Abstract #188

A Phase 1 Clinical Trial of NLG802, a Prodrug of Indoximod with Enhanced Pharmacokinetic Properties

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INTRODUCTION

- Indoximod contributes to enhanced antitumor immunity by relieving indoleamine 2, 3-dioxygenase (IDO)-mediated immunosuppression by mechanisms that involve modulation of aryl hydrocarbon receptor (AhR) signaling and mTOR activation, leading to multiple immunomodulatory effects, including a shift from suppressive Foxp3$^+$ Treg toward Th17 helper T cells and downregulation of IDO expression in dendritic cells[1]
- Indoximod demonstrated an excellent safety profile in human clinical trials at doses of up to 2000 mg BID[2,3]
- Increasing doses of indoximod above 1200 mg BID generally does not result in increased plasma concentration or drug exposure due to limiting dose-dependent oral bioavailability
- NLG802, a pro-drug of indoximod, was specifically engineered to increase the bioavailability of indoximod by leveraging existing mechanisms of absorption, increasing the exposure of indoximod ~5-fold in non-human primates[4]

Figure 1. NLG802 Metabolism

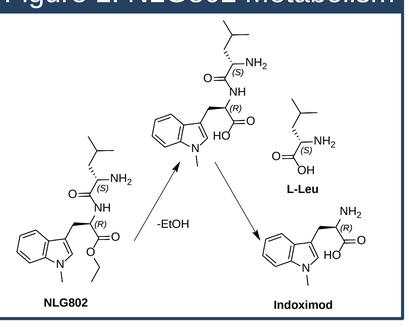


Table 1. Indoximod PD Effects

Pharmacodynamic Effects Mediated by Indoximod	Target Concentration (EC_{50} or $C_{av,ss}$)
Differentiation of activated CD4$^+$ T cells into TH17 vs. Treg	8 µM
Down-modulation of IDO protein and function in human moDCs in vitro	20-30 µM
Down-modulation of IDO protein in murine TDLN	7 µM
Stimulation of CD8$^+$ T_{eff} cell proliferation	20-45 µM
Antitumor activity in murine models	13-30 µM

OBJECTIVES

- To assess safety and toxicity of NLG802
- To determine maximum tolerated dose (MTD) or maximum biologically achievable dose (MBAD) and recommended Phase 2 dose of NLG802
- To assess the pharmacokinetics (PK) of NLG802 and its active metabolite indoximod at increasing dose levels

METHODS

Study Design

- Phase 1 3+3 Dose Escalation Study (NCT03164603)

Adults (≥18 y) with recurrent advanced solid tumors refractory to previous chemotherapy or biological agents
- Eastern Cooperative Oncology Group performance status 0 or 1
- Adequate bone marrow, renal, and liver function
- No active/recent history of autoimmune disease, untreated brain metastases, active infection, serious uncontrolled medical disorder, or pregnancy

→ 180 mg → 363 mg → 726 mg → 1089 mg → 1452 mg → Repeating 28-d cycles until toxicity or disease progression

- PK assessments of both NLG802 and its active ingredient indoximod on Day 1 after first single dose (0–48 h) and at Day 21 (0–12 h) after repeated BID (Q12h) dosing

RESULTS

Patient Characteristics

Table 2. Baseline Demographics

		Total N=26	NLG802 180 mg BID n=3	NLG802 363 mg BID n=4	NLG802 726 mg BID n=4	NLG802 1089 mg BID n=7	NLG802 1452 mg BID n=8
Median age, y (range)		64 (20–81)	41 (41–64)	69 (55–77)	69 (46–81)	63 (43-81)	65 (20-69)
Female, n (%)		12 (46)	2 (67)	2 (50)	1 (25)	2 (29)	5 (63)
Caucasian/white, n (%)		25 (96)	3 (100)	4 (100)	4 (100)	7 (100)	7 (88)
Tumor type, n (%)	**Colorectal**	9 (35)	1 (33)	1 (25)	1 (25)	2 (29)	4 (50)
	Pancreas	7 (27)	0	2 (50)	1 (25)	2 (29)	2 (25)
	Sarcoma	3 (12)	0	0	1 (25)	1 (14)	1 (13)
	Cervical	2 (8)	1 (33)	0	0	0	1 (13)
	Lung	2 (8)	0	0	1 (25)	1 (14)	0
	Bladder	1 (4)	1 (33)	0	0	0	0
	Melanoma	1 (4)	0	1 (25)	0	0	0
	Ovarian	1 (4)	0	0	0	1 (14)	0

- NLG802 has been administered at 5 of 5 dose levels in 26 subjects
- 5 (19%) subjects remain on study, 14 (54%) alive, and 4 (15%) unknown due to withdrawal

