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Trial watch: IDO inhibitors in cancer therapy

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Abbreviations: AHR, aryl hydrocarbon receptor; BIN1, bridging integrator 1; CTLA4, cytotoxic T lymphocyte associated protein 4; DC, dendritic cell; FDA, Food and Drug Administration; GCN2, general control non-derepressible 2; HCC, hepatocellular carcinoma; IDO, indoleamine 2,3-dioxigenase; IFNγ, interferon γ; Kyn, *L*-kynurenine; NK, natural killer; ODN, oligodeoxynucleotide; TDO2, tryptophan 2,3-dioxigenase; TLR, *T*oll-like receptor; Treg, regulatory T cell; Trp, *L*-tryptophan.

Indoleamine 2,3-dioxigenase 1 (IDO1) is the main enzyme that catalyzes the first, rate-limiting step of the so-called "kynurenine pathway", i.e., the metabolic cascade that converts the essential amino acid *L*-tryptophan (Trp) into *L*-kynurenine (Kyn). IDO1, which is expressed constitutively by some tissues and in an inducible manner by specific subsets of antigen-presenting cells, has been shown to play a role in the establishment and maintenance of peripheral tolerance. At least in part, this reflects the capacity of IDO1 to restrict the microenvironmental availability of Trp and to favor the accumulation of Kyn and some of its derivatives. Also, several neoplastic lesions express IDO1, providing them with a means to evade anticancer immunosurveillance. This consideration has driven the development of several IDO1 inhibitors, some of which (including 1-methyltryptophan) have nowadays entered clinical evaluation. In animal tumor models, the inhibition of IDO1 by chemical or genetic interventions is indeed associated with the (re)activation of therapeutically relevant anticancer immune responses. This said, several immunotherapeutic regimens exert robust clinical activity in spite of their ability to promote the expression of IDO1. Moreover, 1-methyltryptophan has recently been shown to exert IDO1-independent immunostimulatory effects. Here, we summarize the preclinical and clinical studies testing the antineoplastic activity of IDO1-targeting interventions.

Introduction

In mammalian cells, the amino acid *L*-tryptophan (Trp) is mainly catabolized via the so-called "kynurenine pathway", i.e., the metabolic cascade that converts it into *L*-kynurenine (Kyn).[1,2] The first, rate-limiting step of the kynurenine pathway can be catabolized by three distinct enzymes, namely, indoleamine 2,3-dioxigenase 1 (IDO1), IDO2, and tryptophan 2,3-dioxigenase (TDO2).[1-7] IDO1 is by far the best characterized of these enzymes as it was involved in the host response to microbial challenges as early as in the late 1970s.[8-11] In particular, IDO1 was proposed to participate in the innate response to pathogens by virtue of its ability to deplete the inflammatory microenvironment of Trp, which is essential not only for most (if not all) eukaryotes, but also for several bacterial species.[12] Several cell types including specific subsets of dendritic cells (DCs), macrophages and immature monocytes express increased levels of IDO1 in response to inflammatory cues such as interferon γ (IFNγ) or signal transducer and activator of transcription 3 (STAT3)-activatory stimuli.[13-18] In 1998, Munn and colleagues demonstrated for the first time that IDO1 exerts immunosuppressive, rather than immunostimulatory, functions, as it prevents the rejection of allogenic fetuses by the maternal immune system.[19] This cornerstone discovery initiated an intense wave of investigation aimed at characterizing the molecular and cellular circuitries that underlie the immunomodulatory activity of IDO1.[1,20] In spite of such an experimental effort, the precise mechanisms by which IDO1 exerts immunosuppressive functions remain to be elucidated. Along similar lines, further experiments are required to understand to which extent IDO2 and TDO2 contribute to Trp catabolism in vivo.[21] Indeed, purified IDO2 exhibits enzymatic activity under specific experimental conditions, but it generally is 20–30-fold less active than IDO1.[22]

According to current models, IDO1 would limit innate and adaptive immune responses by two non-mutually exclusive mechanisms, i.e., by depleting immune effector cells of Trp,[12,23] and by promoting the accumulation of Kyn and some of its derivatives, 3-hydroxykynurenine and 3-hydroxyanthranilic acid.[24,25] A decrease in Trp availability (below 0.5-1 μM,

