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Clinical Trial Results

A Single-arm Phase II Study Combining NLG207, a Nanoparticle Camptothecin, with Enzalutamide in Advanced Metastatic Castration-resistant Prostate Cancer Post-Enzalutamide

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Abstract

Background: Despite the clinical efficacy of enzalutamide monotherapy in patients with advanced prostate cancer, therapeutic resistance and disease progression are inevitable. We proposed a study to evaluate NLG207, a nanoparticle-drug conjugate (NDC) of the potent topoisomerase I inhibitor camptothecin, in combination with enzalutamide, in patients with metastatic castration-resistant prostate cancer (mCRPC) following progression on enzalutamide.

Methods: This was a single-arm, optimal two-stage, phase II study to evaluate the efficacy of NLG207 in combination with enzalutamide in patients with mCRPC who received prior enzalutamide. A lead-in dose escalation evaluated the recommended phase 2 dose of NLG207 in combination with enzalutamide. Patients received NLG207 via IV infusion every 2 weeks and enzalutamide 160 mg orally once daily.

Results: Between March 2019 and June 2021, four patients were accrued to the lead-in dose escalation. Two of the four patients were evaluable and both experienced DLTs at the NLG207 12 mg/m^2 dose level; one DLT was related to a dose delay for noninfective cystitis and myelosuppression, the other a grade 3 noninfective cystitis. Further evaluation of NLG207 in combination with enzalutamide was halted and the study was ultimately terminated. PSA declines from baseline were observed in two patients.

Conclusion: NLG207 12 mg/m^2 in combination with enzalutamide was not well tolerated in patients with mCRPC following several lines of the standard of care therapy.

ClinicalTrials.gov Identifier: NCT03531827.

Key words: metastatic castration-resistant prostate cancer (mCRPC); enzalutamide; NLG207; nanoparticle; noninfective cystitis.

Lessons Learned

- NLG207 in combination with enzalutamide was not well tolerated in patients with mCRPC who previously received enzalutamide and additional lines of the standard of care treatment.

Discussion

This study sought to evaluate the efficacy of NLG207 in combination with enzalutamide in patients with mCRPC who previously progressed on enzalutamide. NLG207 (formerly CRLX101, currently EP0057), a nanoparticle-drug conjugate (NDC) of camptothecin, was previously shown to inhibit HIF-1α protein accumulation and tumor angiogenesis in numerous preclinical models. Building on prior data suggesting that dual targeting of HIF-1α and the androgen receptor (AR) could re-sensitize prostate cancer cells to AR-targeted

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Table 1. Dose-limiting toxicities.

Dose level	Dose of NLG207	Dose of enzalutamide	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity
1	12 mg/m^2	160 mg	4	2	2

therapy, we demonstrated the enhanced efficacy of enzalutamide when given in combination with NLG207 in relevant in vivo models of enzalutamide resistance. NLG207 in combination with enzalutamide was hypothesized to overcome enzalutamide resistance and result in clinically meaningful increases in TTP in patients with mCRPC previously treated with enzalutamide. Our study enrolled a total of 4 patients in the lead-in dose-escalation, of which only two patients were evaluable for toxicity, and both experienced dose-limiting toxicities (noninfective cystitis, neutrophil count decrease) attributable to NLG207 at 12 mg/m^2, invalidating this dose for further investigation and ultimately leading to study termination (Table 1). Although the regimen was deemed intolerable in this patient population, 2 of 4 patients experienced a decline in PSA from baseline as the best response, including one patient with a 56% decline in PSA following 2 weeks of therapy (baseline and 2-week post-PSA values of 33.67 and 14.84 ng/dL, respectively) (Fig. 1). Despite promising preclinical data and PSA declines observed in the study, NLG207 12 mg/m^2 in combination with enzalutamide was intolerable in patients with mCRPC following numerous lines of therapy.

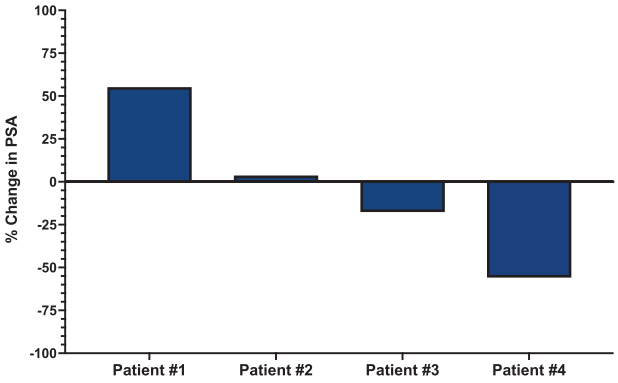

Figure 1. Best prostate-specific antigen (PSA) response in patients treated with NLG207 and enzalutamide.