Safety and Tolerability

- No subject experienced a dose-limiting toxicity within the first 28-day cycle
- The most frequently reported adverse events (AE) regardless of attribution occurring in > 10% of the patients were fatigue (54%), nausea (46%), vomiting (35%), decreased appetite (31%), diarrhea (23%), anemia (15%), constipation (15%), peripheral edema (15%), back pain (15%), abdominal discomfort (12%), arthralgia (12%), dyspepsia (12%) and hypokalemia (12%)
- The most frequently reported NLG802-related AEs for all grade events from different dose cohorts (occurring in ≥3 total subjects) are shown in ***Table 3***
- No serious NLG802-related AEs were observed

Table 3. Treatment-Related Adverse Events Occurring in ≥3 Total Subjects

	Total N=26	NLG802 180 mg BID n=3	NLG802 363 mg BID n=4	NLG802 726 mg BID n=4	NLG802 1089 mg BID n=7	NLG802 1452 mg BID n=8
Fatigue	11 (42%)	1	1	2	3	4
Nausea	10 (38%)	1	1	1	2	5
Vomiting	7 (27%)	0	0	1	4	2
Anemia	3 (12%)	0	0	1	1	1
Diarrhea	3 (12%)	0	0	0	1	2
Decreased appetite	3 (12%)	0	0	0	1	2

Pharmacokinetics (PK)

Figure 2. Time-dependent Mean Plasma Concentration of NLG802 or Indoximod After Oral Dose(s) of NLG802