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according to Munn and colleagues) promotes indeed the accumulation of uncharged tRNA species, resulting in a general control non-derepressible 2 (GCN2)-dependent block in protein synthesis that is often accompanied by cell cycle arrest and (in immune cells) irresponsiveness to immunological challenges.[26-28] Along similar lines, Kyn, 3-hydroxykynurenine and 3-hydroxyanthanilic acid, which signal via the aryl hydrocarbon receptor (AHR),[29] have been shown not only to exert cytostatic and cytotoxic effects on various immune effectors, including $CD8^+$ T lymphocytes, natural killer (NK) cells and invariant NKT cells,[24,25,30-34] but also to inhibit T_H17 cells and to promote the differentiation of naïve $CD4^+$ T cells into $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs),[35-41] as well as the tolerogenic activity of DCs.[42-44] This said, some authors failed to observe a decrease in the proliferation rates of T lymphocytes even in culture media that were completely depleted of Trp.[30] Moreover, while IDO1 may cause significant reductions in Trp availability in vitro, it remains to be demonstrated whether a similar effect occurs in vivo, where Trp concentrations are in the range of 50–100 μM and local decreases in availability are expected to be rapidly compensated upon diffusion from surrounding tissues.[1] Taken together, these observations suggest that drops in the microenvironmental availability of Trp may not be sufficient to exert robust immunosuppressive effects in vivo. As a possibility, the accumulation of Kyn and Kyn derivatives may synergize with local limitations in Trp availability to potently inhibit the proliferation and activation of immune effector cells. This has been shown to occur in vitro.[45,46] Indirect mechanisms may also explain, at least in part, the biological activity of IDO1. IDO1-expressing DCs exert indeed broad and robust immunosuppressive effects as (1) they direct suppress the proliferation and effector of functions of cytotoxic T lymphocytes, NK cells and plasma cells;[14,33,47-49] (2) they promote the conversion of naïve $CD4^+$ T cells into $CD4^+CD25^+FOXP3^+$ Tregs and activate them;[47,48,50-53] and (3) they trigger the immunosuppressive activity in neighboring IDO1-expressing DCs (a process known as bystander suppression).[47,54,55] The upregulation of IDO1 by a specialized subset of DCs (plasmacytoid DCs)[56-58] has also been shown to contribute to the immunosuppressive activity of HIV-1.[59-63] Moreover, progressive HIV-1 infection has been associated with alterations in the intestinal microbiota that affect systemic Trp catabolism.[64] Finally, leukemic cells expressing IDO1 have been reported to resemble IDO1-expressing DCs in their ability to convert naïve $CD4^+$ T cells into $CD4^+CD25^+FOXP3^+$ Tregs.[65,66] Taken together, these observations reinforce the notion that IDO1 mediates robust immunosuppressive effects in both physiological and pathological scenarios.

As opposed to their wild-type counterparts, malignant cells genetically engineered to express IDO1 fail to reactivate a cancer-specific immune responses leading to rejection in mice that are pre-immunized with a dominant tumor-associated antigen.[23] Along similar lines, the loss of the oncosuppressor gene bridging integrator 1 (BIN1) results in increased IDO1 expression in response to IFNγ, an immunosuppressive effect that favors tumor growth in immunocompetent, but not in immunodeficient, mice.[67] Of note, BIN1 is lost or underexpressed in a variety of human neoplasms, including neuroblastoma,[68] melanoma,[69] as well as breast, lung, colorectal and prostate carcinoma.[70-73] Several human tumors also express high levels of IDO1 independent of BIN1, be it in the neoplastic, vascular or immune compartment.[5,23,74-79] In line with this notion, the circulating levels of various Trp metabolites including Kyn are elevated in subjects affected by several tumors, and this parameter has been attributed a predictive value in some patient cohorts.[80-82] This is not surprising when the robust immunosuppressive activity of IDO1 is taken into consideration.

