139] Seventy-nine percent of enrolled patients experienced TRAEs, 17% discontinued treatment due to such effects, one patient showed anticancer partial response, and the maximum tolerated dose (MTD) was not achieved. Thus, the clinical activity of epacadostat plus atezolizumab against NSCLC was deceptive, in line with the hitherto unclear significance of IDO1 expression in this setting.[140] Ultimately, the ECHO-110 study was prematurely terminated due to slow recruitment.

Additional results have recently lent further support to the controversial efficacy of epacadostat administered in combination with immune checkpoint blockers.[141,142] In particular, Mitchell *et al.* reported the results of the Phase I KEYNOTE-037/ECHO-202 (NCT02178722) trial, enrolling 62 individuals with several solid tumors, including 22 melanomas, 12 NSCLCs and 11 RCCs. Eighty-four percent of the patients exhibited tolerable Grade 1/2 TRAEs (such as nausea, pruritus, rash, fatigue and arthralgia), 11% of the subjects discontinued the therapy, and the MTD was not attained.[141] An objective response was observed in 55% of melanoma patients and in some patients with urothelial carcinoma, RCC, head and neck squamous cell carcinoma (HNSCC), endometrial adenocarcinoma or NSCLC (in all cases, independently of PD-L1 expression levels). Altogether, these results suggest an encouraging and durable antitumor activity for this combinatorial regimen that has be to confirmed in additional Phase II studies.[141,143,144] Long and colleagues published the first results for the KEYNOTE-252/ECHO-301 (NCT02752074) assay, a phase III randomized, double-blind study evaluating the efficacy of epacadostat combined with pembrolizumab *versus* placebo plus pembrolizumab in 706 patients with untreated, unresectable or metastatic melanoma.[142] At odds with the findings from ECHO-202 and despite promising preliminary observations, no evidence of improved progression free survival could be documented (4.7 months in the epacadostat plus pembrolizumab arm *versus* 4.9 months in the pembrolizumab only arm). Overall survival was 74% in both groups, and objective response rates were similar in the two arms. Additionally, the most common TRAE, a lipase increase, occurred with a similar frequency in both groups (9% of patients receiving pembrolizumab monotherapy *versus* 10% in individuals receiving the combinatorial regimen).[142]

These disappointing results suggested that this combinatorial therapy did not improve the clinical outcome of melanoma patients receiving pembrolizumab, confirming that the role of epacadostat (or IDO1 inhibitors in general) in advanced solid tumors with robust PD-1 signaling remains unclear. No less than twelve Phase III clinical assays testing this IDO1 selective inhibitor, alone or in combinatorial regimen in different cancer contexts, have been recently been withdrawn, downsized or suspended.[145] Indeed, it remains to be elucidated whether IDO1 constitutes a robust target for the development of anticancer agents. The results of ongoing clinical trials (see below) may clarify whether IDO1 inhibitors are an option to improve the therapeutic activity of PD-1 blockade in some cancer patient populations.[146]

The results of two studies investigating the clinical profile of indoximod have recently been reported. Soliman and colleagues showed that indoximod plus an adenoviral DC vaccine targeting tumor protein p53 (TP53)[147–149] was well tolerated by metastatic breast cancer patients enrolled in a Phase I/II clinical trial. Patients who did not exhibit particular side effects (none of the toxicities required treatment discontinuation) achieved a median progression-free survival of ~13 weeks and a median overall survival of ~21 weeks, suggesting the absence of a statistically significant effect of indoximod.[150] Moreover, preliminary results from the Phase II NCT02077881 assay, enrolling 104 metastatic pancreatic cancer patients treated with indoximod plus gemcitabine and paclitaxel, have been disclosed by Bahary *et al.* Median overall survival was ~11 months, overall response rate was 46% (including one patient experiencing a complete response), and no significant toxicities were documented (anemia, nausea and fatigue being the most common).[151]

Navoximod has been tested as a standalone intervention in patients with advanced or recurrent solid tumors in a Phase I study aiming to assess the antitumor activity, safety, pharmacokinetics and pharmacodynamics of the IDO inhibitor (NCT02048709). Preliminary results by Nayak-Kapoor and colleagues indicate that the MTD was not reached in the 22 enrolled patients, with a single dose-limiting Grade 4 toxicity (lower gastrointestinal hemorrhage). In ≥20% of patients, regardless of causality, TRAEs included vomiting (27%), nausea (36%), pruritus, cough, decreased appetite (41% of each) and fatigue (59%). Grade ≥ 3 TRAEs, reported in 64% of patients, could be attributed to navoximod in two patients (9%). Overall, navoximod was well tolerated at doses up to 800 mg BID and, among patients evaluated for efficacy, 8 (36%) had stable disease and 10 (46%) progressed.[152]

