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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 1200 mg BID
- Increasing doses above 1200 mg BID generally does not result in increased plasma concentration or drug exposure due to limiting dose-dependent oral bioavailability
- To improve bioavailability of indoximod, we developed NLG802, a prodrug that increases oral bioavailability of indoximod ~5-fold in nonhuman primates[2]

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

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

→ **Oral NLG802 BID**

- 180 mg
- 363 mg
- 726 mg
- 1089 mg
- 1452 mg

→ Repeating 28-d cycles until toxicity or disease progression

- PK assessments were performed at Day 1 after first single dose (0–72 h) and at Day 21 (0–12 h) after repeated BID (q12h) dosing

RESULTS

Baseline Demographics

		Total N=11	NLG802 180 mg BID n=3	NLG802 363 mg BID n=4	NLG802 726 mg BID n=4
Median age, y (range)		63 (41–81)	41 (41–64)	69 (55–77)	69 (46–81)
Female, n (%)		4 (45)	2 (67)	2 (50)	1 (25)
Caucasian/white, n (%)		11 (100)	3 (100)	4 (100)	4 (100)
Tumor type, n (%)	Colorectal	3 (27)	1 (33)	1 (25)	1 (25)
	Bladder	1 (9)	1 (33)	0	0
	Cervical	1 (9)	1 (33)	0	0
	Pancreas	3 (27)	0	2 (50)	1 (25)
	Melanoma	1 (9)	0	1 (25)	0
	Sarcoma	1 (9)	0	0	1 (25)
	Lung	1 (9)	0	0	1 (25)

- NLG802 has been administered at 3 of 5 dose levels in 11 subjects

Safety and Tolerability

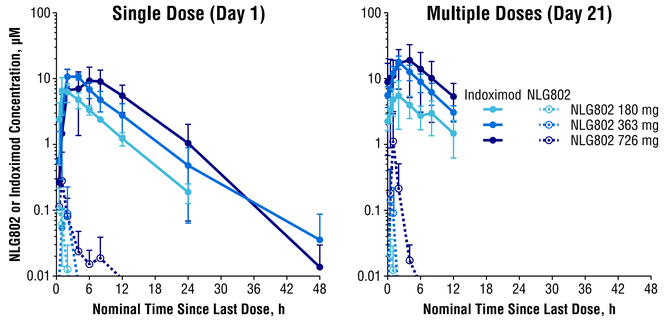
	Total N=11	NLG802 180 mg BID n=3	NLG802 363 mg BID n=4	NLG802 726 mg BID n=4
AEs in >2 subjects				
Fatigue	6	1	3	2
Nausea	5	3	1	1
Peripheral edema	4	2	2	
Subjects with Grade 3 AEs (all unrelated to NLG802), n	4	2	1	1
Type of event*		Abdominal distention, constipation, hypokalemia, back pain, abdominal pain, anemia, ascites, hypophosphatemia, localized edema, edema peripheral, esophagitis	Hypokalemia	Muscular weakness
Subjects with NLG802-related AEs (all Grade 1 or 2), n†	6	1	2	3
Type of event*		↑ LDH, fatigue, ↓ lymphocyte count, nausea	Fatigue, nausea, rash	Abdominal discomfort, ↓ blood Mg, fatigue (2 events), nausea, vomiting

*1 report of each event unless otherwise indicated; †No Grade ≥3 events occurred. AEs, adverse events; LDH, lactate dehydrogenase.

- No subject experienced any dose-limiting toxicities or AEs Grade >3
- There were no NLG802-related AEs leading to discontinuation or serious NLG802-related AEs

Pharmacokinetics

Time-Dependent Mean Plasma Concentration of NLG802 or Indoximod After Oral Dose(s) of NLG802

