**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.

**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). 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. 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.

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. 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. According to current knowledge, the pleiotropic role of IDO in cancer includes the suppression of cytotoxic T lymphocytes (CTL) and natural killer (NK) cells, the generation and activation of regulatory T (TREG) cells and myeloid-derived suppressor cells (MDSCs) as well as the promotion of tumor angiogenesis. The immunomodulatory functions of IDO1 can be attributed to Trp starvation and increased Kyn levels. More specifically, Trp depletion induces cell cycle arrest of T cells and apoptosis through inhibition of the mechanistic target of rapamycin complex 1 (mTORC1), while inducing a stress response that activates the general control nondepressible 2 (GCN2). 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 TREG cells. Alongside, IDO1-expressing dendritic cells (DCs) have been shown to mediate immunosuppressive functions independent of Trp depletion and Kyn accumulation. 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.

IDO1 is widely overexpressed in tumor cells, which has been predominantly associated with poor prognosis. Similarly, increased circulating levels of Trp metabolites, such as indoxyl acetate and indoxyl sulfate, have been linked to hematologic malignancies.
as Kyn, have been detected in patients with various cancers and have been attributed a poor predictive value in some cohorts.\textsuperscript{40–42} Also, IDO1 expression in tumor cells has been linked to the status of the oncosuppressor gene bridging integrator 1 (BIN1).\textsuperscript{43,44} BIN1 is one of the most frequently downregulated genes in human cancer,\textsuperscript{45} due to either abnormal RNA splicing patterns compromising its tumor suppressor function,\textsuperscript{46–48} or increased gene methylation abolishing its expression.\textsuperscript{49,50} In particular, BIN1 is absent or underexpressed in various human neoplasms, such as neuroblastoma,\textsuperscript{51} melanoma,\textsuperscript{52} as well as breast, lung, colorectal and prostate carcinoma.\textsuperscript{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.\textsuperscript{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.\textsuperscript{54} Likewise, higher Kyn/Trp ratio have been shown to predict resistance to programmed cell death 1 (PD1D1, best known as PD-1) blockade in patients with non-small cell lung carcinoma (NSCLC).\textsuperscript{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).\textsuperscript{57}

Thus, IDO inhibition stands out as a promising strategy to (re)instigate 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.\textsuperscript{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.\textsuperscript{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)instigate anticancer immunosurveillance since the publication by Hornyák \textit{et al.} dealing with this topic.\textsuperscript{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.\textsuperscript{65} It is by far the most employed IDO inhibitor in the preclinical literature. Unlike its \textit{L} isomer, which has shown weak inhibitory activity, \textit{D}-1MT isomer neither binds nor inhibits the purified IDO1 enzyme while demonstrating antitumor activity.\textsuperscript{66–68} Therefore, clinical development focused on \textit{D}-1MT (best known as indoximod or NLG8189).\textsuperscript{69} In contrast to direct enzymatic inhibitors of IDO1, indoximod acts downstream of IDO1 to stimulate mTORC1, possibly lowering risks of drug resistance.\textsuperscript{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),\textsuperscript{71} advanced prostate\textsuperscript{72} and lung cancer.\textsuperscript{73} Indeed, IDO1 inhibition with 1MT, synergized with radiotherapy to downregulate T\textsubscript{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.\textsuperscript{73} D-1MT and CTLA4 blockers administration mediated improved therapeutic effects in treatment resistant IDO1-overexpressing HCCs in both subcutaneous and hepatic orthotopic models.\textsuperscript{71} Additionally, CTLA4 blockade induced the IFNγ-dependent upregulation of IDO1 in chemoresistant (but not sensitive) HCCs in mice.\textsuperscript{71} At last, IDO activity positively correlates with disease stage in prostate cancer patients,\textsuperscript{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.\textsuperscript{72} Consistent with the immunosuppressive activity of IDO in this setting, \textit{ex vivo} stimulation of peripheral blood cells with 1-MT increased T cell responses to vaccination.\textsuperscript{72} Recently, Hu \textit{et al.} also demonstrated that a methyltryptophan-paclitaxel (MP) albumin-bound drug conjugate (that links indoximod to the microtubular poison paclitaxel\textsuperscript{74–77} through an ester bond) not only significantly elevates the tumor levels of indoximod and local CD8\textsuperscript{T} populations, but reduces granulocyte-like myeloid derived suppressor cells (G-MDSCs) and T\textsubscript{REG} cells.\textsuperscript{78}

**Epacadostat (INCB024360)**

Epacadostat, also known as INCB024360, is an orally available reversible competitive IDO1 inhibitor. Wachowska and colleagues reported that photodynamic therapy (PDT)\textsuperscript{79–82} induced IDO1 expression within neoplasms as well as in tumor draining lymph node in murine orthotopic breast cancer models.\textsuperscript{83} Mechanistically, granulocytic CD11b\textsuperscript{L}Ly6G\textsuperscript{+} myeloid cells were the major source of IDO1 and strongly infiltrated the tumor bed following PDT.\textsuperscript{83} Although less abundant after PDT, monocyctic CD11b\textsuperscript{L}Ly6C\textsuperscript{+} myeloid cells, could also upregulate IDO1.\textsuperscript{83} Interestingly, depending on the therapeutic scheme of PDT administration, IDO-induced immunosuppression can either be beneficial or lead to systemic toxicity.\textsuperscript{83} Although IL-6 neutralization restored antitumor efficacy, it abolished the synergistic effect of epacadostat and PDT.\textsuperscript{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)\textsuperscript{84–87} and the AHR.\textsuperscript{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.\textsuperscript{89} IDO1 inhibition by navoximod has been shown to decrease plasmatic Kyn/Trp ratios and tumor Kyn levels.\textsuperscript{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. However, in the 4T1 murine breast tumor model, navoximod synergizes with doxorubicin to elicit an antitumor immune response and to control tumor growth.

**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. 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. Recently, BGS-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.

**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. Even at a low concentrations, BMS-986205 successfully inhibits IDO1 and lowers Kyn serum levels.

**Other IDO1 inhibitors**

A few additional IDO1 inhibitors are in preclinical development, including Trp analogs, imidazoles, phenyl benzenesulfonylhydrazides, N-hydroxamidines and LW106. 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. 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). 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. At least in part, these observations could be related to T cell infiltration and IFNg release in the cervical tumor microenvironment. 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.

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. They further established a correlation in melanoma samples between Kyn/Trp ratio and IDO1 but not TDO mRNA levels 4 weeks after nivolumab administration, 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), IDO1 and PD-1.

Mechanistically, following ADCP, absent in melanoma 2 (AIM2) is recruited to the phagosomes by FcγR signaling and activated by DNA from phagocytosed tumor cells. Upon activation, AIM2 upregulates PD-L1 andIDO 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 as well as in mouse models of HER2 breast carcinoma. Additionally, neoadjuvant trastuzumab treatment significantly upregulates PD-L1 and IDO on tumor-associated macrophages (TAMs) from HER2 breast cancer patients, correlating with poor trastuzumab responses. Collectively, these findings suggest that IDO inhibitors may provide syner-

**Published clinical trials**

Komrokji et al. reported preliminary results for the sole published clinical trial monitoring the efficacy of epacadostat administered as standalone intervention. 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. 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).