Results from two clinical trials, testing navoximod in combination with the PD-L1 inhibitor atezolizumab, in patients with advanced cancer, have recently been published.[153,154] Jung *et al.* reported preliminary results from the

NCT02471846 trial, consisting of a 3 + 3 dose-escalation (n = 66) and a tumor-specific expansion (n = 92) phase. Navoximod was given orally every 12 hours for 21 consecutive days of each cycle except for cycle 1, where navoximod administration started on day −1 to measure pharmacokinetics. The maximum administered dose was 1000 mg BID, and the MTD was not reached. Navoximod demonstrated a linear pharmacokinetic profile as plasma Kyn levels decreased in a dose-dependent manner. The most common TRAEs were rash (22%), chromaturia (20%) and fatigue (22%). Some degree of antitumoral activity was observed at all dose levels in various tumor types including breast, cervical, HNSCC, melanoma, neural sheath, NSCLC, ovarian, pancreatic, prostate, RCC and urothelial bladder cancer. Of note, 6 (9%) dose-escalation patients partially responded, and 10 (11%) expansion patients achieved partial or complete responses. Together, these findings proved that this regimen was safe and well tolerated, although there was no clear evidence of benefit from adding navoximod to atezolizumab.[154]

At last, results from a dose-escalation study assessing navoximod alone or in combination with atezolizumab, in Japanese individuals with advanced solid tumors, were reported by Ebata and colleagues.[153] Patients received either navoximod alone in stage 1 (n = 10) or in combination with atezolizumab in stage 2 (n = 10). No dose-limiting toxicities were observed. In stage 1, chromaturia (50%) and maculopapular rash (20%) occurred in ≥20% of patients and Grade ≥ 3 TRAEs were reported in two patients (20%; maculopapular rash and increased lipase). In stage 2, chromaturia (60%) and decreased appetite (40%) occurred in ≥30% of patients, while Grade ≥ 3 TRAEs were reported in three patients (30%; alanine and aspartate aminotransferase increased, hyponatremia, lympho- and neutro-paenia). Stable disease was observed in 5 patients (50%) in stage 1 and 8 patients (80%) in stage 2. Overall, these results suggested that navoximod, as monotherapy and in combination with atezolizumab, was well tolerated in patients with advanced solid tumors.

Similarly, Riccuiti, Luke and colleagues[155-158] reported results for the NCT02658890 study which aimed at testing BMS-986205 administered as monotherapy once daily for 2 weeks followed by nivolumab in advanced bladder cancer. TRAEs (all grades) were reported in 57% of patients with 12% of Grade 3–4 side effects. The most common side effects of any grade were fatigue (15%) and nausea (12%). Nineteen patients (4%) discontinued treatment due to TRAEs, and 3 patients died due to a TRAE (hepatic failure, myocarditis and Stevens-Johnson syndrome). The combination of BMS-986205 and nivolumab was well tolerated in heavily pretreated patients and enhanced tolerability was observed with the 100 mg dose. Preliminary evidence of efficacy was observed in advanced bladder cancer, supporting further evaluation of this combinatorial regimen.

Ongoing clinical trials

When this Trial Watch was being redacted (May 2020), official sources listed 22 clinical trials launched after January 2018 (Table 1) to evaluate the safety and efficacy of IDO1 targeting intervention in cancer patients (source http://www.clinicaltrials.gov). Ten of these studies involve BMS-986205, 9 epacadostat, 1 indoximod, 1 KHK2455 and 1 SHR9146.

