CT151

A Phase II Study of NLG207 in Combination with Weekly Paclitaxel in Patients with Recurrent or Persistent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

*Linda Duska[1], David M. O'Malley[2], Carolyn Krasner[3], Russell J. Schilder[4], Cara Mathews[5], Kathleen Moore[6], Premal H. Thaker[7], Austin Miller[8], Christopher Purdy[8], A.J. Leyco[9] , Christopher Smith[9], Deborah Mercier[9], Lucinda Tennant[9] , Eugene Kennedy[9], Nicholas Vahanian[9], Charles Link[9]

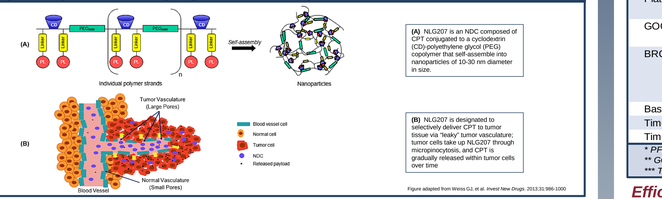
University of Virginia[1], The Ohio State University[2], Dana Farber Cancer Institute[3], Thomas Jefferson University[4], Women & Infants Hospital Rhode Island Warren Alpert School of Medicine of Brown University[5], Stephenson Cancer Center at the University of Oklahoma HSC[6], Washington University[7], Roswell Park Comprehensive Cancer Center[8], NewLink Genetics Corporation[9]

*Presenting author

INTRODUCTION

- NLG207 (formerly CRLX101) is a novel investigational nanoparticle drug conjugate (NDC) (***Figure 1A***) composed of a cyclodextrin-based polymer backbone linked to camptothecin (CPT), a topoisomerase 1 inhibitor
- CPT stabilizes the Topo 1-DNA cleavage complex during DNA replication and prevents Topo 1 mediated DNA relegation, ultimately leading to apoptosis[1]
- NLG207 is designed to selectively deliver CPT to tumor tissue to avoid the toxicity observed with traditional CPT drug delivery (***Figure 1B***) [2]
- NLG207 has been studied in more than 400 patients as monotherapy or in combination with other anticancer agents[3-6]
- In a Phase II trial including recurrent platinum resistant ovarian, fallopian tube, and primary peritoneal cancer patients, NLG207 demonstrated single agent activity with 74% (14/19) of patients showing a net tumor reduction and an overall response rate (ORR) of 16% (3/19) per RECIST criteria[6]

Figure 1. Dynamic Tumor Targeting and Molecule Design



(A) NLG207 is an NDC composed of CPT conjugated to a cyclodextrin (CD)-polyethylene glycol (PEG) copolymer that self-assemble into nanoparticles of 10-30 nm diameter in size.

(B) NLG207 is designed to selectively deliver CPT to tumor tissue via "leaky" tumor vasculature; tumor cells take up NLG207 through micropinocytosis, and CPT is gradually released within tumor cells over time

Figure adapted from Weiss GJ, et al. *Invest New Drugs*. 2013;31:986-1000

METHODS

Study Design

- Phase Ib/II, single-arm, open-label expansion study (ClinicalTrials.gov: NCT02389985)
  - Phase Ib NLG207 dose escalation lead in (N = 9): 12 mg/m^2 IV (n = 3) and 15 mg/m^2 IV (n = 6) in combination with paclitaxel 80 mg/m^2 IV[7]
  - Phase II NLG207 expansion (N = 21): 15 mg/m^2 IV in combination with paclitaxel 80 mg/m^2 IV
  - No dose-limiting toxicities reported at either dose level, thus the RP2D established was NLG207 15 mg/m^2 (every other week) and paclitaxel 80 mg/m^2 (3 weeks on/1 week off)[7]
- Treatment cycle was repeated every 28 days until disease progression or toxicity

Phase 2
Expansion Phase

→ NLG207 15 mg/m^2 Q2W (Day 1, 15)
+
paclitaxel 80 mg/m^2 QW (Day 1, 8, 15)

Primary Objective:
- ORR in recurrent platinum resistant patients who previously received bevacizumab

Secondary Objective:
- PFS6, PFS, DOR in recurrent platinum resistant patients who previously received bevacizumab
- ORR, DOR, PFS6, PFS in recurrent platinum resistant patients