However, while in some cases elevated levels of IDO1 are associated with poor patient prognosis,[76,78] this is not always the case.[77,79,83] Thus, the expression of IDO1 in tumor biopsies positively correlated with disease-free survival in a cohort of hepatocellular carcinoma (HCC) patients. Moreover, the ability of peripheral blood mononuclear cells isolated from HCC patients to lyse HCC cell lines in vitro was directly proportional to IDO1 expression levels in the former.[83] Along similar lines, not only the number of IDO1-expressing microvessels was found to inversely (rather than positively) correlate with the amount of proliferating cancer cells in samples from primary and metastatic renal cell carcinoma patients, but elevated levels of IDO1 in the neoplastic compartment were also associated with long-term patient survival.[79] These observations indicate that IDO1 may not always support tumor growth by virtue of its immunosuppressive functions.

Since IDO1 is upregulated in response to several inflammatory cues, including IFNγ and CpG oligodeoxynucleotides (ODNs),[13,14,84-86] IDO1 may indeed constitute a marker of a clinically relevant inflammatory or immune response, in thus far resembling other IFNγ-responsive molecules.[87,88] Moreover, at least theoretically, the overexpression of IDO1 by neoplastic cells should have a direct negative outcome on tumor growth as a result of the GCN2-dependent phosphorylation of eukaryotic translation initiation factor 2A (EIF2A) and the consequent arrest in protein synthesis.[26,28,89] Accordingly, the ability of IFNγ to mediate antineoplastic effects in vitro is more pronounced in IDO1-competent cancer cells than in their IDO1-incompetent counterparts, and it can be at least partially reversed by the supplementation of Trp in the culture medium.[90,91] Furthermore, the proliferation of malignant cells implanted in syngeneic hosts appears to be limited when these cells are induced to upregulate IDO1.[92] Taken together, these observations indicate that the impact of IDO1 expression by malignant, vascular or immune components of the neoplastic microenvironment on tumor growth is less clear than generally thought.

Interestingly, developing tumors appear to recruit abundant amounts of $IDO1^+$ DCs,[93] which may engage in a mutually reinforcing circuit with Tregs that express cytotoxic T lymphocyte associated protein 4 (CTLA4). In this scenario, CTLA4 has been proposed to initiate a forkhead box O3 (FOXO3)-dependent signal transduction cascade resulting in the upregulation of IDO1 (in DCs),[94,95] which in turn would activate Tregs via the GCN2 and AHR pathway.[35,38,45,53] This signaling circuit may

be relevant for the establishment of an immunosuppressive microenvironment in human neoplasms. In line with this notion, the combined inhibition of IDO1, CTLA4, and CD274 (an immunosuppressive molecule best known as PD-L1)[96,97] has recently been shown to mediate superior therapeutic effects against well-established gliomas, in mice.[98] Moreover, elevated expression levels of IDO1 at baseline have been associated with improved clinical outcome in melanoma patients treated with the CTLA4-targeting antibody ipilimumab.[99]

In this Trial Watch,[100-102] we discuss preclinical and clinical findings about the inhibition of IDO1 as a strategy for the re(activation) of tumor-targeting immune responses, and summarize clinical trials recently initiated to test this therapeutic paradigm in cancer patients. As a note, no IDO1 inhibitor is currently approved for use in humans by the US Food and Drug Administration (FDA) or equivalent agencies worldwide.

Preclinical and Clinical Development of IDO1 Inhibitors for Cancer Therapy

During the last decade, 1-methyltryptophan, a competitive inhibitor of IDO1 (and IDO2) that exists as a mixture of chiral isoforms (i.e., 1-methyl-*D*-tryptophan and 1-methyl-*L*-tryptophan), and genetic interventions specifically targeting IDO1 have been shown to inhibit tumor growth in rodent tumor models, along with the (re)elicitation of an anticancer immune response.[23,67,103-108] However, targeting IDO1 as a standalone therapeutic intervention often fail to cause tumor eradication and to prevent disease progression. Thus, IDO1-targeting agents have been investigated for their ability to improve the efficacy of multiple chemotherapeutics, and some combinatorial regimens of this type had promising results in preclinical scenarios.[1,67,109]

Relatively recently, these findings convinced some oncologists on the possibility to test the safety and therapeutic potential of 1-methyl-*D*-tryptophan (also known as indoximod and NLG8189), second-generation IDO1 inhibitors (such as the orally available agent INCB024360 and NLG919), and IDO1-targeting vaccines in cancer patients.[74,75,110-120] So far, the pharmacological profile of several other IDO1 inhibitors–including 1-methyl-*L*-tryptophan, methylthiohydantoin tryptophan, brassinin and derivatives, annulin B and derivatives, exiguamine A and derivatives, as well as INCB023843–appears to be suboptimal for clinical development.[1,20,67,112,121-126]

