Indoleamine-2,3-dioxygenase-1 (IDO1) Inhibitors-
a novel antineoplastic approach

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Outline

- Background
- Methods
- Potential IDO-1 small molecule inhibitors
- Clinical Application
- Questions
In cancer immunotherapy, antibody drugs function as checkpoint inhibitors for various cancers. Side effects from antibodies are harsh. Currently, researchers are searching for an effective treatment for cancers involving a new potential mechanism, an IDO-1 small molecule inhibitor (Indoleamine-2,3-dioxygenase-1).

Qian S et al. RSC Adv. 2016; 6, 7575-7581.
Background

- IDO-1 is overexpressed in a variety of tumors.
  - Enzyme responsible for converting tryptophan (TRP) into kynurenine (KYN).
- IDO catabolism of TRP allows cancerous cells to escape the immune response and various checkpoints.
- When TRP is depleted, GLK1 is blocked leading to inhibition of a signaling molecule mTOR (mTORC1), resulting in autophagy and anergized T cells.
  - Additionally, depletion of TRP leads to KYN production.
  - KYN binds to AhR transcription factor, initiating Treg differentiation which further creates an immunosuppressed environment where cancer cells can also program a pathogenic inflammatory response, creating an environment that is more viable to survival and progression.

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Study Objective

- Currently, there are no FDA-approved IDO-1 small molecule inhibitors.

- Objective: To find IDO-1 small molecule inhibitors in trials, describe their characteristics, stage in clinical trials, patents, and how they can be used to improve cancer therapy.
Methods

- Literature search on potential IDO-1 inhibitors
- Searched broadly using Pubmed, Embase, Google, and Medline
- Mesh term examples:
  - “Indoleamine-Pyrrole 2,3,-Dioxygenase”, GDC-0919; also known as NLG919 and RG6078
  - “Indoleamine 2,3-dioxygenase 1, human” AND “Neoplasms”
- Patents: Google Patents
- Medline based search produced few desired results
Molecular Analyses Reveal Inflammatory Mediators in the Solid Component and Cyst Fluid of Human Adenomatous Cranioopharyngioma.


PMID: 28659336

1. A randomised, open-label, phase 2 study of the IDO1 inhibitor epacadostat (NCB024360) versus tamoxifen as therapy for biochemically recurrent (CA-125 relapse)-only epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer.


PMID: 28696809

2. Expression of Indoleamine 2,3-Dioxygenase Gene Is a Feature of Poorly Differentiated Non-
NOVEL IDO INHIBITORS AND METHODS OF USE

This application claims priority under 35 U.S.C. §119 (e) to US Provisional Application No. 60/527,449, filed on December 5, 2003, and US Provisional Application No. 60/458,162, filed on March 27, 2003, the entire contents of both applications are incorporated by reference herein.

FIELD OF THE INVENTION This invention relates to the field of oncology.

Specifically, the invention provides novel chemotherapeutic agents and methods of using such agents for the treatment of cancer.

BACKGROUND OF THE INVENTION

Tumors characteristically express atypical, potentially immunoreactive antigens that are collectively referred to as tumor antigens. Accumulating evidence suggests that the failure of the immune system to mount an effective response against progressively growing tumors is not attributable to a lack of recognizable tumor antigens. Immunosuppression by tumors is poorly understood and mechanisms by which tumors may escape immune surveillance have been poorly explored. Recently, it has been shown that cytotoxic T cells become tolerantized by a reduction in local concentrations of tryptophan that are elicited by indoleamine 2,3 dioxygenase (IDO) activity. IDO is an oxidoreductase that catalyzes the rate-limiting step in tryptophan catabolism. This enzyme is structurally distinct from tryptophan dioxygenase (TDO), which is responsible for dietary tryptophan catabolism.

Claims

WHAT IS CLAIMED IS:

1. A compound having indoleamine 2,3 dioxygenase

(IDO) inhibitory activity, said compound having a formula selected from the group consisting of formula (I):

wherein R₂ is H or lower alky; R₃ is H, R₃ is selected from the group consisting of: (a)

wherein R₄ and R₅ are independently selected from the group of H and...
Results

- There are currently several small molecule IDO-1 inhibitors in various phases of pre-clinical and clinical trials. Some of these IDO-1 inhibitors include:
  - Epacadostat (INCB024360) from Incyte Therapeutics
  - GDC-0919 from NLG and Roche companies
  - F001287 from BMS (now BMS-986205)
  - Indoximod from New Link Genetics
Epacadostat (INCB024360)

- Mechanism: selective inhibition of human IDO1 with little activity against other related enzymes
- Phase I: to determine safety and tolerability
  - Generally well tolerated
  - Achieved best response in 34.6% of patients
- Phase I/II preliminary results
  - Combination of Epacadostat with Pembrolizumab
  - Potential clinical activity as a combination therapy
- Phase III trials just beginning

MedKoo Biosciences, Inc[Internet]. Available from: http://www.medkoo.com/products/6778
Clinicaltrials.gov [Internet]. Available from: https://clinicaltrials.gov/ct2/show/NCT02752074
GDC-0919

- In phase I clinical trials as a single agent
  - Efficacy and safety
- Administered in 50 - 80 mg doses twice daily on a 21 days on and 7 days off schedule for 12 months
- Drug activity based on Kyn:Trp ratio and assessment made every 2 cycles
- Sample size of 19 patients:
  - Acceptable safety profile and stabilized the disease. The median duration was 3 cycles and 77 days
- IDO1 and PD-L1 are both expressed concomitantly in many tumor cells and act complementary in the suppression of the immune system
  - Pursuit of GDC 0919 plus atezolizumab combination therapy in preclinical trials

BMS-986205 (formerly F001287)

- IDO 1 inhibitor acquired by Bristol-Myers Squibb from Flexus
- Phase I/II clinical trial stages
  - Safety and efficacy trials
    - AEs leading to discontinuation, deaths, and clinical laboratory test abnormalities
  - In combination with monoclonal antibodies
    - nivolumab and ipilimumab
- Study to go 3 years for evaluation of outcomes
  - Goal is treatment
  - Currently recruiting

Indoximod

- IDO 1 inhibitor by NewLink Genetics
- Currently in phase 2 clinical trials across various cancer indications
- Allows cancer cells to “be seen” and therefore targeted by other various treatments
- Orally available tryptophan mimetic with immuno-activating and anti-neoplastic activities
  - Inhibits IDO 1 pathway by:
    - Counteracting immunosuppressive effects of kynurenine.
    - Activating multiple immune cells (effector cells)
    - Preventing activation of regulatory T cells (Tregs)
    - Re-programing Tregs into helper T cells

IDO Pathway Inhibitors. NewLink Genetics.
Potential Clinical Application?

- IDO-1 inhibitors can provide therapeutic use as a **combination therapy** resulting in more effective and enhanced anti-cancer treatment.
- IDO-1 inhibitors may be used as an adjunct in traditional chemotherapy agents and vaccines
  - Tumors have a mechanism allowing it to quickly develop resistance
- **Combined therapy** promotes more successful killing of cancer cells by enhancement immunity and prevention of immune system evasion.
- **Small molecules and IDO1 inhibitors** may be the future of cancer therapy.
Questions...
Thank you.

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