Eligibility Criteria

- Age ≥ 18 years old with histologically recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
- Measurable disease as defined by RECIST 1.1 with at least one target lesion
- At least 1 prior platinum-based chemo regimen for management of primary disease
- Adequate organ function, GOG performance status ≤1

RESULTS

Patient Characteristics

- The study accrued 30 patients (all completed at least 1 cycle) between July 2015 and January 2017; baseline and disease characteristics are presented in ***Table 1***

Table 1. Baseline Patient and Disease Characteristics

Characteristics		N = 30
Age, median (range), years		62 (44 - 76)
Tumor type	Ovarian	22
	Fallopian Tube	3
	Primary Peritoneal	5
Total # of prior therapies	< 3	13
	≥ 3	17
Prior bevacizumab treatment	Yes	19
	No	11
Prior platinum therapy status	Resistant	17
	Sensitive	13
Platinum Free Interval (PFI)*	< 6 months	9
	≥ 6 months	21
GOG** Performance Status	0	20
	1	10
BRCA status	No mutation	22
	Genetic variant, favor polymorphism	1
	Deleterious mutation	3
	Unknown	4
Baseline CA-125 level, U/mL, median (range)		420 (10 - 8886)
Time to latest prior platinum-based treatment***, months, median (range)		11 (1 - 27)
Time to initial diagnosis, months median (range)		22 (6 - 123)

** PFI is from last platinum-based treatment to subsequent disease progression*
*** GOG = GOG Foundation, Inc.*
**** Time from 1st dose of study drug to end of latest prior platinum-based treatment*

Efficacy

Table 2. Primary and Secondary Endpoints

Endpoint	All Patients N = 30	Previous Bevacizumab Patients N = 19
ORR (per RECIST 1.1)	8 (26.7%) *CI 14.2%, 44.4%* (CR=1; PR=7)	6 (31.6%) *CI 15.5%, 54.0%* (CR=1; PR=5)
mDOR (months)	6.0 *CI 3.6, 8.0*	4.9 *CI 3.6, 8.0*
mPFS (months)	5.4 *CI 3.7, 7.6*	5.4 *CI 2.2, 7.6*
PFS-6	41% *CI 0.22, 0.67*	41% *CI 0.23, 0.60*

Table 3. Best Response Platinum Status*

Best Response	Platinum Resistant N = 17	Platinum Sensitive N = 13
CR	0 (0.0%)	1 (7.7%)
PR	7 (41.2%)	4 (30.8%)
SD	5 (29.4%)	7 (53.8%)
PD	5 (29.4%)	1 (7.7%)

**including unconfirmed response*

Figure 2. Progression Free Survival (A) and Duration of Response by Platinum Sensitivity (B)

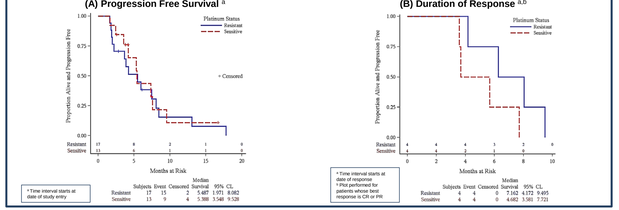


Figure 3. Duration of Therapy, Best Response and Patient Disposition, N = 30

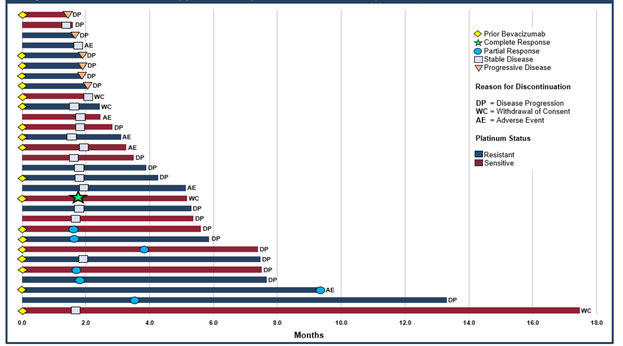
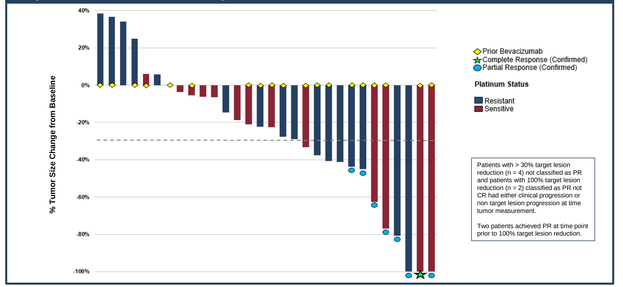