A further clinical investigation targeting the HIF-AR axis in patients with the prostate center will require the discovery and optimization of more tolerable agents targeting HIF-1α signaling in the future.

Author disclosures and references available online.

Trial Information	
Disease	Prostate cancer, advanced
Stage of disease/treatment	Metastatic castration-resistant
Prior therapy	Prior enzalutamide treatment
Type of study	Single-arm phase II study with lead-in dose escalation
Primary endpoint	To evaluate the anti-tumor activity of NLG207 at the recommended phase II dose (RP2D) combined with enzalutamide with respect to treatment response, defined as ≥50% PSA decline or stable disease on imaging following 5 months of treatment.
Secondary endpoints	To validate the RP2D of NLG207 in combination with enzalutamide To evaluate the duration of response as defined by a sustained >30% decline in PSA, overall survival, and changes in measurable disease as determined by Response Evaluation Criteria in Solid Tumors (RECIST) and Prostate Cancer Working Group 3 (PCWG3) for the treatment combination
Investigator's assessment	Poorly tolerated/not feasible Study prematurely terminated due to toxicity of the investigational agent

Additional Details of Endpoints or Study Design

The study was designed with a lead-in cohort of 3–6 patients to confirm the expected MTD of NLG207 in combination with enzalutamide (Fig. 2). The first two patients withdrew from the study to seek other therapy before experiencing toxicities or having a response assessment. DLT assessments occurred over 3 months (Fig. 3).

Exploratory Endpoints:

- To evaluate the pharmacokinetic profile of NLG207 (both total drug and released camptothecin) and enzalutamide in plasma.
- To evaluate the underlying mechanism of camptothecin-induced cystitis.
- To evaluate the pharmacodynamic activity of NLG207 and enzalutamide using surrogate biomarkers to measure acquired treatment resistance mediated by angiogenesis and androgen receptor signaling (eg, VEGF, CTCs, AR-V7).
- To evaluate the activity of NLG207 and enzalutamide with respect to the prevalence of circulating tumor cells with high genomic instability.
- To explore possible correlations between clinical response and biomarkers of DNA damage response (eg, DNA damage response panel).

Drug Information	Drug 1	Drug 2
Generic/working name	NLG207 (formerly CRLX101, currently EP0057)	Enzalutamide
Company name	Ellipsis	Astellas
Drug type	Nanoparticle-drug conjugate (NDC)	Small molecule
Drug class	Topoisomerase I inhibitor	Androgen receptor antagonist
Dose	12 mg/m^2	160 mg
Route	Intravenous (IV)	Oral
Schedule of administration	Every 2 weeks	Daily

Patient Characteristics	
Number of patients, male	4
Stage	Metastatic castration-resistant
Age: median (range)	74 (69-76) years
Number of prior systemic therapies: median(range)	3 (3-4)
Performance status: ECOG	0-0 1-4 2-0 3-0 4-0

Primary Assessment Method	
Title	Response, safety, and efficacy evaluation
Number of patients screened	4
Number of patients enrolled	4
Number of patients evaluable for toxicity	2
Number of patients evaluated for efficacy	0

Assessment, Analysis, and Discussion

Completion	Study terminated prior to completion
Investigator's Assessment	Poorly tolerated/not feasible. The study was terminated due to intolerable toxicity (ie, noninfective cystitis) attributed to NLG207 in patients with mCRPC.