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.\textsuperscript{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-naïve 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.\textsuperscript{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,\textsuperscript{129-131} to 29 patients with stage IIIIB/IV NSCLC previously treated with platinum derivatives,\textsuperscript{132-136} chemotherapy in conjunction with a folic acid analogue.\textsuperscript{137-139} Seventy-nine percent of enrolled patients experienced TRAEs, 17% discontinued treatment due to such effects, one patient showed antitumor 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{143} 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 to be confirmed in additional Phase II studies.\textsuperscript{144,143,144} 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. 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 \textit{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 \textit{versus} 10% in individuals receiving the combinatorial regimen).\textsuperscript{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.\textsuperscript{145} Indeed, it remains to be elucidated whether IDO1 constitutes a robust target for the development of antitumor 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.\textsuperscript{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)\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{153,154} Jung et al. reported preliminary results from the
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.155 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, lymphopenia, 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 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 combination 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 vaccine that enhances an immune response against brachyury,39 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,166 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 combination 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 bevacizumab170,171 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)
| Drug        | Indication                        | Status              | Phase | Co-therapy                                                                 | NCT             |
|------------|-----------------------------------|---------------------|-------|-----------------------------------------------------------------------------|-----------------|
| BMS-986205 | Advanced solid tumors             | Not recruiting      | I/II  | As single agent then combined with nivolumab                              | NCT03792750     |
|            |                                   | Recruiting          | I/II  | Combined with nivolumab and relatlimab                                    | NCT03459222     |
| Bladder cancer |                                   | Combined with nivolumab ± BCG | I/II  |                              | NCT03519256     |
| Endometrial cancer | Recruiting  | Combined with cisplatin, gemcitabine and nivolumab | III    |                              | NCT03661320     |
| Glioblastoma | Recruiting                        | Combined with nivolumab | I     |                              | NCT04106414     |
| HCC        | Recruiting                        | Combined with nivolumab ± temozolomide | III    |                              | NCT04047706     |
| HNSCC      | Recruiting                        | Combined with nivolumab | I/II  |                              | NCT03695250     |
| Melanoma   | Withdraw                           | Combined with nivolumab | II    |                              | NCT04007588     |
| HCC        | Recruiting                        | Combined with nivolumab ± chemotheraphy | III    |                              | NCT03417037     |
| NSCLC      | Withdraw                           | Combined with pembrolizumab | II    |                              | NCT03823673     |
| Epacadostat| Advanced rectal cancer            | Suspended           | I     | Combined with XELOX regimen and radiotherapy                            | NCT03516708     |
| Bladder cancer | Not yet recruiting                   | Combined with pembrolizumab | II    |                              | NCT03823131     |
| ESCC       | Not yet recruiting                 | Combined with pembrolizumab ± tavo-EP gene therapy | II    |                              | NCT03532295     |
| Gastroesophageal adenocarcinoma |                                 | Combined with pembrolizumab | II    |                              | NCT03463161     |
| Glioblastoma Glioma | Not yet recruiting                   | Combined with pembrolizumab and tavo-EP gene therapy | II    |                              | NCT03493945     |
| HNSCC      | Recruiting                        | Combined with pembrolizumab | II    |                              | NCT03602586     |
| Metastatic prostate cancer | Recruiting  | Combined with ALT-03, BN-Brachyury and M7824 | I/II  |                              | NCT03432676     |
| Ovarian clear cell carcinoma | Suspended  | Combined with pembrolizumab | I     |                              | NCT04049669     |
| Pancreatic cancer | Withdrawal                         | Combined with pembrolizumab | II    |                              | NCT03915405     |
| Indoximod  | Pediatric solid tumors            | Recruiting          | II    | Combined with chemoradiotherapy                                           | NCT03491631     |
| KHK2455    | Bladder cancer                    | Recruiting          | I     | Combined with nivolumab                                                  | NCT03491631     |
| SHR9146    | Advanced solid tumors             | Recruiting          | I     | Combined with SHR-1210 ± apatinib                                        |                 |

**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, capecitabe + 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), and reducing the relative amount of tumor-infiltrating CD4+CD25+FOXP3+ T_{REG} cells 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, but also increases overall survival (by ~3 months) in advanced urothelial carcinoma and exhibits good tolerability when administered to patients with advanced solid tumors in combination with epacadostat. Moreover, Chu et al. have recently demonstrated that the manipulation of the immune microenvironment with IDO1 inhibition enhances patient responses to existing therapies.

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) for preoperative chemoradiotherapy, has been suspended to ensure patient safety during the Covid19 epidemics.

BMS-986205 is mainly being administered to cancer patients simultaneously receiving nivolumab (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 (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 and the toll like receptor 2 (TLR2)/TLR4 agonist HTI-1090, bacillus Calmette–Guérin (BCG), and the DNA alkylating agents lomustine and temozolomide. Finally, the safety and efficacy of SHR9146 (also known as HTI-1090), combined with the experimental PD-1 inhibitor SHR-1210 with or without the vascular endothelial growth factor receptor (VEGFR) inhibitor apatinib, 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 anti-neoplastic effects along with the reactivation of anticaner 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 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-tryptophan
- mAb: Monoclonal antibody
- MDSC: Myeloid-derived suppressor cells
- 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
- TREG: Regulatory T
- Trp: L-tryptophan

**Acknowledgments**

LG is supported by a Breakthrough Level 2 grant from the US Department of Defense (DoD), Breast Cancer Research Program (BRCR) (#B180476P1), by the 2019 Laura Ziskin Prize in Translational Research (#ZP-6177, PI: Formenti) from the Stand-Up to Cancer (SU2C), by a Mantle Cell Lymphoma Research Initiative (MCL-RI, PI: Chen-Kiang) grant from the Leukemia and Lymphoma Society (LLS), by a startup grant from the Dept. of Radiation Oncology at Weill Cornell Medicine (New York, US), by industrial collaborations with Lytix (Oslo, Norway) and Phosplatin (New York, US), and by donations from Phosplatin (New York, US), the Ligue contre le Cancer (équipe labellisée); Cancéropôle Ile-de-France; US23/CNRS UMS3655; Association pour la recherche sur le cancer (ARC); UHCs (New York, US), and by donations from Phosplatin (New York, US), the LeDucq Foundation; the RHU Torino Lumière; the Seerave Institut Universitaire de France; LeDucq Foundation; the LabEx Immuno-Association “Le Cancer du Sein, Parlons-en!”; Cancéropôle Ile-de-France; UHCs (New York, US), and by donations from Phosplatin (New York, US), the European Research Area frame of E-Rare-2, the ERA-Net for Research on Rare Diseases; AMMICa Agence National de la Recherche (ANR) – Projets blancs; ANR under the Republic). GK is supported by the Ligue contre le Cancer (équipe labellisée); Fondation Carrefour; High-end Foreign Expert Program in China; the SIRIC Stratified Oncology Cell DNA Repair and Tumor Personalized Medicine (CARPEM).

**References**

1. Downay AB, Tuttle JB, Verhoest PR. Challenges and opportunities in the discovery of new therapeutics targeting the kynurenine pathway. J Med Chem. 2015;58(22):8762–8782. doi:10.1021/acs.jmedchem.5b04061.

2. Mellor AL, Munn DH. Tryptophan catabolism and regulation of adaptive immunity. J Immunol. 2003;170:5809–5813. doi:10.4049/jimmunol.170.12.5809.

3. Elad Y, van der Leek AP, Yanishevsky Y, Kozyszyk AJ. The kynurenine pathway as a novel link between allergy and the gut microbiome. Front Immunol. 2017;8:1374. doi:10.3389/fimmu.2017.01374.

4. Platten M, Nollen EAA, Rohrig UF, Fallarino F, Opitz CA. Tryptophan metabolism as a common therapeutic target in cancer, neurodegeneration and beyond. Nat Rev Drug Discov. 2019;18:379–401.