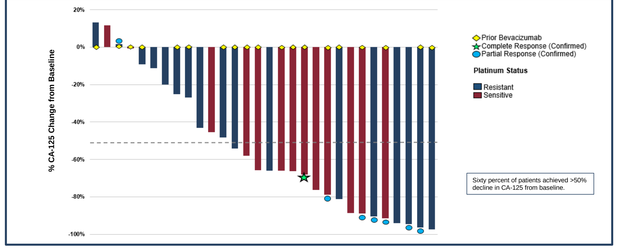
Figure 4. Best % Tumor Size Change from Baseline



Patients with > 30% target lesion reduction (n = 4) not classified as PR and patients with 100% target lesion reduction (n = 2) classified as PR not CR had either clinical progression or non target lesion progression at time tumor measurement.

Two patients achieved PR at time point prior to 100% target lesion reduction.

Figure 5. Best % CA-125 Change from Baseline



Sixty percent of patients achieved >50% decline in CA-125 from baseline.

Safety

- The most frequently reported treatment-related AEs for all grade events (occurring in ≥ 10% of patients) and all grade 3/4 events are shown in ***Table 4***
- The most frequently reported adverse events (AE): neutropenia, fatigue, alopecia and nausea
- Three patients experienced treatment-related serious adverse events (SAE): febrile neutropenia, urinary tract infection (UTI), and abdominal pain
- Four deaths were reported during the evaluation period: 3 patients died of disease and 1 patient was not related to treatment or disease

Table 4. Treatment-Related Adverse Events Occurring in ≥ 10% of Patients

Preferred term	ALL Grades N = 30, n (%)	Grade 3/4 N = 30, n (%)
Neutrophil count decreased	20 (67)	13 (43)
Fatigue	18 (60)	-
Alopecia	17 (57)	-
Nausea	13 (43)	-
Peripheral sensory neuropathy	11 (37)	-
Vomiting	7 (23)	-
Infusion related reaction	6 (20)	-
Diarrhea	5 (17)	-
Edema limbs	5 (17)	-
Hypomagnesemia	5 (17)	-
Anemia	4 (13)	3 (10)
Constipation	4 (13)	-
Mucositis oral	4 (13)	-
Urinary tract infection	4 (13)	1 (3)
Anorexia	3 (10)	-
Cystitis noninfective	3 (10)	1 (3)
Dizziness	3 (10)	-
Dyspnea	3 (10)	-
Hematuria	3 (10)	2 (7)
Hypertension	3 (10)	1 (3)
Hypokalemia	3 (10)	1 (3)
Myalgia	3 (10)	-
Rash maculo-papular	3 (10)	-

CONCLUSIONS

- NLG207 is a potentially best-in-class topoisomerase 1 inhibitor that demonstrates antitumor activity in recurrent ovarian cancer including those who have become resistant to platinum therapy
- The combination of NLG207 plus weekly paclitaxel was well tolerated in heavily pre-treated patients
- The adverse event profile of this combination is consistent with that seen for paclitaxel as a single agent except for cystitis, hematuria and UTI
- NLG207 warrants further investigation as a single agent or in combination therapy regimens for recurrent ovarian, fallopian tube or primary peritoneal cancer, particularly in platinum resistant patients

References

1. Lin CJ, et al. *Oncotarget*.2016 Jul 5;7(27):42408-42421
2. Clark AJ, et al. *PNAS*. 2016; vol. 113 (no. 14): 3850-3854
3. Weiss GJ, et al. *Invest New Drugs*. 2013;31:986-1000
4. Krasner CN, et al. *J Clin Oncol*. 2014;32:Abstract 5581
5. Keefe SM, et al. *Ann Oncol*. 2016;27:1579-85
6. Pham E, et al. *Clin Can Res*. 2014; 21(4); 808–18
7. Krasner, CN, et al. *Ann Oncol*. 2016;32: Abstract 1483

Acknowledgments

We thank the study patients, their families, caregivers, investigators and the study staff for their participation. The study was conducted in collaboration with GOG Foundation/Partners.