Enzalutamide is a potent second-generation androgen receptor antagonist that has been shown to improve overall survival in patients with metastatic castration-resistant prostate cancer (mCRPC).[1,2] Disease progression on enzalutamide monotherapy is inevitable and treatment duration is limited secondary to acquired resistance. Acquired resistance following enzalutamide treatment is most frequently characterized via androgen receptor (AR) alterations (eg, AR amplification, AR splice variation) and associated with the shorter time to progression (TTP).[3-6] In addition to AR alterations, intra-tumoral hypoxia has been implicated in facilitating aggressive tumor phenotypes, metastatic potential, and acquired resistance to AR-targeted treatments.[7-11] Notably, hypoxia-inducible factor (HIF)-1α, the master transcription factor in hypoxia, can alter cellular metabolism, promoting tumor angiogenesis, anaerobic metabolism, immunity, adaptation, and invasion.[11,12] HIF-1α inhibition was shown to enhance the activity of enzalutamide in vitro, reducing AR- and HIF--α-regulated gene transcription and inhibiting cell growth.[7]

NLG207 (formerly CRLX101, currently EP0057), a nanoparticle-drug conjugate (NDC) of the potent topoisomerase I inhibitor, camptothecin,[13] was previously shown to inhibit both HIF-1α protein accumulation and tumor angiogenesis in numerous preclinical models.[14-17] In a prostate cancer xenograft model with AR amplification and AR splice variant expression (eg, AR-V7), combination treatment with NLG207 and enzalutamide resulted in significant reductions in tumor growth, with re-sensitization of tumors to enzalutamide. In vitro, NLG207 as a single agent was shown to down-regulate full-length AR and AR-V7 expression, and significantly down-regulate AR target-gene expression (PSA and ERG) when in combination with enzalutamide.[18] Based on these findings, NLG207 in combination with enzalutamide was hypothesized to overcome enzalutamide resistance and result in clinically meaningful increases in TTP in patients with mCRPC despite prior disease progression on enzalutamide monotherapy.

NCT03531827 (study design and dose escalation summarized in Figs. 2 and 3, respectively) enrolled a total of four patients in the lead-in dose escalation arm between March 2019 and June 2021. The NLG207 starting dose of 12 mg/m^2 IV every 2 weeks was selected based on a previously established maximum tolerated dose of 15 mg/m^2 as a single agent. The key characteristics of the patients are summarized in Table 2. Two of the study participants (Patients 1 and 4) withdrew from the study in favor of alternative treatment options prior to completing the DLT period and prior to the start of cycle 2 and were, therefore, ineligible for NLG207 DLT evaluation. The remaining study participants (Patients 2 and 3) were both eligible for DLT evaluation and both experienced DLTs at least possibly attributable to NLG207 12 mg/m^2. Patient 2 experienced Grade 3 noninfective cystitis starting 2 days after the 5th dose of NLG207 12 mg/m^2 (patient was not dose-escalated due to Grade 2 anemia and increasing fatigue), resulting in hospitalization and a DLT. NLG207 was stopped but the patient continued to receive enzalutamide 160 mg once daily. The patient died several weeks later; death was deemed possibly related to both NLG207 and disease progression, as his hematuria and anemia never fully resolved. Patient 3 developed hematuria several days prior to the scheduled 4th dose of NLG207; the Grade 2 noninfective cystitis resulted in holding the NLG207 dose. Further NLG207 dosing delays secondary to Grade 2 decreased neutrophil count and unresolved AEs resulted in a DLT and permanent discontinuation of NLG207. The 12 mg/m^2 dose of NLG207 in combination with enzalutamide 160 mg was deemed intolerable in this mCRPC population.

Though most adverse events related to NLG207 are frequently seen with chemotherapy, the bladder-associated toxicity in patients with mCRPC led to the termination of this study. Noninfective cystitis and hematuria of any grade are known toxicities associated with NLG207 treatment and have been reported in prior phases I and II studies.[19-23] Hydration and frequent voiding have been suggested as mitigation strategies, especially during the first 48 h post-infusion, primarily to limit the accumulation of camptothecin in the bladder.[23] Despite reported patient compliance and intravenous hydration pre- and post-NLG207 administration, Grades 2 and 3 cystitis still occurred. Urinary alkalinization with sodium bicarbonate has also been proposed for cystitis prevention in patients at risk for bladder toxicity[13,24-26]; though we were unable to evaluate preemptive sodium bicarbonate, oral sodium bicarbonate following symptom onset was given to Patient 3 with limited clinical benefit. Given the severity of reported symptoms and limited effective treatment options to manage noninfective cystitis, the decision was made to terminate the study. Lower doses of NLG207 were not explored.