5. Yoshida R, Imanishi J, Oku T, Kishida T, Hayashi O. Induction of pulmonary indoleamine 2,3-dioxygenase by interferon. Proc Natl Acad Sci U S A. 1981;78:129–132. doi:10.1073/pnas.78.1.129.

6. Munn DH, Zhou M, Attwood J, Boldarev I, Conway SJ, Marshall B, Brown C, Mellor AL. Prevention of allogeneic fetal rejection by tryptophan catabolism. Science. 1998;281:1191–1193. doi:10.1126/science.281.5380.1191.

7. Sidransky H. Tryptophan and carcinogenesis: review and update on how tryptophan may act. Nutr Cancer. 1997;29:181–194. doi:10.1080/10498928709514623.

8. Uyttenhove C, Ploetze I, Theate I, Stroobant V, Colaud D, Parmentier N, Boon T, Van den Eynde BJ. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med. 2003;9(10):1269–1274. doi:10.1097/01.nm934.

9. Munn DH, Shafizadeh E, Attwood JT, Boldarev I, Pashine A, Mellor AL. Inhibition of T cell proliferation by macrophage tryptophan catabolism. J Exp Med. 1999;189:1363–1372. doi:10.1084/jem.189.1363.

10. Prendergast GC, Malachowski WJ, Mondal A, Scherle P, Muller AJ. Indoleamine 2,3-dioxygenase and its therapeutic inhibition in cancer. Int Rev Cell Mol Biol. 2018;336:175–203.

11. Prendergast GC, Smith C, Thomas S, Mandik-Nayak L, Laury-Kleintop I, Metz R, Muller AJ. Indoleamine 2,3-dioxygenase pathways of pathogenic inflammation and immune escape in cancer. Cancer Immunol Immunother. 2014;63(7):721–735. doi:10.1007/s00262-014-1549-4.

12. Terness P, Bauer TM, Rose I, Dufour C, Watzlik A, Simon H, Opelz G. Inhibition of allogeneic T cell proliferation by indoleamine 2,3-dioxygenase-expressing dendritic cells: mediation of suppression by tryptophan metabolites. J Exp Med. 2002;196:447–457. doi:10.1084/jem.20020052.

13. Rao S, Gharib K, Han A. Cancer Immunosurveillance by T Cells. Int Rev Cell Mol Biol. 2019;342:149–173.

14. Frumento G, Rotondo R, Tonetti M, Benatti U, Conte R, Moretta L, Moretta A, Vitale M. The tryptophan catabolite 1-methyl-tryptophan inhibits the surface expression of NKp46- and NKG2D-activating receptors and regulates NK-cell function. Blood. 2004;104(18):5809–5816.

15. Prendergast GC, Smith C, Thomas S, Mandik-Nayak L, Laury-Kleintop I, Metz R, Muller AJ. Indoleamine 2,3-dioxygenase pathways of pathogenic inflammation and immune escape in cancer. Cancer Immunol Immunother. 2014;63(7):721–735. doi:10.1007/s00262-014-1549-4.

16. Fallarino F, Grohmann U, Hwang KW, Aronboa C, Vaccia C, Bianchi R, Belladonna ML, Fioretti MC, Alegre M-L, Puccetti P, et al. Modulation of tryptophan catabolism by regulatory T cells. Nat Immunol. 2003;4(12):1206–1212. doi:10.1038/ni003.

17. Schaff MB, Garg AD, Agostonis P. Defining the role of the tumor vasculature in antitumor immunity and immunotherapy. Cell Death Dis. 2018;9:115. doi:10.1038/s41419-017-0061-0.
18. Smith C, Chang MY, Parker KH, Beury DW, DuHadaway JB, Flick HE, Boulden J, Sutanto-Ward E, Soler AP, Laury-Kleintop LD, et al. IDO is a nodal pathogenic driver of lung cancer and metastasis development. Cancer Discov. 2012;2:722–735. doi:10.1158/2159-8290.CD-12-0014.

19. Bronte V, Brandau S, Chen S-H, Colombo MP, Frey AB, Greten TF, Manduziato S, Murray PJ, Ochoa A, Ostrand-Rosenberg S, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. Nat Commun. 2016;7(1):12150. doi:10.1038/ncomms12150.

20. Elliott LA, Doherty GA, Sheahan K, Ryan EJ. Human tumor-infiltrating myeloid cells: phenotypic and functional diversity. Front Immunol. 2017;8:86. doi:10.3389/fimmu.2017.00086.

21. Gaber T, Chen Y, Krauss PL, Buttgereit F. Metabolism of T lymphocytes in health and disease. Int Rev Cell Mol Biol. 2019;342:95–148.

22. van Baren N, Van den Eynde BJ. Tryptophan-degrading enzymes in tumor immune resistance. Front Immunol. 2015;6:34. doi:10.3389/fimmu.2015.00034.

23. Eichner R, Fernandez-Saiz V, Targosz BS, Bassermann F. Cross talk networks of mammalian target of rapamycin signaling with the ubiquitin proteasome system and their clinical implications in multiple myeloma. Int Rev Cell Mol Biol. 2019;343:219–297.

24. Bilir C, Sarisozen C. Indoleamine 2,3-dioxygenase (IDO): only an enzyme or a checkpoint controller? J Oncol Sci. 2017;3(2):52–56. doi:10.1016/j.jons.2017.04.001.

25. Munn DH, Sharma MD, Baban B, Harding HP, Zhang Y, Ron D, Mellor AL. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. Immunology. 2005;22:633–642. doi:10.1016/j.immuni.2005.03.013.

26. Fougeray S, Mami I, Bertho G, Beaune P, Thervet E, Pallet N. Tryptophan depletion and the kinase GCN2 mediate IFN-gamma-induced autophagy. J Immunol. 2012;189:2954–2964. doi:10.4049/jimmunol.1201214.

27. McGaha TL.IDO-GCN2 and autothagy in inflammation. Oncotarget. 2015;6:21771–21772. doi:10.18632/oncotarget.4846.

28. Nguyen NT, Kimura A, Nakahama T, Chinen I, Masuda K, Nohara K, Fuji-Kuriyama Y, Kishimoto T. Aaryl hydrocarbon receptor negatively regulates dendritic cell immunogenicity via a kynurenine-dependent mechanism. Proc Natl Acad Sci U S A. 2010;107:19961–19966. doi:10.1073/pnas.101465107.

29. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aaryl hydrocarbon receptor can generate regulatory T cells. J Immunol. 2010;185(6):3190–3198. doi:10.4049/jimmunol.0903670.

30. Grohmann U, Puccetti P. The Coevolution of IDO1 and AhR in the emergence of the regulatory T Cells in mammals. Front Immunol. 2015;6:58. doi:10.3389/fimmu.2015.00058.

31. Kotisias F, Cebrian I, Allootti A. Antigen processing and presentation. Int Rev Cell Mol Biol. 2019;348:69–121.

32. Balan S, Saxena M, Bhardwaj N. Dendritic cell subsets and locations. Int Rev Cell Mol Biol. 2019;348:1–68.

33. Derks RA, Jankowska-Gan E, Xu Q, Burlingham WJ. Dendritic cell type. Immunity. 2015;42:3190–3198. doi:10.4049/jimmunol.1500345.

34. Muller AJ, Prendergast GC. Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. Nat Med. 2005;11:312–319. doi:10.1038/nm1196.