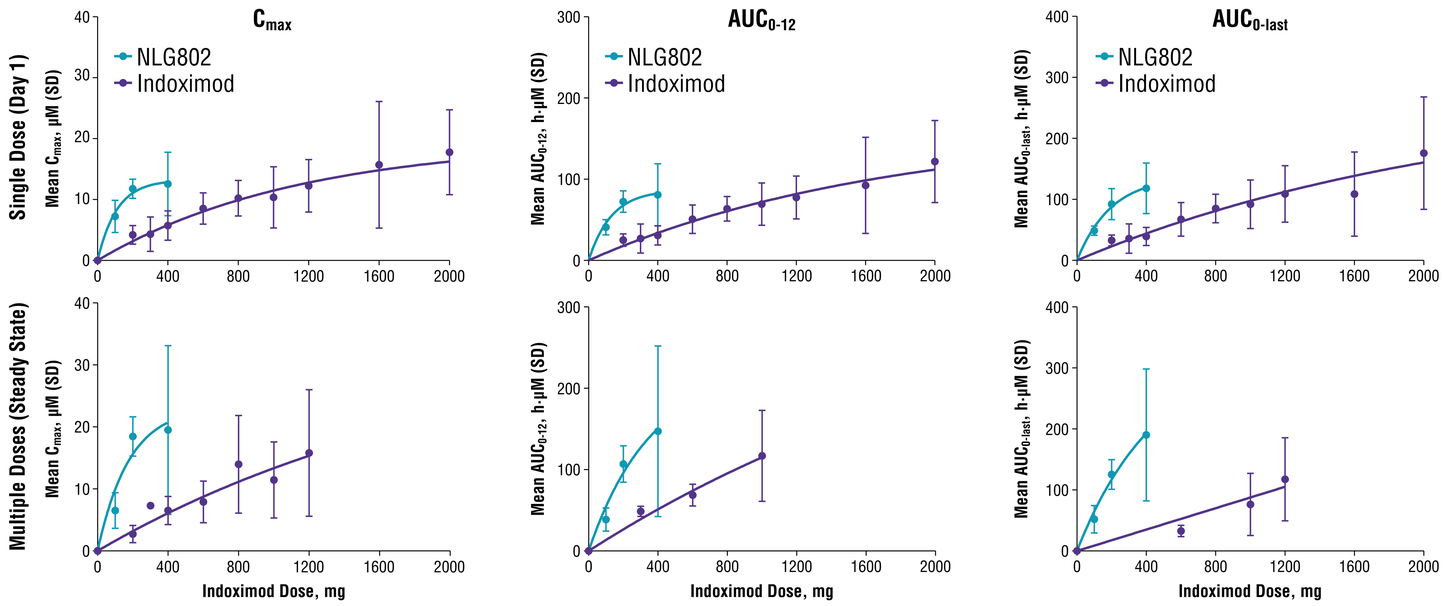


PK Parameters for Indoximod after Single (Day 1) or Multiple (Day 21) NLG802 Doses

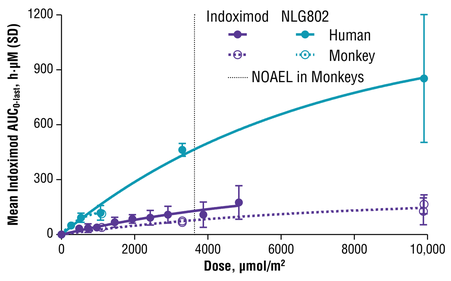
Indoximod Molar Equivalent Dose	NLG802 180 mg: n=3		NLG802 363 mg: n=4		NLG802 726 mg: n=4	
	100 mg		200 mg		400 mg	
	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21*
C_{max}, μM	7.2 (2.7)	6.5 (2.9)	11.8 (1.6)	18.5 (3.2)	12.5 (5.2)	19.5 (13.6)
T_{max}, h	1.3 (0.6)	2.2 (1.8)	2.5 (1.0)	2.5 (1.0)	7.0 (4.2)	3.3 (1.2)
$T_{1/2}$, h	4.4 (0.7)	5.6 (1.7)	4.7 (1.9)	4.1 (1.2)	4.4 (1.0)	6.0 (4.2)
$AUC_{0\text{-}12}$, h·μM	40.9 (9.4)	38.7 (14.2)	72.6 (13.3)	106.9 (22.4)	80.7 (38.3)	147.1 (104.9)
$AUC_{0\text{-}inf}$, h·μM	48.8 (7.6)	52.1 (22.6)	92.2 (25.5)	125.5 (24.4)	118.1 (41.5)	190.2 (108.3)
CL/F, L/h	17.2 (2.6)	19.0 (11.0)	19.2 (6.6)	13.5 (2.5)	30.4 (8.4)	21.0 (9.3)
V/F, L	110.0 (34.0)	137.0 (29.0)	120.0 (24.0)	79.0 (23.0)	192.9 (68.4)	190.3 (164.6)

*1 subject did not complete dose-limiting toxicity window due to rapid disease progression. Values are given as mean (standard deviation [SD]). $AUC_{0\text{-}12}$, area under concentration-time curve from time 0 to 12 h; $AUC_{0\text{-}inf}$, 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.

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



Indoximod Exposure in Monkeys and Humans After Single Oral Dose of NLG802 or Indoximod at Allometrically Scaled Molar-Equivalent Doses



NOAEL, no-observed-AE level.

Maximum Tolerated Dose or Maximum Biologically Achievable Dose

- NLG802 MTD/MBAD had not been reached at time of analysis
  - 1 subject (726 mg dose) did not complete dose-limiting toxicity window due to rapid disease progression and was replaced

Antitumor Activity at Time of Analysis

- 2 subjects achieved a best response of stable disease per RECIST 1.1 criteria, with 1 subject having durable stable disease >8 cycles
- 5 subjects (45%) remained on study, 5 (45%) were alive, and 1 unknown due to withdrawal (10%)

CONCLUSIONS

- Overall, NLG802 was well tolerated, with no unexpected safety signals
- At the time of this analysis, MTD/MBAD had not been reached
- NLG802 produced 4-fold increases in C_{max} and AUC after a single dose, and 4–5.5 fold increases in C_{max} and AUC after continuous BID dosing compared with the molar equivalent of indoximod dosing
- Average accumulation ratios for indoximod after repeated NLG802 BID dosing were 1.2, 1.4, and 1.6 at doses of 180, 363, and 726 mg, respectively
- Daily exposure at steady state after NLG802 726 mg BID dosing was ~300 h·μM, which compared favorably to 240 h·μM obtained with indoximod 1200 mg BID
- Average steady-state plasma concentration after NLG802 726 mg BID dosing was 12.5 μM compared with ~10 μM for indoximod 1200 mg BID dose

REFERENCES **1.** Brincks EL, et al. AACR 2018, poster 3753; **2.** Mautino M, et al. AACR 2017, poster 4076.

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