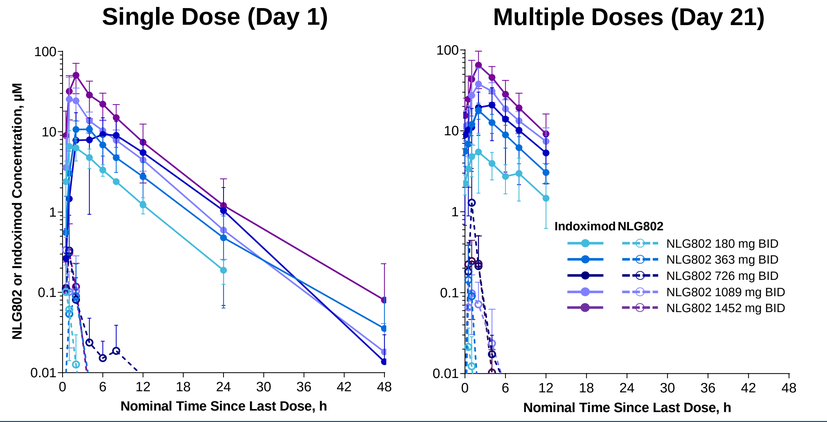


Figure 3. Indoximod Exposure in Monkeys and Humans*

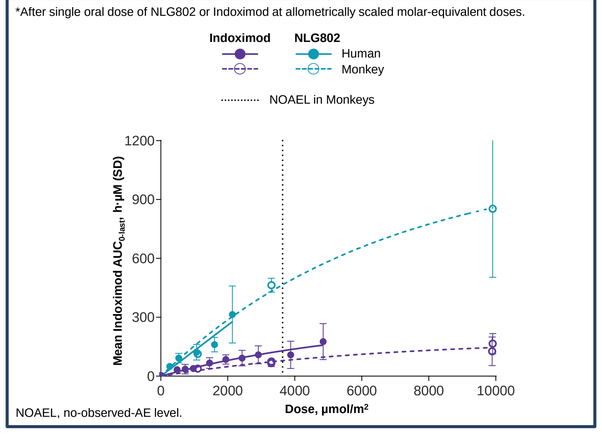
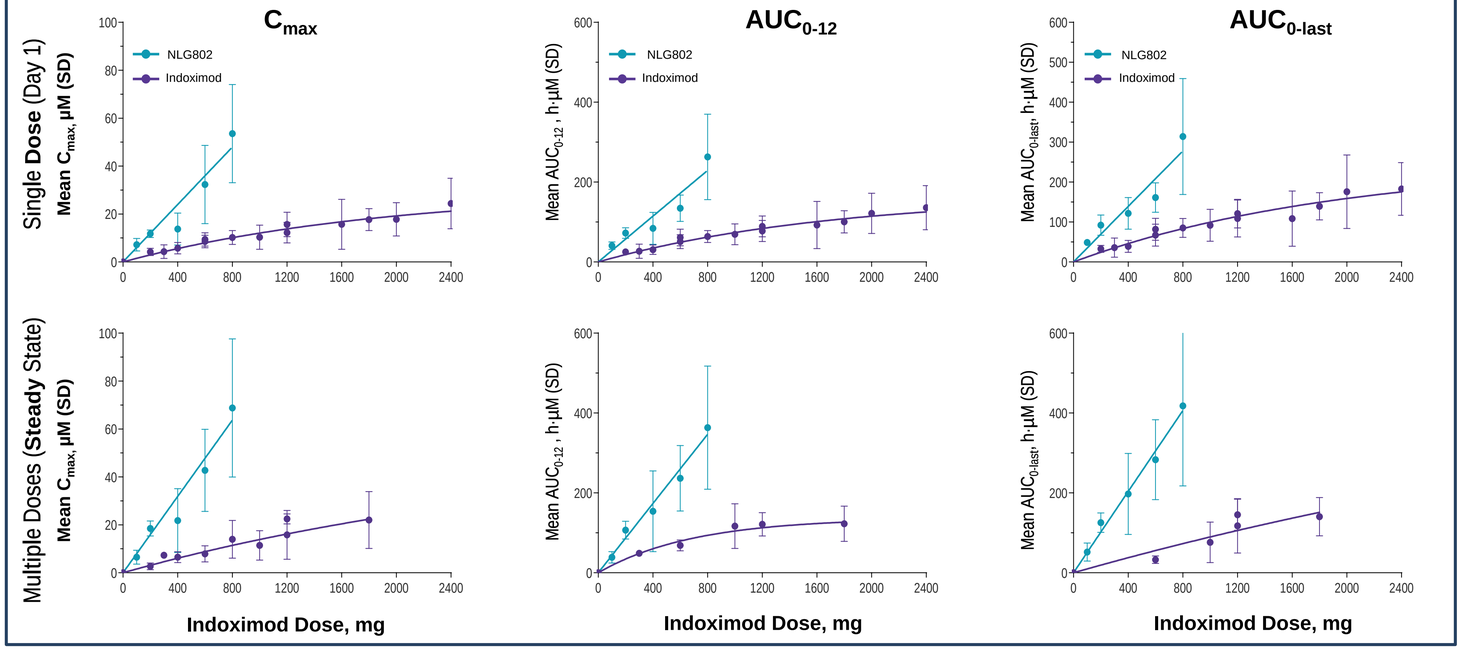


Table 4. PK Parameters for Indoximod after Single (Day 1) or Multiple (Day 21) NLG802 Doses

	NLG802 180 mg n=3		NLG802 363 mg n=4		NLG802 726 mg n=4		NLG802 1089 mg n=7		NLG802 1452 mg n=7	
Indoximod molar equivalent dose	**100 mg**		**200 mg**		**400 mg**		**600 mg**		**800 mg**	
	Day 1	**Day 21**	**Day 1**	**Day 21**	**Day 1**	**Day 21***	**Day 1**	**Day 21***	**Day 1**	**Day 21**
C_{max}, µM	7.2 (2.6)	6.5 (2.9)	11.8 (1.6)	18.5 (3.2)	13.8 (6.6)	21.8 (13.3)	32.3 (16.4)	42.7 (17.2)	53.6 (20.5)	68.8 (28.8)
T_{max}, h	1.4 (0.6)	2.2 (1.8)	2.5 (1.0)	2.5 (1.1)	7.0 (4.2)	3.3 (1.2)	1.9 (0.9)	2.3 (0.9)	2.0 (0.0)	2.6 (1.0)
C_{12h}, µM	1.2 (0.3)	1.5 (0.9)	2.8 (1.0)	3.1 (0.8)	5.5 (2.4)	5.3 (3.1)	4.5 (1.2)	7.4 (3.5)	7.4 (5.1)	9.2 (7.0)
$T_{1/2}$, h	4.3 (0.7)	5.5 (1.7)	4.8 (1.9)	3.9 (1.1)	4.4 (0.7)	6.0 (4.2)	4.4 (0.8)	4.6 (1.9)	4.6 (1.1)	3.4 (0.9)
AUC_{0-12}, h·µM	40.4 (9.9)	38.3 (13.8)	70.4 (12.2)	105.4 (21.3)	81.3 (35.4)	152.4 (98.5)	133.4 (31.8)	235.7 (80.7)	263.5 (108.3)	362.9 (154.4)
AUC_{0-inf}, h·µM	48.4 (7.9)	51.4 (22.1)	91.0 (25.5)	123.2 (23.2)	118.6 (37.1)	194.9 (96.9)	161.1 (36.0)	289.7 (115.5)	315.0 (147.8)	414.3 (196.7)
CL/F, L/h	17.4 (2.8)	19.2 (10.9)	19.7 (6.7)	13.9 (2.5)	29.9 (8.0)	19.6 (7.6)	32.8 (9.7)	19.1 (5.8)	24.6 (8.9)	19.3 (8.3)
V/F, L	119.3 (33.7)	136.2 (29.9)	125.5 (22.7)	77.5 (22.6)	169.5 (42.6)	185.5 (168.1)	207.4 (57.6)	119.4 (48.1)	156.4 (48.6)	91.8 (40.4)