35. Pan K, Liang X, Zhang H, Zhao J, Wang D, Li J, Lian Q, Chang AE, Li Q, Xia J. Characterization of bridging integrator 1 (BIN1) as a potential tumor suppressor and prognostic marker in hepatocellular carcinoma. Mol Med. 2012;18:507–511. doi:10.1016/j.molmed.2011.03.019.

36. Prendergast GC, Muller AJ, Ramalingam A, Chang MY. BAR the door: cancer suppression by amphiphysin-like genes. Biochim Biophys Acta. 2009;1795:25–36. doi:10.1016/j.bjba.2008.09.001.

37. Ge K, Duhadaway J, Du W, Herlyn M, Rodeck U, Prendergast GC. Mechanism for elimination of a tumor suppressor: aberrant splicing of a brain-specific exon causes loss of function of Bin1 in melanoma. Proc Natl Acad Sci U S A. 1999;96:9689–9694. doi:10.1073/pnas.96.17.9689.

38. Karmi R, de Stanchina E, Lowe SW, Sinha R, Mu D, Krainer AR. The gene encoding the splicing factor SF2/ASF is a proto-oncogene. Nat Struct Mol Biol. 2007;14:185–193. doi:10.1038/nsmb1209.

39. Pineda-Lucena A, Ho CSW, Mao DYL, Sheng Y, Laister RC, Tong SL, Leder P, Greten TF, Mandruzzato S, Murray PJ, Ochoa A, Ostrand-Rosenberg S, et al. A structure-based model of the c-Myc/Bin1 protein interaction shows alternative splicing of Bin1 and c-Myc phosphorylation are key binding determinants. J Mol Biol. 2005;351(1):182–194. doi:10.1016/j.jmb.2005.05.046.

40. Mckenna ES, Tamayo P, Cho Y-J, Tillman EJ, Mora-Blanco EL, Rosenbaum AD, Smith C, Chang MY, Parker KH, Beury DW, DuHadaway JB, Flick HE, Boulden J, Sutanto-Ward E, Soler AP, Laury-Kleintop LD, et al. IDO1 expression is associated with immune tolerance and poor prognosis in patients with surgically resected esophageal cancer. Ann Surg. 2019;269:1101–1108. doi:10.1097/SLA.0000000000002754.

41. Yu CP, Fu S-F, Chen X, Ye J, Ye Y, Kong L-D, Zhu Z. The clinicopathological and prognostic significance of IDO1 expression in human solid tumors: evidence from a systematic review and meta-analysis. Cell Physiol Biochem. 2018;49:134–143. doi:10.1159/000492849.

42. Berthon C, Fontenay M, Corm S, Briche I, Allorge D, Hennart B, Lhermitte M, Quesnel B. Metabolites of tryptophan catabolism are elevated in sera of patients with myelodysplastic syndromes and inhibit hematopoietic progenitor amplification. Leuk Res. 2013;37:573–579. doi:10.1016/j.leukres.2013.02.001.

43. Creelan BC, Antonia SJ, Bepler G, Garrett TJ, Simon GR, Solimini LH. Indoleamine 2,3-dioxygenase activity and clinical outcome following induction chemotherapy and concurrent chemoradiation in Stage III non-small cell lung cancer. Oncoimmunology. 2013;2(3):e23428. doi:10.4161/onci.23428.

44. Yoshikawa T, Hara T, Tsurumi H, Goto N, Hoshi M, Kitagawa J, Kanemura N, Kasahara S, Ito H, Takemura M, et al. Serum concentration of L-kynurenine predicts the clinical outcome of patients with diffuse large B-cell lymphoma treated with R-CHOP. Eur J Haematol. 2010;84(4):304–309. doi:10.1111/j.1600-0609.2009.01393.x.

45. Muller AJ, Duhadaway JB, Donover PS, Sutanto-Ward E, Prendergast GC. Induction of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. Nat Med. 2005;11:312–319. doi:10.1038/nm1196.

46. Brodin KH, van der Putten K, Zhang H, Zhou J, Wang D, Li J, Lian Q, Chang AE, Li Q, Xia J. Characterization of bridging integrator 1 (BIN1) as a potential tumor suppressor and prognostic marker in hepatocellular carcinoma. Mol Med. 2012;18:507–511. doi:10.1016/j.molmed.2011.03.019.
10

1. Tajiri T, Liu X, Thompson PM, Tanaka S, Suitsa S, Zhao H, Maris JM, Prendergast GC, Hogarty MD. Expression of a MYCN-interacting isoform of the tumor suppressor BIN1 is reduced in neuroblastomas with unfavorable biological features. Clin Cancer Res. 2003;9:3345–3355.

2. Chang MY, Boulden J, Sutanto-Ward E, Duhadaway JB, Soler AP, Muller AJ, Prendergast GC. Bin1 ablation in mammary gland delays tissue remodeling and drives cancer progression. Cancer Res. 2007;67:100–107. doi:10.1158/0008-5472.CAN-06-2742.

3. Ge K, Duhadaway J, Sakamura D, Wechsler-Reya R, Reynolds C, Prendergast GC. Losses of the tumor suppressor BIN1 in breast carcinoma are frequent and reflect deficits in programmed cell death capacity. Int J Cancer. 2000;85:376–383.

4. Marin-Acevedo JA, Dholaria B, Soyan AE, Knutson KL, Chumski S, Lou Y. Next generation of immune checkpoint therapy in cancer: new developments and challenges. J Hematol Oncol. 2018;11:39. doi:10.1186/s13045-018-0582-8.

5. Botticelli A, Cerbelli B, Lionetto L, Zizzari I, Salati M, Pisano A, Federica M, Simmaco M, Nuti M, Marchetti P, et al. Can IDO activity predict primary resistance to anti-PD-1 treatment in NSCLC? J Transl Med. 2018;16:219. doi:10.1186/s12976-018-1595-3.

6. Moss PK, Tran S, Minhas PS. Revisiting IDO and its value as a predictive marker for anti-PD-1 resistance. J Transl Med. 2019;17:31. doi:10.1186/s12976-019-1784-8.

7. Li H, Bullock K, Gjurao C, Braun D, Shukla SA, Bossé D, Lalani AKA, Gopal S, Jin C, Horak C, et al. Metabolomic adaptations and correlates of survival to immune checkpoint blockade. Nat Commun. 2019;10:4346. doi:10.1038/s41467-019-12361-9.

8. Muller AJ, Prendergast GC. Marrying immunotherapy with chemotherapy: why say IDO? Cancer Res. 2005;65:8065–8068. doi:10.1158/0008-5472.CAN-05-2213.

9. Pilotte L, Larrieu P, Stroobant V, Colau D, Dolusic E, Frederick R, Johnson M, Mellor AL, Prendergast GC. Losses of the tumor suppressor BIN1 in breast carcinoma are frequent and reflect deficits in programmed cell death capacity. Int J Cancer. 2000;85:376–383.

10. Krysko DV, Mathieu C, Agostinis P. ROS-induced autophagy in cell death. Autophagy. 2013;9:1292–1307. doi:10.4161/auto.25399.

11. Wachowska M, Stachura J, Tonecka K, Fidyt K, Braniewska A, Sas Z, Kotula I, Rygiel TP, Boon L, Golab J, et al. Inhibition of IDO activity of human dendritic cells. Blood. 2008;111 (4):2152–2154. doi:10.1182/blood-2007-10-116111.

12. Garry AD, Agostinis P. ER stress, autophagy and immunogenic cell death in photodynamic therapy-induced anti-cancer immune responses. Photochem Photobiol Sci. 2014;13:474–487. doi:10.1038/photobiol.2012.2.