In particular, epacadostat is being tested together with a brachyury-targeted antitumor vaccine, a transforming growth factor beta (TGFβ) trap-anti-PD-L1 antibody (M7824), and an IL-15/IL-15RA superagonist (ALT-803) in patients affected by metastatic castration-resistant prostate cancer (NCT03493945).[159]

BN-Brachyury is a novel recombinant vector-based therapeutic cancer vaccine that enhances an immune response against brachyury,[37] a transcription factor that plays a key role in epithelial-mesenchymal transition (EMT) and is overexpressed in prostate adenocarcinoma.[160–163] M7824, a bifunctional fusion protein composed by 2 extracellular domains of a TGFβ trap and a human IgG1 anti PD-L1 mAb,[164,165] is able to reverse the EMT, to promote ADCC *in vitro*,[165] and promising evidence of immunostimulatory and clinical activity in solid tumors has been provided.[166,167] ALT-803 is a fusion protein that stimulates both T and NK cells *via* agonism of the IL-2 and IL-15 receptors, thus supporting ADCC induction in synergy with M7824.[168,169] This combinatorial regimen is a promising therapeutic option because of the activation of vaccine-derived tumor-specific T cells (by ALT-803) that is boosted by M7824 and epacadostat.

NCT03532295 is the only trial testing the safety and preliminary efficacy of epacadostat in subjects affected by brain tumors. The synergy among this IDO1 inhibitor, radiotherapy, the vascular endothelial growth factor A (VEGFA)-targeting antibody bevacizumab[170,171] and the humanized, hinge-stabilized IgG4, targeting the interaction of PD-1 with PD-L1 and PD-L2, INCMGA00012 (also known as MGA012),[172] might activate a pronounced anti-cancer immune response thus leading to tumor regression and improved outcome. Along similar lines, the remaining clinical trials that involve epacadostat assess safety and preliminary efficacy of the IDO1 inhibitor combined with pembrolizumab (and other immunotherapeutic regimens).[173–175] In particular, NCT03823131 evaluates the efficacy of tavokinogene telseplasmid (tavo) electroporation (EP), pembrolizumab, and epacadostat against unresectable HNSCC (as compared to pembrolizumab monotherapy). Moreover, the tolerability, safety and preliminary efficacy of epacadostat and pembrolizumab were tested in patients affected by (i) advanced pancreatic cancer with chromosomal instability or homologous recombination repair deficiency (HRD) (NCT03432676), (ii) esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma and gastroesophageal adenocarcinoma (NCT03592407), (iii) HNSCC recurring after PD-1/PD-L1 therapy (NCT03463161), and (iv) ovarian clear cell carcinoma (NCT03602586). However, two of these studies are currently listed as "Withdrawn" (NCT03432676, because the trial is no longer financed by the main supporter, and NCT03592407, due to safety concerns), while two other studies have been "Suspended" (NCT03602586, for scheduled interim monitoring) or "Terminated" (NCT03463161, due to a conflict of interest among the investigators). In the Phase II NCT03592407 study, the administration of neoadjuvant epacadostat plus pembrolizumab (followed by standard chemoradiation)

Table 1. Clinical trials testing IDO-1 inhibitors in oncological indications.

Drug	Indication	Status	Phase	Co-therapy	NCT
BMS-986205	Advanced solid tumors	Active not recruiting	I/II	As single agent then combined with nivolumab	NCT03792750
		Recruiting	I/II	Combined with nivolumab and relatlimab	NCT03459222
	Bladder cancer	Recruiting	II	Combined with nivolumab ± BCG	NCT03519256
		Recruiting	III	Combined with cisplatin, gemcitabine and nivolumab	NCT03661320
	Endometrial cancer	Recruiting	II	Combined with nivolumab	NCT04106414
	Glioblastoma	Recruiting	I	Combined with nivolumab and radiotherapy ± temozolomide	NCT04047706
	HCC	Recruiting	I/II	Combined with nivolumab	NCT03695250
	HNSCC	Recruiting	II	Combined with nivolumab	NCT03854032
	Melanoma	Withdrawn	II	Combined with nivolumab	NCT04007588
	NSCLC	Withdrawn	III	Combined with nivolumab ± chemotherapy	NCT03417037
Epacadostat	Advanced rectal cancer	Suspended	I	Combined with XELOX regimen and radiotherapy	NCT03516708
	Bladder cancer	Not yet recruiting	II	Combined with pembrolizumab	NCT03832673
	ESCC Esophageal adenocarcinoma Gastroesophageal adenocarcinoma	Withdrawn	II	Combined with pembrolizumab	NCT03592407
	Glioblastoma Glioma	Not yet recruiting	II	Combined with bevacizumab, INCMGA00012 and radiotherapy	NCT03532295
	HNSCC	Recruiting	II	Combined with pembrolizumab and tavo-EP gene therapy	NCT03823131
	HNSCC	Terminated	II	Combined with pembrolizumab	NCT03463161
	Metastatic prostate cancer	Recruiting	I/II	Combined with ALT-03, BN-Brachyury and M7824	NCT03493945
	Ovarian clear cell carcinoma	Suspended	II	Combined with pembrolizumab	NCT03602586
	Pancreatic cancer	Withdrawn	II	Combined with pembrolizumab	NCT03432676
Indoximod	Pediatric solid tumors	Recruiting	II	Combined with chemoradiotherapy	NCT04049669
KHK2455	Bladder cancer	Recruiting	I	Combined with avelumab	NCT03915405
SHR9146	Advanced solid tumors	Not yet recruiting	I	Combined with SHR-1210 ± apatinib	NCT03491631