The first-in-man Phase I clinical trial involving indoximod enrolled a total of 48 adults with refractory solid malignancies (NCT00567931).[114] In this dose-escalation study, oral indoximod was well tolerated up to a dose of 2000 mg twice a day, major toxicities being Grade 1 fatigue (1 case) and Grade 2 hypophysitis (2 cases, in patients previously subjected to several immunotherapies). Moreover, of 7 evaluable patients who received 200 mg indoximod per day (10 were originally enrolled on this dose), 5 experienced objective responses or disease stabilization.[114]

Nowadays, the results of another study investigating the clinical profile of indoximod have been partially released (NCT01191216).[115] In this Phase I clinical trial, indoximod was tested as a means to support the therapeutic profile of docetaxel (a microtubular poison currently approved by the US FDA for the treatment of various neoplasms).[115,127,128] This study was conducted on 27 patients with metastatic solid tumors to determine the maximum tolerated dose of indoximod given in combination with docetaxel.[115] Patients were assigned to receive 300, 600, 1000, 1200 and 2000 mg indoximod p.o. twice a day, in combination with either 60 or 75 mg/m^2 docetaxel every 3 weeks. The most common side effects were fatigue (58.6%), anemia (51.7%), hyperglycemia (48.3%), infection (44.8%), and nausea (41.4%). Out of 22 evaluable patients, 4 experienced partial responses and 9 disease stabilization. The authors recommended a dose of 1200 mg indoximod twice a day in combination with 75 mg/m^2 docetaxel every 3 weeks for testing in a Phase II study, which they initiated themselves on a cohort of metastatic breast carcinoma patients (NCT01792050).[117]

Preliminary results are also available from 2 distinct clinical trials assessing the safety and efficacy of INCB024360 in oncological indications (NCT01195311; NCT01604889).[75,119,120] NCT01195311, which has been completed, was a Phase I, open-label, dose-escalation study to determine the safety, tolerability, pharmacokinetics and pharmacodynamics of INCB024360 in subjects with advanced malignancies. In this setting, 52 patients were enrolled to receive 50–700 mg INCB024360 p.o. twice a day in 28-d cycles until disease progression or inacceptable toxicity. The most frequent Grade 3 or 4 side effects were abdominal pain, hypokalemia, and fatigue (9.6% each) and 2 dose-limiting toxicities were recorded. Significant reduction in the circulating Kyn/Trp ratio were observed in all patients, but there were no objective responses. Still, 15 patients achieved disease stabilization, lasting more than 112 d in 7 of them.[75,119] NCT01604889, which is still ongoing, is a Phase I/II randomized, blinded, placebo-controlled study testing ipilimumab in combination with placebo or INCB024360 or in subjects with unresectable or metastatic melanoma.[120] In this setting, 7 patients were assigned to receive 300 mg INCB024360 p.o. twice a day plus 3 mg/kg ipilimumab i.v. every 3 weeks, and enrollment was stopped when 5 patients developed clinically significant elevations of circulating alanine transaminase (after 30–76 days of treatment). Six out of 7 patients were evaluable at discontinuation and all exhibited disease stabilization. Of note, corticosteroids and treatment discontinuation were sufficient to resolve hepatic symptoms. A second cohort of eight patients receiving ipilimumab in combination with 25 mg INCB024360 p.o. twice a day was enrolled. One of these subjects experienced dose-limiting hepatic toxicity (Grade 3 aspartate aminotransferase elevation), while immunological side effects were manageable with temporary treatment discontinuation. At first evaluation, the disease control rate was 75%, 3 patients achieved radiologically confirmed partial responses, and 3 patient experienced disease stabilization for 79, 148, and >127 d.[120]

Finally, Iversen and colleagues have recently reported the results of a Phase I clinical trial evaluating the safety and therapeutic profile of an IDO1-targeting, peptide-based vaccine