** 1 subject did not complete dose-limiting toxicity window. Values are given as mean (standard deviation [SD]). AUC_{0-12}, area under concentration-time curve from time 0 to 12 h; AUC_{0-inf}, AUC from time 0 to infinity; C_{max}, maximum concentration; CL/F, oral clearance; T_{max}, time to C_{max}; $t_{1/2}$, half life; V/F, apparent volume of distribution.*

Figure 4. Indoximod Exposure Parameters After Single or Repeated Molar-Equivalent Oral Doses of Indoximod or NLG802



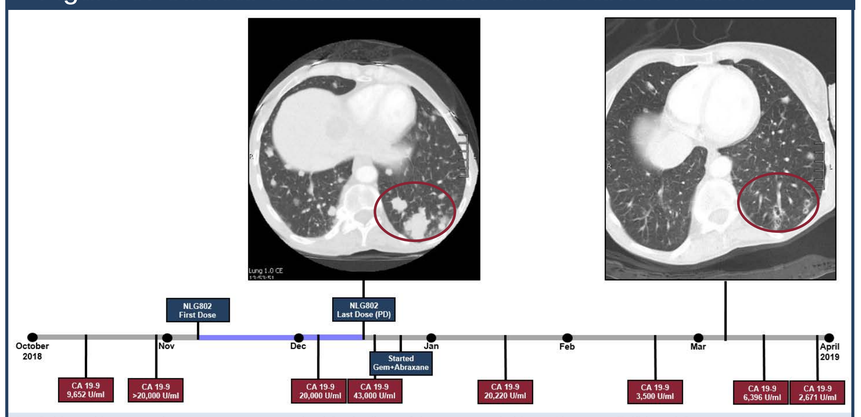
Maximum Tolerated Dose (MTD)

- NLG802 MTD/MBAD was not reached
  - 1 subject did not complete first 28-day cycle due to rapid disease progression (726 mg); 1 subject did not take 80% of NLG802 in first cycle (1089 mg); 1 subject withdrew within 2 hr of dosing (1452 mg); all were replaced

Antitumor Activity

- 6 subjects achieved a best response of stable disease per RECIST 1.1 criteria, with 1 subject having durable stable disease > 9 months
- 1 subject had an interesting partial response after NLG802 treatment was discontinued due to progressive disease on study and the subject was re-challenged with chemotherapy. ***Figure 5***

Figure 5. Clinical Course of mPancreatic Cancer Patient



- Subject with metastatic pancreas cancer received 3 prior lines of therapy: gemcitabine + Abraxane, Folfiri, and Camptosar + gem – Last dose 07Oct2018, started NLG802 (1089mg BID) on 07Nov2018, ended NLG802 on 15Dec2018 due to disease progression, patient also had elevated liver function tests up to grade 3 at end of treatment
- Re-challenged with gemcitabine + Abraxane, started Dec2018, received 2 cycles, Imaging Mar2019 showed PR with 38% tumor reduction (RECIST), but functional status improved to ECOG PS0, overall tumor burden reduced by >75% and cachexia reversed
- CA19-9 levels dropped 94% from levels prior to re-challenge (43,000 to 2,671 U/ml)

CONCLUSIONS

- Overall, NLG802 was well tolerated, with no unexpected safety signals
- MTD/MBAD has not been reached, RP2D established at 1452 mg BID based on achieving exposure levels required for PD effects of indoximod (Table 1)
- After continuous BID dosing at 1452 mg, NLG802 produced 6-fold increase in C_{max} and 4.7-fold increase in AUC compared with molar equivalent of indoximod dosing
- Daily exposure at steady state after NLG802 1452 mg Q12h dosing was ~726 µM·h, which compared favorably to 240 µM·h obtained with indoximod 1200 mg BID
- Average steady-state plasma concentration after NLG802 1452 mg Q12h dosing was 30.3 µM compared with ~10 µM for indoximod 1200 mg BID dose
- NLG802 warrants further investigation as a single agent or in combination therapy regimens

References: ***1.*** *Brincks EL, et al. AACR 2018, poster 3753;* ***2.*** *Jackson E, et al. ASCO 2013, poster 3026;* ***3.*** *Soliman HH, et al. ASCO 2014, poster TPS3124;* ***4.*** *Mautino A, et al. AACR 2017, poster 4076*

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