13. Wachowska M, Stachura J, Tonecka K, Fidyt K, Braniewska A, Sas Z, Kotula I, Bygiel TP, Boon L, Golab J, et al. Inhibition of IDO leads to IL-6-dependent systemic inflammation in mice when the IDO activity of human dendritic cells. Blood. 2008;111 (4):2152–2154. doi:10.1182/blood-2007-10-116111.
combined with photodynamic therapy. Cancer Immunol Immunother. 2020. doi:10.1007/s00262-020-02528-5.

84. Shen S, Nisso-Santana M, Adjemian S, Takehara T, Malik S, Minoux H, Souqueur S, Mariño G, Lachkar S, Senovilla L, et al. Cytoplasmic STAT3 represses autophagy by inhibiting PKR activity. Mol Cell. 2012;48(5):667–680. doi:10.1016/j.molcel.2012.09.013.

85. Yang H, Yamazaki T, Pietrocola F, Zhou H, Zitvogel L, Ma Y, Kroemer G, Gust KM, Shariat SF. STAT3 inhibition enhances the therapeutic efficacy of immunogenic chemotherapy by stimulating type 1 interferon production by cancer cells. Cancer Res. 2015;75(18):3812–3822. doi:10.1158/0008-5472.CAN-15-1122.

86. Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer. 2009;9:798–809. doi:10.1038/nrc2734.

87. Johnson DE, O’Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Oncol. 2018;15:234–248. doi:10.1038/nrclinonc.2018.8.

88. Litzenburger UM, Opitz CA, Sahm F, Rauschenbach KJ, Trump S, Johnson DE, O’Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Oncol. 2018;15:234–248. doi:10.1038/nrclinonc.2018.8.

89. Nafia I, Toulmonde M, Bortolotto D, Chaibi A, Bodet D, Rey C, Vitale I, Goubar A, Baracco EE, Remédios C, et al. Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy. Nat Med. 2014;20:1301–1309. doi:10.1038/nm.3944.

90. Winters M, DuHadaway JB, Pham KN, Lewis-Ballester A, Badir S, Wai J, Sheik E, Yeh S-R, Prendergast GC, Muller AJ, et al. DIaryl hydroxylamines as pan or dual inhibitors of indoleamine 2,3-dioxygenase-1, indoleamine 2,3-dioxygenase-2 and tryptophan 2,3-dioxygenase. Eur J Med Chem. 2019;162:455–464. doi:10.1016/j.ejmech.2018.11.010.

91. Fu R, Zhang Y-W, Li H-M, Li Y-C, Zhao L, Guo Q-L, Lu T, Weiss SJ, Li Z-Y, Wu Z-Q, et al. LW106, a novel indoleamine 2,3-dioxygenase 1 inhibitor, suppresses tumour progression by limiting stroma-immune crosstalk and cancer stem cell enrichment in tumour micro-environment. Br J Pharmacol. 2018;175(14):3034–3049. doi:10.1111/bph.14351.

92. Prendergast GC, Malachowski WP, DuHadaway JB, Muller AJ. Discovery of IDO1 Inhibitors: from Bench to Bedside. Cancer Res. 2017;77:6795–6811. doi:10.1158/0008-5472.CAN-17-2285.

93. Heeren AM, van Dijk I, Berry DRAI, Khellil M, Ferris D, Kole J, Musters RJP, Thijssen VL, Mom CH, Kenter GG, et al. Indoleamine 2,3-dioxygenase expression pattern in the tumor microenvironment predicts clinical outcome in early stage cervical cancer. Front Immunol. 2018;9:1598. doi:10.3389/fimmu.2018.01598.

94. Li H, Ning S, Ghandi M, Kryukov GV, Gopal S, Deik A, Souza A, Pierce K, Keskula P, Hernandez D, et al. The landscape of cancer cell line metabolism. Nat Med. 2019;25:850–860. doi:10.1038/s41591-019-0404-8.

95. Wong DJ, Hurviz SA. Recent advances in the development of anti-HER2 antibodies and antibody-drug conjugates. Ann Transl Med. 2014;2:122.

96. Baselga J, Albanell J. Mechanism of action of anti-HER2 monoclonal antibodies. Ann Oncol. 2001;12(Suppl 1):S35–41. doi:10.1093/annonc/12.suppl_1.S35.

97. Su S, Zhao J, Xing Y, Zhang X, Liu J, Ouyang Q, Chen J, Su F, Liu Q, Song E, et al. Immune checkpoint inhibition overcomes ADCC-induced immunosuppression by macrophages. Cell. 2018;175(442–457):e22. doi:10.1016/j.cell.2018.09.007.

98. Antibody-dependent cellular cytotoxicity renders macrophages immunosuppressive. Cancer Discov. October 12 2018. doi:10.1158/2159-8290.CD-RW2018-176.

99. Lopez-Soto A, Gonzalez S, Smyth MJ, Galluzzi L. Control of metastasis by NK Cells. Cancer Cell. 2017;32:135–154. doi:10.1016/j.ccell.2017.06.009.

100. Vanpouille-Box C, Demaria S, Fornenti SC, Galluzzi L. Cytosolic DNA sensing in organismal tumor control. Cancer Cell. 2018;34:361–378. doi:10.1016/j.ccell.2018.05.013.

101. Kroemer G, Senovilla L, Galluzzi L, Andre F, Zitvogel L. Natural and therapy-induced immunosurveillance in breast cancer. Nat Med. 2015;21:1128–1138. doi:10.1038/nm.3944.

102. Mittal D, Vijayan J, Neijssen J, Kreijtz J, Habraken MMJ, Van Enenmaa H, Van Elsaas A, Smyth MJ. Blockade of ErbB2 and PD-1/PD-L1 using a bispecific antibody to improve targeted anti-ErbB2 therapy. Oncomunology. 2019;8:e1648171. doi:10.1000/j.11523-017-0547-9.

103. Bai Z, Huang H, Chen J, Zhang X, Ding Y. Identification of novel imidazoles as IDO1 inhibitors through microwave-assisted one-pot multicomponent reactions. Arch Pharm (Weinheim). 2019;352:e1900165. doi:10.1002/ardp.201900165.

104. Cheng MF, Hung M-S, Song J-S, Lin S-Y, Lin Y-W, Wu M-H, Hsiao W, Hsieh C-L, Wu J-S, Chao Y-S, et al. Discovery and structure-activity relationships of phenyl benzenesulfonylhydrazides as novel indoleamine 2,3-dioxygenase inhibitors. Bioorg Med Chem Lett. 2014;24:3403–3406. doi:10.1016/j.bmcl.2014.05.084.

105. Winters M, DuHadaway JB, Pham KN, Lewis-Ballester A, Badir S, Wai J, Sheik E, Yeh S-R, Prendergast GC, Muller AJ, et al. Diaryl hydroxylamines as pan or dual inhibitors of indoleamine 2,3-dioxygenase-1, indoleamine 2,3-dioxygenase-2 and tryptophan 2,3-dioxygenase. Eur J Med Chem. 2019;162:455–464. doi:10.1016/j.ejmech.2018.11.010.

106. Yeh S-R, Prendergast GC, Muller AJ, et al. Indoleamine 2,3-dioxygenase (IDO): recent developments and first clinical experiences. Target Oncol. 2018;13:125–140. doi:10.1007/s11523-017-0547-9.
116. Triulzi T, Forte L, Regondi V, Di Modica M, Ghirelli C, Carcangiu ML, Sondrini L, Balsari A, Tagliabue E. HER2 signaling regulates the tumor immune microenvironment and trastuzumab efficacy. Oncoimmunology. 2019;8:e152942. doi:10.1080/2162402X.2018.1512942.

117. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, Castro G, Untch M, Smith I, Gianni L, et al. 11 years’ follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389:1195–1205. doi:10.1016/S0140-6736(16)32616-2.

118. Tolaney SM, Wardley AM, Zambelli S, Hilton JF, Troso-Sandoval TA, Ricci F, Im S-A, Kim S-B, Johnston SR, Chan A, et al. Atebrinaclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised, open-label, phase 2 trial. Lancet Oncol. 2020;21(6):763–775. doi:10.1016/S1470-2045(20)30112-1.

119. Dumas A, Vaz Luis I, Bovagnet T, El Mouhebb M, Di Meglio A, Pinto S, Charles C, Dauchy S, Delalage S, Arveux P, et al. Impact of breast cancer treatment on employment: results of a multicenter prospective cohort study (CANTO). J Clin Oncol. 2020;38:734–743. doi:10.1200/JCO.2019.39.0726.

120. Modi S, Saura C, Yamashita T, Park YH, Kim S-B, Tamura K, Andre F, Iwata H, Ito Y, Tsurutani J, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610–621. doi:10.1056/NEJMoa1914510.

121. Komroki RS, Weis S, Mailloux AW, Zhang L, Padron E, Sallman D, Lancet JE, Tinsley S, Nardelli LA, Pinilla-Ibarz J, et al. A phase II study to determine the safety and efficacy of the oral inhibitor of indoleamine 2,3-dioxygenase (IDO) enzyme INCB024360 in patients with myelodysplastic syndromes. Clin Lymphoma Myeloma Leuk. 2019;19(3):157–161. doi:10.1016/j.clml.2018.12.005.

122. Cseh AM, Niemeyer CM, Yoshimi A, Catala A, Frühwald MC, Hasle H, van den Heuvel-eibrink MM, Lauten M, De Moerloose B, Smith OP, et al. Therapy with low-dose azacitidine for MDS in children and young adults: a retrospective analysis of the EWOG-MDS study group. Br J Haematol. 2016;172(6):930–936. doi:10.1111/bjh.13915.

123. Jabbour E, Short NJ, Montalban-Braun R, Huang X, Bueso-Ramos CE, Liu J, Gan L, Zhang X-Y, Cao S-H, et al. A non-linear association between blood tumor mutation burden and prognosis in NSCLC patients receiving atezolizumab. Oncoimmunology. 2020;9(1):1731072. doi:10.1080/2162402X.2020.1731072.

124. Scott LJ. Azacitidine: a review in myelodysplastic syndromes and myeloproliferative neoplasms. Jabbour E, Short NJ, Montalban-Braun R, Huang X, Bueso-Ramos CE, Liu J, Gan L, Zhang X-Y, Cao S-H, et al. A non-linear association between blood tumor mutation burden and prognosis in NSCLC patients receiving atezolizumab. Oncoimmunology. 2020;9(1):1731072. doi:10.1080/2162402X.2020.1731072.

125. Vitale I, Sistigu A, Manic G, Rudqvist N-P, Trojanoski Z, Galluzzi L. Mutagenic and antigenic landscape in tumor progression and cancer immunotherapy. Trends Cell Biol. 2019;29(5):396–416. doi:10.1016/j.tcb.2019.01.003.

126. Michelle J, Vitale I, Galluzzi L, Adam J, Olaussen KA, Kepp O, Sennovilla T, Talhouqi I, Guegan J, Enot DP, et al. Cisplatin resistance associated with PARP hyperactivation. Cancer Res. 2013;73(7):2271–2280. doi:10.1158/0008-5472.CAN-12-3000.

127. Vaccelli E, Galluzzi L, Rousseau V, Rigoni A, Tesniere A, Delahaye N, Schlemmer M, Luckeraw A, Adjeman S, et al. Loss-of-function alleles of p53R2X and TLR4 fail to affect the response to chemotherapy in non-small cell lung cancer. Oncoimmunology. 2012;13(27):271–278. doi:10.1016/j.jci.2011.10.008.

128. Tolaney SM, Wardley AM, Zambelli S, Hilton JF, Troso-Sandoval TA, Ricci F, Im S-A, Kim S-B, Johnston SR, Chan A, et al. Atebrinaclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised, open-label, phase 2 trial. Lancet Oncol. 2020;21(6):763–775. doi:10.1016/S1470-2045(20)30112-1.
pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301; KEYNOTE-252): a phase 3, randomised, double-blind study. Lancet Oncol. 2019;20:1083–1097. doi:10.1016/S1470-2045(19)30274-8.

143. Luther C, Swami U, Zhang J, Milhem M, Zakaria Y. Advanced stage melanoma therapies: detailing the present and exploring the future. Crit Rev Oncol Hematol. 2019;133:99–111. doi:10.1016/j.critrevonc.2018.11.002.

144. Lara P, Bauer TM, Hamid O, Smith DC, Gajewski TF, Gangadhar TC, Somer BG, Schmidt EV, Zhang Y, Gowda H, et al. Epacadostat plus pembrolizumab in patients with advanced RCC: preliminary phase I/II results from ECHO-202/KEYNOTE-037. J Clin Oncol. 2017;35:15_suppl, 4515–4515.

145. Mazzarella L, Duso BA, Trapani D, Belli C, D’Amico P, Ferraro E, Viale G, Curigliano G. The evolving landscape of ‘next-generation’ immune checkpoint inhibitors: A review. Eur J Cancer. 2019;117:14–31. doi:10.1016/j.ejca.2019.04.035.

146. Garber K. A new cancer immunotherapy suffers a setback. Science. 2018;360:588. doi:10.1126/science.360.6389.588.

147. Hafner A, Bulyk ML, Jambhekar A, Lahav G. The multiple tumor suppressor p53 to mitochondria for cancer therapy. Cell Cycle. 2008;7:1949–1955. doi:10.4161/cc.7.13.6222.

148. Bykov VJN, Eriksson SE, Bianchi J, Wiman KG. Targeting mutant IDO in cancer: scientific rationale and therapeutic implications. Crit Rev Oncol Hematol. 2019;20:1083–1097. doi:10.1016/S1470-2045(19)30275-6.

149. Luther C, Swami U, Zhang J, Milhem M, Zakaria Y. Advanced stage melanoma therapies: detailing the present and exploring the future. Crit Rev Oncol Hematol. 2019;133:99–111. doi:10.1016/j.critrevonc.2018.11.002.

150. Mazzarella L, Duso BA, Trapani D, Belli C, D’Amico P, Ferraro E, Viale G, Curigliano G. The evolving landscape of ‘next-generation’ immune checkpoint inhibitors: A review. Eur J Cancer. 2019;117:14–31. doi:10.1016/j.ejca.2019.04.035.

151. Luther C, Swami U, Zhang J, Milhem M, Zakaria Y. Advanced stage melanoma therapies: detailing the present and exploring the future. Crit Rev Oncol Hematol. 2019;133:99–111. doi:10.1016/j.critrevonc.2018.11.002.

152. Nayak-Kapoor A, Hao Z, Sadek R, Dobbins R, Marshall L, Bahary N, Wang-Gillam A, Somer BG, Lee JS, O'Rourke MA, Bykov VJN, Eriksson SE, Bianchi J, Wiman KG. Targeting mutant IDO in cancer: scientific rationale and therapeutic implications. Crit Rev Oncol Hematol. 2019;20:1083–1097. doi:10.1016/S1470-2045(19)30275-6.