(NCT01219348).[74,129,130] In this setting, 15 individuals with metastatic non-small cell lung carcinoma achieving disease stabilization upon standard-of-care chemotherapy received an IDO1-derived peptide s.c. in combination with the Toll-like receptor 7 (TLR7) agonist imiquimod.[131,132] No severe side effects were recorded, 1 patient achieved a partial response one year after vaccination, and 6 patients experienced prolonged (>8.5 months) disease stabilization. Moreover, the overall survival of these individuals was significantly improved as compared to that of similar patients excluded from the study owing to HLA expression profile. A majority of subjects enrolled in the study also developed IDO1-specific $CD8^+$ T cells and manifested significant reductions in the amounts of circulating Tregs as compared to baseline levels. Taken together, these data suggest that not only pharmacological agents, but also other means of targeting IDO1 may provide clinical benefits to cancer patients.

As per official sources (http://www.clinicaltrials.gov), 2 additional clinical trials have been initiated to investigate the safety and efficacy of IDO1 inhibitors in oncological indications but have been interrupted. In particular, NCT00739609, testing indoximod as a standalone therapeutic intervention in subjects with relapsed or refractory solid tumors, has been terminated owing to lack of accrual, while NCT01982487, assessing the ability of INCB024360 to boost the efficacy of a NY-ESO-1-targeting recombinant vaccine,[133,134] has been withdrawn prior to enrollment, for undisclosed reasons.

Ongoing Clinical Trials

When this Trial Watch was being redacted (August 2014), official sources listed no less than 16 clinical trials launched to evaluate the safety and efficacy of IDO1-targeting interventions in cancer patients (source http://www.clinicaltrials.gov). Six of these trials involve indoximod (NCT01042535; NCT01560923; NCT01792050; NCT02052648; NCT02073123; NCT02077881), 8 INCB024360 (NCT01604889; NCT01685255; NCT01822691; NCT01961115; NCT02042430; NCT02118285; NCT02166905; NCT02178722), 1 NLG919 (NCT02048709), and 1 an IDO1-derived peptide (NCT02077114) (**Table 1**).

In particular, indoximod is being tested in combination with (1) docetaxel (NCT01792050, see above) or an experimental DCbased vaccine (NCT01042535),[116,135,136] in subjects with metastatic breast carcinoma; (2) temozolomide (an alkylating agent currently employed against glioma, astrocytoma and melanoma),[137,138] in patients with primary brain neoplasms (NCT02052648); (3) ipilimumab,[139,140] in adults with metastatic melanoma (NCT02073123); (4) gemcitabine (an immunostimulatory nucleoside analog approved for the treatment of several carcinomas)[141-144] and paclitaxel (a microtubular poison used against a wide panel of neoplasms),[145,146] in patients with metastatic pancreatic cancer (NCT02077881); and (5) sipuleucel-T (also known as Provenge®, the sole DC-based preparation currently approved by the US FDA for use in humans),[135,136] in individuals with refractory metastatic prostate carcinoma (NCT01560923).

In addition, INCB024360 is being evaluated: (1) as a standalone therapeutic intervention, in subjects with myelodysplastic syndromes (NCT01822691) or women with tumors of the reproductive tract (NCT01685255; NCT02042430); (2) in combination with ipilimumab (NCT01604889, see above), or a mixture of MHC Class I-restricted peptides[147,148] (NCT01961115), in patients with unresectable or advanced melanoma; (3) in association with the intraperitoneal delivery of haploidentical NK cells and interleukin-2,[149-151] (NCT02118285) or a DC-targeted variant of NY-ESO-1[152,153] and a TLR3 agonist[154,155] (NCT02166905), in women with reproductive tract cancers; and (4) in combination with a monoclonal antibody targeting the immunosuppressive receptor programmed cell death 1 (PDCD1, best known as PD-1),[156-158] in subjects with advanced solid tumors (NCT02178722).

Finally, the safety and preliminary efficacy of NLG919 employed as a standalone therapeutic intervention are being assessed in patients with advanced solid tumors (NCT02048709), while an IDO1-derived peptide is being tested in combination with either ipilimumab or vemurafenib (an FDA-approved inhibitor of mutant BRAF)[159-162] in subjects with unresectable Stage III or IV melanoma (NCT02077114).