Planned plasma exposure-response analyses were not performed due to limited accrual, however, we previously published plasma concentration-time curves for 3 patients[13] and pooled this data with NCT02769962 to generate a population-pharmacokinetic (popPK) model.[24] Based on our model, the highest concentrations of free camptothecin occur in the 48 h following infusion,[24] consistent with the onset of Patient 2's symptoms 2 days post-infusion. For Patient 3, however, symptom onset was reported on Day 10 post-infusion; a plasma trough concentration collected and measured five days later showed low, detectable levels of both free and nanoparticle-bound camptothecin. While our findings in the mCRPC population are limited, it appears the onset of bladder-associated toxicity does not correlate with increased plasma concentrations of camptothecin, and may result from prolonged exposure in the bladder, even at low concentrations; such findings further support our decision to terminate this study.

Notwithstanding limited time on NLG207 therapy, 2 of the 4 patients experienced a decline in PSA from baseline as the best response, including a 56% PSA decline following two weeks of therapy (baseline and 2 weeks post-PSA values of 33.67 and 14.84 ng/dL, respectively) (Fig. 1). Following discontinuation of NLG207, Patient 3 received enzalutamide treatment on-study for 41 weeks until radiographic disease progression; though the TTP was unexpectedly long for a patient with mCRPC who received 4 previous lines of therapy,[27] this cannot be definitively tied to combination drug exposure.

NLG207 in combination with enzalutamide was not a tolerable regimen in patients with mCRPC following numerous lines of therapy. Intolerable toxicities, most notably bladder-associated adverse events, were observed in both patients

who received at least 3 doses of NLG207 (Tables 3 and 4). A further clinical investigation targeting the HIF-AR axis in patients with prostate center will require better-tolerated agents targeting HIF-1α signaling in the future.

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Conflict of Interest

The National Cancer Institute has Cooperative Research and Development Agreements (CRADAs) with EMD Serono, Immunity Bio, and Therion Biologics. These CRADAs provide resources for the co-development of experimental agents. James Gulley has a patent filed entitled "Combination PDL1 and TGF-beta blockage in patients with HPV+ malignancies.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

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Figures and Tables

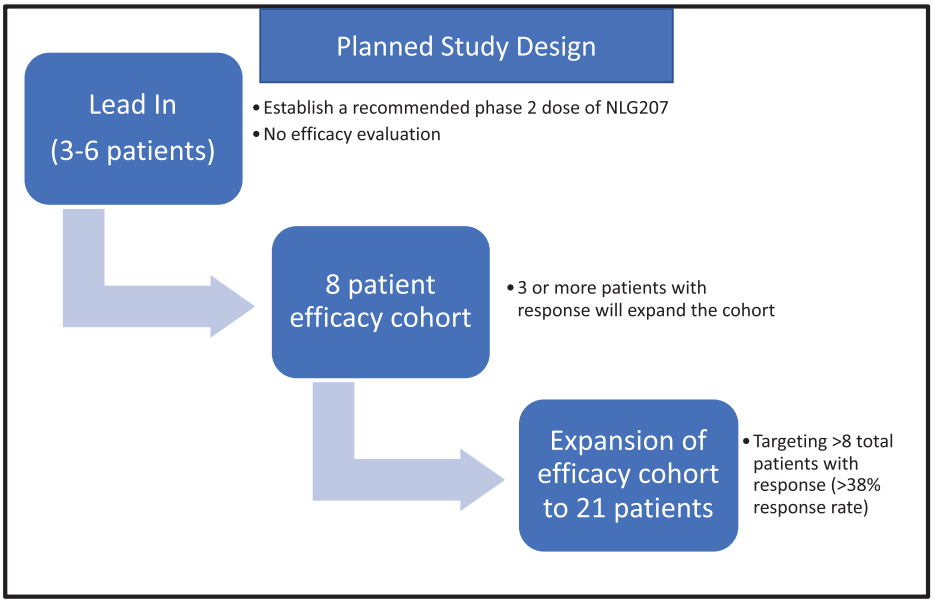

Figure 2. Study overview.