Abbreviations: BCG, bacillus Calmette–Guérin; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; tavo-EP, pUMVC3-hIL-12-NGVL33 tavokinogene telseplasmid-electroporation; XELOX, capecitabine + oxaliplatin.

aimed at verifying the capacity of this combinatorial regimen to ameliorate the lymphoid compartment of the tumor, thus increasing the abundance of $CD8^+$ CTLs expressing the effector molecule granzyme B (GZMB),[176] and reducing the relative amount of tumor-infiltrating $CD4^+CD25^+FOXP3^+$ T_{REG} cells[177-182] (with respect to $CD8^+$ cells). Of note, the therapeutic profile of this neoadjuvant combinatorial regimen is currently assessed in a Phase II study (NCT03832673) enrolling patients with muscle-invasive bladder cancer (MIBC). Indeed, the published literature lends robust support to the notion that pembrolizumab not only is an encouraging neoadjuvant therapy for the treatment of PD-$L1^+$ MIBC and neoplasm with high mutational burden,[183–185] but also increases overall survival (by ~3 months) in advanced urothelial carcinoma[185,186] and exhibits good tolerability when administered to patients with advanced solid tumors in combination with epacadostat.[141] Moreover, Chu *et al.* have recently demonstrated that the manipulation of the immune microenvironment with IDO1 inhibition enhances patient responses to existing therapies.[187]

Finally, the Phase I trial NCT03516708, evaluating the efficacy of epacadostat administered to locally advanced rectal cancer patients, in the context of the so-called XELOX regimen (capecitabine plus oxaliplatin)[188–191] for preoperative chemoradiotherapy, has been suspended to ensure patient safety during the Covid19 epidemics.[192–194]

BMS-986205 is mainly being administered to cancer patients simultaneously receiving nivolumab[195] (NCT03792750, NCT03459222, NCT03519256, NCT03661320, NCT04106414, NCT04047706, NCT03695250, NCT03854032, NCT04007588, NCT03417037). Patients affected by advanced solid tumors are treated with BMS-986205 plus nivolumab alone (NCT03792750) or combined with the anti-lymphocyte activating 3 (LAG3) agent relatlimab[54,196–199] (NCT03459222). The Phase II study NCT03519256, enrolling subjects with high-risk, non-MIBC, is monitoring the therapeutic profile of BMS-986205 combined with two drugs already approved for some types of bladder cancer such as nivolumab[200-204] and the toll like receptor 2 (TLR2)/TLR4 agonist[205-209] bacillus Calmette–Guérin (BCG).[210–212] Along similar lines, the Phase III study NCT03661320 compared the efficacy, tolerability and safety of three therapeutic regimens for MIBC: neoadjuvant standard of care chemotherapy with cisplatin[213-217] and gemcitabine,[218,219] (NAC) *versus* NAC combined with nivolumab or nivolumab plus BMS-986205, followed by continuation of adjuvant immunotherapy (nivolumab with or without the IDO1 inhibitor) post radical cystectomy.[220]

Additionally, four ongoing studies aim at elucidating the therapeutic profile of BMS-986205 in combination with nivolumab in patients affected by endometrial carcinoma or endometrial carcinosarcoma (NCT04106414), unresectable or metastatic HCC (NCT03695250), stage II to IV HNSCC (NCT03854032), as well as stage III or IV melanoma (NCT04007588). In particular, the NCT04007588 assay was planned to compare the effectiveness of neoadjuvant PD-1 blockade alone or combined with IDO1 inhibition or with the CTLA4 checkpoint blockers ipilimumab.[125–127,221,222] However, NCT04007588 has been "Withdrawn" (due to slow accrual). Untreated stage IV or recurrent NSCLC patients were also to be enrolled in NCT03417037, planned to test the combination of BMS-986205 and nivolumab given with or without chemotherapy. Also, NCT03417037 is currently listed as "Withdrawn" (due to changes in the business objectives of the investors). Finally, the safety, side effects and preliminary efficacy of BMS-986205, nivolumab and standard radiation therapy, with or without temozolomide, are being assessed in individuals with newly diagnosed glioblastoma (NCT04047706).

