First in Human Phase 1 Study of the Novel Indoleamine-2,3-dioxygenase (IDO) Inhibitor NLG919

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INTRODUCTION

The main function of the IDO pathway is the regulation of acquired local and peripheral immune tolerance in normal and pathological conditions, particularly in the tumor microenvironment. [1,2].

IDO is an enzyme that catalyzes the initial and rate limiting step in the conversion of tryptophan to kynurenine.

- Tryptophan depletion enhances the number and function of the Treg (suppressive) arm of the immune system and inhibits the effector T cell (stimulatory) arm
- Kynurenine metabolites may augment the suppressive effects on inflammation and immune responses

In cancer, IDO can be expressed directly by the tumor cells or induced indirectly in host antigen presenting cells. The IDO pathway mediates an acquired immune tolerance towards tumors, allowing tumors to thwart an immune response by the host. Therefore, the IDO pathway is an attractive target for cancer drug development.

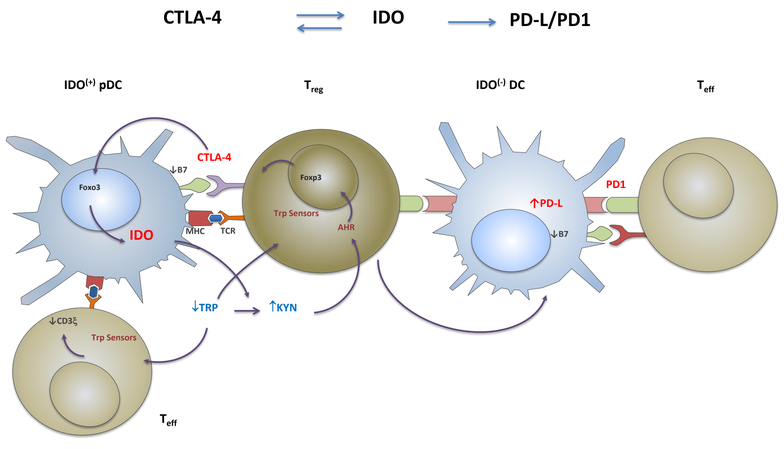
- NLG919 inhibits the enzymatic activity of IDO

Agents that inhibit the IDO pathway have been shown to act synergistically with each other as well as with chemotherapy and other checkpoint inhibitors, such as anti-CTLA-4, anti-PD-1, and anti-PD-L1.

This first trial in humans is designed to evaluate the safety and toxicity of NLG919 in advanced solid tumors for which no standard therapy exists.

KEY IMMUNE CHECKPOINTS

Figure 1



OVERVIEW

Open label phase 1, dose escalation study of NLG919 for patients with advanced solid tumor malignancies.

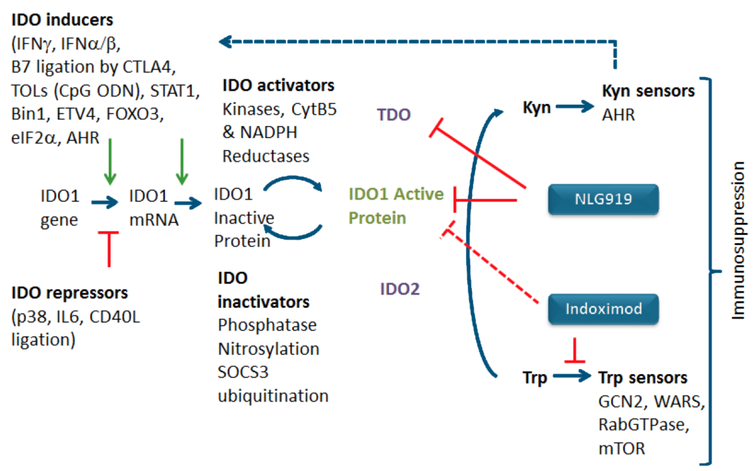
Adult patients with solid tumors that are refractory to previous lines of chemotherapy or biological agents. There must be imaging confirmation of tumor progression or regrowth.

