Introduction

- The IDO pathway mediates immunosuppressive effects through the metabolism of Trp by tumor cells, leading to decreased T cell function and proliferation.
- Expression of the IDO1 gene by tumor cells or host APCs can inhibit tumor-specific T cell responses.
- High expression of IDO correlates with worse clinical prognosis in patients with a variety of malignancies.
- Therefore, targeting the IDO pathway via inhibition of the IDO enzyme or blocking its downstream signaling effects is a prime target for small-molecule immunomodulatory drugs in cancer.

IDO Pathway

- IDO1 inhibitors (IDOIs) like Indoximod (BFT25), LV1620, E714, ETV4, eIF2α, and AHR
- IDO activators like NADPH Reductases, Kinases, CytB5 & SOCS3, Nitrosylation, Phosphatase, and mTOR and AHR that can affect differentiation and proliferation of T cells.
- IDO1 repressors
- AHR
- αETV4, eIF2α
- CpG ODN, STAT1, Bin1,
- B7 ligation, FOXO3

Lead Development Candidate: NLG919

- NLG919, a novel indoleamine-2,3-dioxygenase (IDO)-pathway inhibitor drug candidate for cancer therapy

Pharmacokinetics

- Mouse
- Human IDO Cmax: 29 nM
- IDO Ki: 7.2 nM
- Drug-Like Property
- HBD 2
- SA 56
- PPB %Fu 52
- Sol pH 7.4 mg/mL 213
- PPB % Fu 52
- MW <500
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Antitumor Activity

- NLG919 potently inhibits the IDO pathway in vivo and in cell based assays (EC50 <75 nM).
- NLG919 is orally bioavailable and has a favorable pharmacokinetic and toxicity profile.
- Oral administration of NLG919 reduces the [Kyn] in plasma and tissue by ~50%.
- Using human IDO+ pDCs in allogeneic MLR reactions, NLG919 potently blocked IDO-induced T cell suppression and restored robust T cell responses with EC50=130 nM.
- Oral administration of NLG919 plus pmel-1/vaccine produced a dramatic collapse of tumor size within 4 days of vaccination (95% reduction in tumor volume compared to controls receiving pmel-1-vaccine alone without NLG919).

Conclusions

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- NLG919 and Indoximod have synergistic antitumor activity.
- In conclusion, NLG919 is a potent IDO pathway inhibitor with desirable pharmacological properties, suitable for the treatment of immunosuppression associated with cancer.