The NCT03915405 clinical assay explores the therapeutic potential of KHK2455 combined with the PD-L1 blocker avelumab[223-225] in individuals with locally advanced or metastatic urothelial carcinoma. In particular, the tolerability and safety of the regimen will be evaluated during the first phase of the study (dose-escalation), while pharmacodynamics, pharmacokinetics, and preliminary antitumor activity will be assessed during the expansion phase.

The principal purpose of NCT04049669 is to monitor the efficacy of daily oral administration of indoximod[10,226,227] concomitant to chemo-immunotherapy and radiotherapy (for eligible individuals) in subverting immune tolerance and improving clinical outcome of pediatric patients affected by relapsed or refractory glioblastoma, medulloblastoma or ependymoma, as well as by newly-diagnosed diffuse intrinsic pontine glioma (DIPG). In particular, the core therapeutic regimen consists of oral administration of temozolomide[228-230] and indoximod, preceded by either low-dose or partial-field radiation (cohort B), or full-dose radiation (cohort C, including all newly diagnosed DIPG patients and some relapsed ependymoma patients), or corresponded to the starting treatment (cohort A, patients not eligible to re-irradiation). If patients accept continuing the indoximod treatment they undergo two "salvage" regimens including either cyclophosphamide[189,190,231,232] plus etoposide[233,234] or the DNA alkylating agents lomustine[235-237] and temozolomide.

Finally, the safety and efficacy of SHR9146 (also known as HTI-1090),[238,239] combined with the experimental PD-1 inhibitor SHR-1210 with or without the vascular endothelial growth factor receptor (VEGFR) inhibitor apatinib,[240–243] are being assessed in patients with advanced or metastatic solid tumors (NCT03491631).

Concluding remarks

Most investigators in the field agree that IDO1 inhibition can synergize with immune checkpoint blockers. While immune checkpoint blockers remove molecular brakes on cytotoxic T cells, they also stimulate the production of IDO1, which, in a negative feedback loop involving AHR activation, shuts down the immune response. Thus, IDO1-targeting drugs should enhance immune checkpoint blockers efficacy. Although our understanding of the biological effects of IDO1 inhibitors is incomplete, these compounds appear to trigger efficient antineoplastic effects along with the re(activation) of anticancer immunosurveillance, at least in preclinical tumor models. However, clinical efficacy remains limited. The exact mechanisms by which IDO1 restrains the immune system as well as the nature of the immune cells affected by IDO1 remains unclear. In particular, precisely determining to which extent IDO1 inhibitors operate on-target may allow for the development of novel agents that would exclusively trigger tumor-targeting immune response without systemic side effects. Indeed, some IDO1 inhibitors directly bind to the AHR[88] and could

therefore have immunosuppressive effects as Kyn does, which would be the opposite of the drug's intent. Along the same line, the failure of numerous trials implicating epacadostat has highlighted the need of in-depth research of modes of action before launching combinatorial regimens. Therefore, it appears urgent to disentangle the signaling pathways and metabolic circuitries influenced by IDO1.

Abbreviations

1MT	1-methyl-tryptophan
ADCC	Antibody-dependent cellular cytotoxicity
CTL	Cytotoxic T lymphocyte
EMT	Epithelial-mesenchymal transition
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
IDO	Indoleamine 2,3-dioxygenase
IFN	Interferon
IL	Interleukin
Kyn	*L*-kynurenine
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cells
MDT	Maximum tolerated dose
MIBC	Muscle-invasive bladder cancer
NK	Natural killer
NSCLC	Non-small cell lung cancer
PDT	Photodynamic therapy
RCC	Renal cell carcinoma
TRAE	Treatment-related adverse event
T_{REG}	Regulatory T
Trp	*L*-tryptophan

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