In cancer immunotherapy, antibody drugs function as checkpoint inhibitors and the side effects are harsh. Researchers are investigating an effective anticancer treatment involving a new potential mechanism, IDO1 small molecule inhibitor. IDO1 is overexpressed in a variety of tumors. Enzyme responsible for converting tryptophan (TRP) into kynurenine (KYN). IDO catalysis 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.

Depletion of TRP leads to KYN production. KYN binds to AhR transcription factor, initiating Treg differentiation.

- Creates an immunosuppressed environment.
- Cancer cells can also program a pathogenic inflammatory response, making an environment more viable to survival and progression.

Purpose

- No FDA-approved IDO1 small molecule inhibitors currently.
- Find IDO1 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, and Google
- Mesh term examples:
  - "Indoleamine-Pyrole 2,3-Dioxygenase, GDC-0919; also known as NLG919 and RG6078; "Indoleamine 2,3-dioxygenase 1, human" AND "Neoplasms"
- Patents: Google Patents

Results

Epacadost (INCB024360)

- Epacadost is the current IDO1 inhibitor with the most extensive clinical trials.
- Determined to be generally well-tolerated in Phase I trials.
- Only 34.6% of patients achieved best response.
- Further trials were needed to determine efficacy as combination therapy.
- Phase I/II preliminary results suggest efficacy as a combination agent with pembrolizumab.

GDC-0919

- Phase I clinical trials were completed to determine safety and efficacy.

BMS-986205 (formerly F001287)

- Phase I clinical trials were done to determine safety and efficacy.
- Beginning Phase II trials to look at combination therapy with nivolumab and ipilimumab.

Idoximod

- Idoximod has begun Phase I clinical trials of dose escalation and combination with various immunologics.

Conclusions

- Current cancer immunotherapy agents cause many harsh side effects.
  - There is desire to find effective treatments while minimizing patient adverse effects.
- IDO1 inhibition is being investigated as a potential mechanism in antineoplastic therapy.
- IDO1 inhibitors can provide therapeutic use as a combination therapy.
- IDO1 inhibitors may be used as an adjunct in traditional chemotherapy agents and vaccines.
- Tumors have a mechanism allowing them to quickly develop resistance.
- Combined therapy promotes more successful killing of cancer cells by enhancing immunity and preventing immune system evasion.
- There are many IDO1 small molecule inhibitors in various phases of pre-clinical and clinical trials.
- Small molecules and IDO1 inhibitors may be the future of cancer therapy.

Disclosures

- Connor Dierks, PharmD Candidate 2019: Nothing to disclose
- Jillian Ginger, PharmD Candidate 2019: Nothing to disclose
- Lynn Tang PharmD Candidate 2019: Nothing to disclose
- Zhendong Jin, PhD: Nothing to disclose

References


Zhendong Jin, PhD: Nothing to disclose.

Gangadhar Beatty, PharmD Candidate 2019: Nothing to disclose

Connor Dierks, PharmD Candidate 2019: Nothing to disclose

Jillian Ginger, PharmD Candidate 2019: Nothing to disclose

PharmD Student 2019: Nothing to disclose.

Nothing to disclose.

Nothing to disclose.

Nothing to disclose.

Nothing to disclose.