This trial is designed to enroll up to 36 patients. The dose of NLG919 is escalated according to a revised 3+3 design.

NLG919 is administered orally twice daily for the first 21 days of repeating 28 day cycles. Patients may receive drug until disease progression.

IDO PATHWAY

Figure 2



OBJECTIVES

The purpose of this study is to determine the safety and appropriate dose for future studies of NLG919.

Primary Objectives

- Evaluate the safety and toxicity of NLG919 in advanced solid tumors for which no standard therapy exists
- Define the Maximum Tolerated Dose (MTD), Maximum Biologically Effective Dose (MBED) and/or Recommended Phase 2 Dose (RP2D) of NLG919 in advanced solid tumors

Secondary Objectives

- Pharmacokinetics of NLG919
- Measure plasma kynurenine to serum tryptophan ratio
- Overall response rates (CR+PR+SD) to NLG919 in advanced solid tumors
- Overall survival by Kaplan-Meier analysis

STUDY SCHEMA

A revised 3+3 dose escalation design with a single intra-patient 100% dose escalation for the first dose level cohort is used.

- NLG919 is supplied in 50 mg and 200 mg capsules
- Dose escalation is proceeds according to the following scheme:

DOSE LEVEL (COHORT)	DOSE OF NLG919	# of Patients
1	50 mg po q 12 hr	1-6
2	100 mg po q 12 hr	3-6
3	200 mg po q 12 hr	3-6
4	400 mg po q 12 hr	3-6
5	600 mg po q 12 hr	3-6
6	800 mg po q 12 hr	3-6

- Initial patient enrolled at 50 mg twice daily. After completion of one cycle at that dose with no dose limiting toxicities (DLT) the next 3 patients start at the 100 mg twice daily dose.
- After the 100 mg cohort completes one cycle of treatment with no DLTs, the patient enrolled in the 50 mg cohort allowed to escalate to the 100 mg dose as well.

All cohorts follow the dose escalation rules outlined below.

- The first 3 patients at the 100mg dose are enrolled in the dose cohort one week apart
- To start a new dose cohort at a higher dose level, the first patient is enrolled at the new dose level only after the third patient enrolled at the previous lower dose level has been treated for two weeks. This provides time to monitor for adverse effects
- Delayed onset DLTs occurring in a lower dose cohort after the next dose level cohort has been opened will halt accrual to the current dose level until the adverse event(s) are analyzed and it is deemed safe to proceed.

CONCLUSION

- IDO Pathway is an attractive target in therapeutic interventions aimed at restoring the immune response towards the tumor
- Drugs that inhibit the enzymatic activity of IDO, like NLG919, or that inhibit the effects of IDO activity, like indoximod, are expected to bring a significant benefit to an active immunotherapy
- Combining IDO pathway inhibition with other treatments that activate an immune response or interfere with tumor tolerance represents a promising approach to optimize efficacy
- Combination therapies could include immunizing with tumor vaccines (i.e. HyperAcute™), chemotherapy, and other check point inhibitors (targeting CTLA-4 or PD-1/PD-L1). These combinations will be evaluated in our planned phase 1b program for NLG919.
- The potential additive benefits that IDO inhibition might bring to these regimens could be:
  1. To enhance an otherwise suboptimal immune response by targeting a second, independent immunoregulatory pathway (checkpoints)
  2. To remove local immunosuppression within the tumor, thereby enabling circulating effector cells generated by another strategy to function within the tumor (chemotherapy and vaccines)
  3. To help prevent tolerance from being re-acquired when it has been broken by another active immunotherapy (vaccines)

REFERENCES

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3. Mautino et al. AACR 2014 Abstract #1633
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CLINICAL TRIALS IDENTIFIER

ClinicalTrials.gov Identifier: NCT02048709
For information on this study, see: http://clinicaltrials.gov/ct2/show/NCT02048709

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