153. Luther C, Swami U, Zhang J, Milhem M, Zakaria Y. Advanced stage melanoma therapies: detailing the present and exploring the future. Crit Rev Oncol Hematol. 2019;133:99–111. doi:10.1016/j.critrevonc.2018.11.002.

154. Luther C, Swami U, Zhang J, Milhem M, Zakaria Y. Advanced stage melanoma therapies: detailing the present and exploring the future. Crit Rev Oncol Hematol. 2019;133:99–111. doi:10.1016/j.critrevonc.2018.11.002.

155. Ricciuti B, Leonardi GC, Puccetti P, Fallarino F, Bianconi V, Sahebkar A, Baglio S, Chiari R, Pirro M. Targeting indoleamine-2,3-dioxygenase in cancer: scientific rationale and clinical evidence. Pharmacol Ther. 2019;196:105–116. doi:10.1016/j.pharmthera.2018.12.004.

156. Luke JJ, Taberner J, Joshua A, Desai J, Varga AI, Moreno V, Desai J, Markman B, Gomez-Roca CA, De Braud FG, Patel SP, et al. BMS-986205, an indoleamine 2,3-dioxygenase 1 inhibitor (IDO1), in combination with nivolumab (nivo): updated safety across all tumor cohorts and efficacy in advanced bladder cancer (advBC). J Clin Oncol. 2019;37:7. doi:10.1200/JCO.2019.37.7_suppl.358.
181. Vacchelli E, Semeraro M, Adam J, Stoll G, Louvet E, Chaba K, Poirier-Colame VP, Dartigues P, Zitvogel L, Kroemer G. The impact of regulatory T cell infiltration in surgically resected esophageal cancer. Genes Cancer. 2017;8(4):20840–20850. doi:10.18632/oncotarget.4428.

182. Ciotti M, Angeletti S, Minieri M, Giovannetti M, Benvenuto D, Hakenberg OW. Nivolumab for the treatment of bladder cancer. Expert Opin Biol Ther. 2017;17:1309–1315. doi:10.1080/13543784.2017.1307690.

183. Solinas C, Migliori E, De Silva P, Willard-Gallo K. LAG3: the immune checkpoint under the microscope. J Immunol. 2017;198(11):4985–4991. doi:10.4049/jimmunol.1700712.

184. Long L, Zhang X, Chen F, Pan Q, Phiphatwatchara P, Zeng Y, Zhou L. Characterization of a novel anti-human lymphocyte actin inducing receptor. J Immunol. 2015;194(12):6880–6890. doi:10.4049/jimmunol.1501653.

185. Solinas C, Migliori E, De Silva P, Willard-Gallo K. LAG3: the immune checkpoint under the microscope. J Immunol. 2017;198(11):4985–4991. doi:10.4049/jimmunol.1700712.

186. Hoehler T, von Wichert G, Schimanski C, Kanzler S, Moehler MH, Hinke A, Seufferlein T, Siebler J, Hochhaus A, Arnold D, et al. Phase II trial of capecitabine and oxaliplatin in combination with bevacizumab and imatinib in patients with metastatic colorectal cancer: AIO KRK 0205. Br J Cancer. 2013;109:1408–1413. doi:10.1093/bjc/azt349.

187. Pol J, Vacchelli E, Aranda F, Castoldi F, Eggermont A, Cremer I, Sautès-Fridman C, Fucikova J, Galon J, Spisek R, et al. Trial Watch: immunogenic cell death inducers for anticancer chemotherapy. Oncoimmunology. 2015;4(4):e1008866. doi:10.1080/2162402X.2015.1008866.

188. Hoehler T, von Wichert G, Schimanski C, Kanzler S, Moehler MH, Hinke A, Seufferlein T, Siebler J, Hochhaus A, Arnold D, et al. Phase II/III trial of capecitabine and oxaliplatin in combination with bevacizumab and imatinib in patients with metastatic colorectal cancer: AIO KRK 0205. Br J Cancer. 2013;109:1408–1413. doi:10.1093/bjc/azt349.
bladder cancer (NMIBC): checkMate 9UT. Journal of Clinical Oncology. 2019;37(Suppl):TPS493-TPS493

216. Yuh BE, Gladney W, Plesa G, Vapiwala N, Carpenter E, Maude SL, Lal P, Lacey SF, Melenhorst JJ, Sebro R, et al. A phase I clinical trial of PSMA-directed/TGFβ-insensitive CAR-T cells in metastatic castration-resistant prostate cancer. J Clin Oncol. 2019;37:7. doi: 10.1200/JCO.2019.37.7_suppl.TPS347.

215. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Grabosch S, Bulatovic M, Zeng F, Ma T, Zhang L, Ross M, Rentsch CA, Bosshard P, Mayor G, Rieken M, Puschel H, Wirth G, Martinez R, Tapia G, De Muga S, Hernández A, Cao MG, Ji N, Mukherjee N, Morales EE, Tomasini ME, Hurez V, Uehori J, Matsumoto M, Tsuji S, Akazawa T, Takeuchi O, Akira S, Mata-Haro V, Cekic C, Martin M, Chilton PM, Casella CR, Vanpouille-Box C, Hoffmann JA, Galluzzi L. Pharmacological modulation of nucleic acid sensors - therapeutic potential and persisting obstacles. Nat Rev Drug Discov. 2019;18:85–867. doi: 10.1038/s41573-019-0043-2.

214. Smith M, Garcia-Martinez E, Pitter MR, Facikova J, Spisek R, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: toll-like receptor agonists in cancer immunotherapy. Oncoimmunology. 2018;7:e1526250. doi: 10.21420/2018.1526250.

213. Vanpouille-Box C, Hoffmann JA, Galluzzi L. Pharmacological modulation of nucleic acid sensors - therapeutic potential and persisting obstacles. Nat Rev Drug Discov. 2019;18:85–867. doi: 10.1038/s41573-019-0043-2.

212. Mata-Haro V, Cekic C, Martin M, Chilton PM, Casella CR, Mitchell TC. The vaccine adjuvant monophosphoryl lipid A as a TRIF-biased agonist of TLR4. Science. 2007;316:1628–1632. doi: 10.1126/science.1138963.

211. Uehori J, Matsumoto M, Tsuji S, Akazawa T, Takeuchi O, Akira S, Mata-Haro V, Cekic C, Martin M, Chilton PM, Casella CR, Vanpouille-Box C, Hoffmann JA, Galluzzi L. Pharmacological modulation of nucleic acid sensors - therapeutic potential and persisting obstacles. Nat Rev Drug Discov. 2019;18:85–867. doi: 10.1038/s41573-019-0043-2.

210. Uehori J, Matsumoto M, Tsuji S, Akazawa T, Takeuchi O, Akira S, Mata-Haro V, Cekic C, Martin M, Chilton PM, Casella CR, Vanpouille-Box C, Hoffmann JA, Galluzzi L. Pharmacological modulation of nucleic acid sensors - therapeutic potential and persisting obstacles. Nat Rev Drug Discov. 2019;18:85–867. doi: 10.1038/s41573-019-0043-2.

209. Yuh BE, Gladney W, Plesa G, Vapiwala N, Carpenter E, Maude SL, Lal P, Lacey SF, Melenhorst JJ, Sebro R, et al. A phase I clinical trial of PSMA-directed/TGFβ-insensitive CAR-T cells in metastatic castration-resistant prostate cancer. J Clin Oncol. 2019;37:7. doi: 10.1200/JCO.2019.37.7_suppl.TPS347.