Concluding Remarks

Although 1-methyl-*L*-tryptophan inhibits IDO1 much more efficiently that its *D* counterpart in cell-free assays and in cellula,[1,51,163-165] the immunostimulatory potential of the latter in vivo is superior.[6,109,166] This explains why indoximod is currently developed in the clinic and 1-methyl-*L*-tryptophan not. Moreover, it adds to an increasing amount of evidence indicating that indoximod exerts IDO1-independent immunostimulatory effects.[1] For instance, several immunostimulatory agents including IFNγ,[167,168] CpG ODNs[84,169] and monoclonal antibodies specific for tumor necrosis factor receptor superfamily, member 9 (TNFRSF9, best known as 4-1BB or CD137)[170-173] have been shown to mediate therapeutic effects in preclinical or clinical scenarios in spite of their ability to upregulate IDO1 expression. Nonetheless, indoximod loses its ability to suppress tumor growth in *Ido1*$^{-/-}$ mice.[109] Taken together, these observations suggest that the anticancer activity of indoximod may rely on mechanisms other than the inhibition of the enzymatic activity of IDO1.[174] In further support of this notion, indoximod has recently been shown to interfere with the transcription and translation of IDO1,[175,176] and to inhibit Trp transporters of the plasma membrane.[177]

Although our understanding of the biological effects of indoximod and other IDO1 inhibitors is incomplete, these molecules appear to mediate potent antineoplastic effects along with the re(activation) of anticancer immunosurveillance. Precisely determining to which extent these effects are on-target (i.e., they stem from the blockage of Trp catabolism) may allow for the development of novel agents that promote a therapeutically relevant tumor-targeting immune response but fail to provoke systemic metabolic disturbances

Table 1. Ongoing clinical trials testing the clinical profile of IDO1 inhibitors in cancer patients

Agent	Indications	Phase	Status	Notes	Ref.
Indoximod	Brain neoplasms	I/II	Recruiting	Combined with temozolomide	NCT02052648
	Breast carcinoma	I/II	Active, not recruiting	Combined with an experimental DC-based vaccine	NCT01042535
		II	Recruiting	Combined with docetaxel	NCT01792050
	Melanoma	I/II	Recruiting	Combined with ipilimumab	NCT02073123
	Pancreatic carcinoma	I/II	Not yet recruiting	Combined with gemcitabine and paclitaxel	NCT02077881
	Prostate carcinoma	II	Recruiting	Combined with sipuleucel-T	NCT01560923
INCB024360	MDS	II	Active, not recruiting	As single agent	NCT01822691
	Melanoma	I/II	Recruiting	Combined with ipilimumab	NCT01604889
		II	Recruiting	Combined with a multipeptide-based vaccine	NCT01961115
	Reproductive tract tumors	n.a.	Recruiting	As single agent	NCT02042430
		I	Recruiting	Combined with the adoptive transfer of NK cells and IL-2	NCT02118285
		I/II	Recruiting	Combined with DC-targeted NY-ESO-1 and polyICLC	NCT02166905
		II	Recruiting	As single agent	NCT01685255
	Solid tumors	I/II	Recruiting	Combined with a PDCD1-targeting monoclonal antibody	NCT02178722
NLG919	Solid tumors	I	Recruiting	As single agent	NCT02048709
IDO1-derived peptide	Melanoma	I	Recruiting	Combined with ipilimumab or vemurafenib	NCT02077114

Abbreviations: DC, dendritic cell; IDO1, indoleamine 2,3-dioxigenase1; IL-2, interleukin-2; MDS, myelodysplastic syndrome; n.a., not available; NK, natural killer; PDCD1, programmed cell death 1; polyICLC, polyinosinic:polycytidylic acid, stabilized in poly-*L*-lysine and carboxymethylcellulose. *Based on clinical trials not completed, withdrawn, terminated or suspended at the day of submission (source http://www.clinicaltrials.gov).

as they inhibit IDO1 at the whole body level. In this setting, it would be very interesting to see whether the antineoplastic activity of indoximod is preserved in mice expressing a catalytically inactive variant of Ido1. The results of this and other experiments aimed at disentangling the complex signaling pathways and metabolic circuitries controlled by IDO1 are urgently awaited.

Disclosure of Potential Conflicts of Interest

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