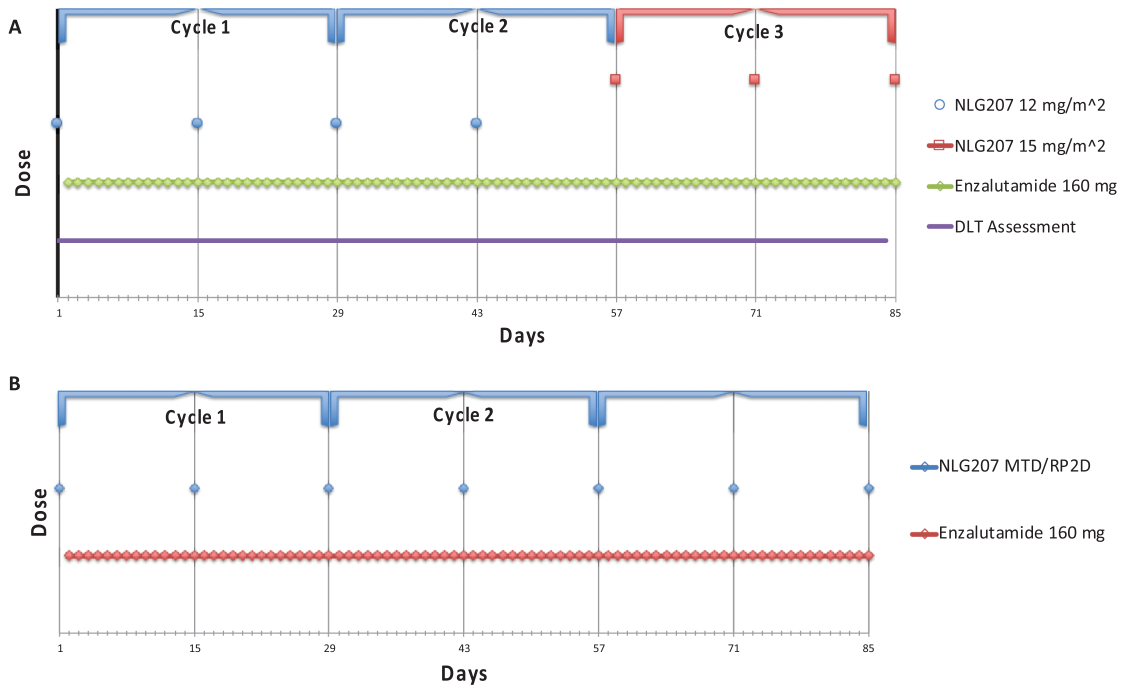

Figure 3. Dosing strategies. The dosing schema for the lead-in dose escalation with DLT assessment (**A**) and for the remainder of the study following confirmation of the MTD/RP2D (**B**).

Table 2. Patient-specific characteristics.

Characteristic	Patient #1	Patient #2	Patient #3	Patient #4
Age, years	69	75	72	76
Race	Caucasian	Caucasian	African American	Caucasian
Weight (kg)	71.6	85.6	70.4	78.2
ECOG performance status	1	1	1	1
On-study PSA (ng/dL)	143	136.3	51.08	33.67
Site(s) of metastasis	Bone	Bone, liver, lymph node	Bone	Bone, liver, lymph node
Gleason score at diagnosis	8	7	9	N/A
Prior treatments (includes enzalutamide)	Abiraterone, Cabazitaxel, Carboplatin/Docetaxel, Durvalumab/Olaparib	Sipuleucel-T, Docetaxel, Abiraterone, Cabazitaxel	Radium-223, Docetaxel, Abiraterone	Docetaxel, Abiraterone, Carboplatin

Table 3. Adverse events (attribution to NLG207 unless otherwise noted).

Adverse event	Grade, *n* (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Dizziness	[a]1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	[a]1 (25)
Fatigue	0 (0)	[b]1 (25)	0 (0)	0 (0)	0 (0)	[b]1 (25)
Nausea	0 (0)	2 (50)	0 (0)	0 (0)	0 (0)	2 (50)
Anemia	0 (0)	2 (50)	2 (50)	0 (0)	0 (0)	3 (75)
Lymphocyte decrease	1 (25)	2 (50)	0 (0)	0 (0)	0 (0)	2 (50)
White blood cell decrease	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	1 (25)
Neutrophil count decrease	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)	1 (25)
Cystitis (noninfective)	0 (0)	1 (25)	1 (25)	0 (0)	0 (0)	2 (50)
Hematuria	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	1 (25)
Not otherwise specified	0 (0)	0 (0)	0 (0)	0 (0)	[c]1 (25)	1 (25)

[a]Attribution to enzalutamide.
[b]Attribution to both NLG207 and enzalutamide.
[c]Deemed possibly related to both disease progression and NLG207.

Table 4. Serious adverse events.

Name	Grade	Attribution
Noninfective cystitis	3	NLG207