208. Yuh BE, Gladney W, Plesa G, Vapiwala N, Carpenter E, Maude SL, Lal P, Lacey SF, Melenhorst JJ, Sebro R, et al. A phase I clinical trial of PSMA-directed/TGFβ-insensitive CAR-T cells in metastatic castration-resistant prostate cancer. J Clin Oncol. 2019;37:7. doi: 10.1200/JCO.2019.37.7_suppl.TPS347.

207. Park J, Kim CG, Shim J-K, Kim JH, Lee H, Lee JE, Kim MH, Zhai L, Spranger S, Binder DC, Gritsina G, Lauing KL, Giles FJ, Patel MR, Ellerton J, Infante JR, Agrawal M, Gordon M, Aljumaily R, Britten CD, Dirix L, Lee K-W, Taylor M, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol. 2018;19(1):51–64. doi: 10.1016/S1470-2045(17)30900-2.

206. Hellmann MD, Ciuleanu T-E, Pluzanski A, Lee JS, Otterson GA, Audiger-Valette C, Minenca E, Lindaroud N, Burgers S, Salman P, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med. 2018;378:2093–2104. doi: 10.1056/NEJMoa1801946.

205. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melibar C, Choeurie TK, Plimack ER, Barthélémy P, Porta C, George S, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277–1290. doi: 10.1056/NEJMoa1712126.

204. Tripathi A, Plimack ER. Immunotherapy for urothelial carcinoma: current evidence and future directions. Curr Urol Rep. 2018;19:109. doi: 10.1007/s11934-018-0851-7.

203. Watanabe T, Gaedicke S, Guffart E, Firat E, Niedermann G. Adding indometh to hypofractionated radiotherapy with anti-PD-1 checkpoint blockade enhances early NK and CD8(+) T-cell-dependent tumor activity. Clin Cancer Res. 2020;26:945–956. doi: 10.1158/1078-0432.CCR-19-0476.

202. Zhai L, Spranger S, Binder DC, Gritsina G, Luang KL, Giles FJ, Wainwright DA. Molecular pathways: targeting IDO1 and other tryptophan dioxygenases for cancer immunotherapy. Clin Cancer Res. 2015;21(24):5427–5433. doi: 10.1158/1078-0432.CCR-15-0420.

201. Park J, Kim CG, Shim J-K, Kim JH, Lee H, Lee JE, Kim MH, Haam K, Jung I, Park S-H, et al. Effect of combined anti-PD-1 and anti-PD-L1 antibody avelumab against multiple carcinoma cell types. Oncoimmunology. 2018;7(11):e1460018. doi: 10.21420/2018.7.e1460018.

200. Oliver T, Moore MJ, Zimmermann A, Arning M. Long-term survival in patients with bladder cancer (NMIBC): checkMate 9UT. Journal of Clinical Oncology. 2018;36(21):2093–2104. doi: 10.1200/JCO.2018.36.21_suppl.e1526250.

199. Davis Y, Glaveo V, Song H, Zhang L, Beltz U, Wang X, Liu P, Liu X, Jiang Y, et al. Long-term survival of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Urol. 2015;193(6):1502–1507. doi: 10.1016/j.juro.2015.03.060.
231. Schiavoni G, Mattei F, Di Pucchio T, Santini SM, Bracci L, Belardelli F, Proietti E. Cyclophosphamide induces type I interferon and augments the number of CD44(hi) T lymphocytes in mice: implications for strategies of chemoimmunotherapy of cancer. Blood. 2000;95:2024–2030. doi: 10.1182/blood.V95.6.2024.

232. Schiavoni G, Sistigu A, Valentini M, Mattei F, Sestili P, Spadaro F, Sanchez M, Lorenzi S, D’Urso MT, Belardelli F, et al. Cyclophosphamide synergizes with type I interferons through systemic dendritic cell reactivation and induction of immunogenic tumor apoptosis. Cancer Res. 2011;71:768–778. doi: 10.1158/0008-5472.CAN-10-2788.

233. Brown RA, Herzig RH, Wolff SN, Frei-Lahr D, Pineiro L, Bolwell BJ, Lowder JN, Harden EA, Hande KR, Herzig GP, et al. High-dose etoposide and cyclophosphamide without bone marrow transplantation for resistant hematologic malignancy. Blood. 1990;76:473–479. doi: 10.1182/blood.V76.3.473.473.

234. Sirachainan N, Pakakasama S, Anurathapan U, Hansasuta A, Dhanachai M, Khongkhatithum C, Jinawath A, Mahachoklertwattana P, Hongeng S. Outcome of newly diagnosed high risk medulloblastoma treated with carboplatin, vincristine, cyclophosphamide and etoposide. J Clin Neurosci. 2018;56:139–142. doi: 10.1016/j.jocn.2018.06.028.

235. Jakacki RI, Cohen KJ, Buxton A, Krailo MD, Burger PC, Rosenblum MK, Brat DJ, Hamilton RL, Eckel SP, Zhou T, et al. Phase 2 study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: a report of the Children’s Oncology Group ACNS0423 study. Neuro Oncol. 2016;18, 1442–1450 (2016).

236. van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MCM, Delattre J-Y, Bernsen HJJ, Frenay M, Tijssen CC, Grisold W, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendrogloma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol. 2013;31(3):344–350. doi: 10.1200/JCO.2012.43.2229.

237. Wick W, Gorlia T, Bendszus M, Taphoorn M, Sahm F, Harting I, Brandes AA, Taal W, Domont J, Idbaih A, et al. Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med. 2017;377(20):1954–1963. doi: 10.1056/NEJMoa1707358.

238. Komiyi T, Huang CH. Updates in the clinical development of epacadostat and other indoleamine 2,3-dioxygenase 1 inhibitors (IDO1) for human cancers. Front Oncol. 2018;8:423. doi: 10.3389/fonc.2018.00423.

239. Xu X, Ren J, Ma Y, Liu H, Rong Q, Feng Y, Wang Y, Cheng Y, Ge R, Li Z, et al. Discovery of cyanopyridine scaffold as novel indoleamine-2,3-dioxygenase 1 (IDO1) inhibitors through virtual screening and preliminary hit optimisation. J Enzyme Inhib Med Chem. 2019;34(1):250–263. doi: 10.1080/14756366.2018.1480614.

240. Liu K, Ren T, Huang Y, Sun K, Bao X, Wang S, Zheng B, Guo W. Apatinib promotes autophagy and apoptosis through VEGFR2/STAT3/BCL-2 signaling in osteosarcoma. Cell Death Dis. 2017;8(8):e3015. doi: 10.1038/cddis.2017.422.

241. Scott LJ. Apatinib: a review in advanced gastric cancer and other advanced cancers. Drugs. 2018;78(7):747–758. doi: 10.1007/s40265-018-0903-9.

242. Xu J, Zhang Y, Jia R, Yue C, Chang L, Liu R, Zhang G, Zhao C, Zhang Y, Chen C, et al. Anti-PD-1 antibody SHR-1210 combined with apatinib for advanced hepatocellular carcinoma, gastric, or esophageagastic junction cancer: an open-label, dose escalation and expansion study. Clin Cancer Res. 2019;25:515–523. doi: 10.1158/1078-0432.CCR-18-2484.

243. Feng H, Cheng X, Kuang J, Chen L, Yuen S, Shi M, Liang J, Shen B, Jin Z, Yan J, et al. Apatinib-induced protective autophagy and apoptosis through the AKT-mTOR pathway in anaplastic thyroid cancer. Cell Death Dis. 2018;9:1030. doi: 10.1038/s41419-018-1054-3.