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Abstract 5538

LIO-1: Lucitanib + Nivolumab in Patients With Advanced Solid Tumors—Updated Phase 1b Results and Initial Experience in Phase 2 Ovarian Cancer Cohort (NCT04042116; ENGOT-GYN3/AGO/LIO)

Erika Hamilton,[1] Camille Gunderson Jackson,[2] Ramez N. Eskander,[3] Floor J. Backes,[4] Vicky Makker,[5] Fernanda Musa,[6] Alexander Olawaiye,[7] Jill Alldredge,[8] Bhavana Pothuri,[9] Angeles Alvarez Secord,[10] Nicole Concin,[11,12] Antonio González-Martín,[13] Jowell Go,[14] Kenton Wride,[14] Denise Lepley,[14] Terri Cameron,[15] Manish R. Patel[16]

[1]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [2]Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [3]UC San Diego Moores Cancer Center, La Jolla, CA, USA; [4]Ohio State University Wexner Medical Center and James Cancer Hospital, Columbus, OH, USA; [5]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical Center, New York, NY, USA; [6]Swedish Cancer Institute, Seattle, WA, USA; [7]Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA; [8]Anschutz Cancer Pavilion, Aurora, CO, USA; [9]Laura and Isaac Perlmutter Cancer Center at NYU Langone, New York, NY, USA; [10]Duke Cancer Institute, Duke University School of Medicine, Durham, NC, USA; [11]Ev. Kliniken Essen Mitte, Germany; [12]Medizinische Universität Innsbruck, Austria; [13]Clínica Universidad de Navarra, Madrid, Spain; [14]Clovis Oncology, Inc., Boulder, CO, USA; [15]Clovis Oncology UK Ltd., Cambridge, UK; [16]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL, USA.

CONCLUSIONS

- **Phase 1b cohort data defined the recommended phase 2 starting dose as lucitanib 6 mg orally once daily and nivolumab 480 mg intravenously every 28 days**
  - **Data suggest that the combination of lucitanib + nivolumab has promising antitumor activity (47.1% disease control rate) with a manageable safety profile across multiple tumor types**
- **The phase 2 study is ongoing; data from the initial 24 patients enrolled into stage 1 of the phase 2 ovarian cancer (OC) cohort are presented**
  - **In this heavily pretreated patient population, 1 confirmed partial response was seen**
  - **The OC cohort is closed to further enrollment, but ongoing patients continue to be followed**
  - **Safety is consistent with that reported in the phase 1b portion of the study**
- **An individualized safety-based lucitanib dose-titration strategy (including escalation from 6, to 8, to 10 mg once daily) appears feasible, as explored in the phase 2 OC cohort. Further investigation of this strategy is ongoing**

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Corresponding author: *Erika Hamilton*; ehamilton@tnonc.com.

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REFERENCES

1. Bello et al. *Cancer Res*. 2011;71:1396-405.
2. Mahoney et al. *Clin Ther*. 2015;37:764-82.
3. Hamilton et al. *Ann Oncol*. 2020;31(suppl 4):S480-1.

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INTRODUCTION

- Lucitanib is an oral tyrosine kinase inhibitor that selectively inhibits VEGFR1–3, PDGFRα/β, and FGFR1–3[1]
- Nivolumab is a human monoclonal antibody that binds to programmed cell death receptor 1 (PD-1) and blocks its interaction with programmed cell death ligand 1 (PD-L1) and 2, releasing PD-1–mediated inhibition of the antitumor immune response[2]
- The LIO-1 study (NCT04042116; ENGOT-GYN3/AGO/LIO) is assessing the efficacy and safety of the combination of lucitanib + nivolumab in patients with advanced and metastatic solid tumors. Phase 1b of the study identified the recommended phase 2 dose of oral lucitanib as 6 mg once daily (QD) + nivolumab (480 mg intravenously [IV] every 28 days)[3]
- Phase 2 is evaluating the efficacy and safety of lucitanib + nivolumab in patients with advanced gynecologic malignancies (endometrial, cervical, ovarian, and clear-cell ovarian/endometrial cancers) through a Simon 2-stage study design, using individualized dose titration for lucitanib to optimize exposure and potential benefit of the combination
- Here, we present updated phase 1b results in patients with advanced solid tumors and describe the initial experience for stage 1 of the phase 2 ovarian cancer (OC) cohort

METHODS

- The phase 1b dose-escalation portion of LIO-1 utilized a 4+3 dose-escalation design and enrolled patients with advanced solid tumors with no satisfactory treatment options
  - Lucitanib was evaluated at doses of 6, 8, and 10 mg QD in combination with a fixed dose of nivolumab at 480 mg IV every 28 days
  - Dose-limiting toxicities (DLTs) were assessed during the first 28 days of treatment
  - Tumor response was assessed by investigators per Response Evaluation Criteria In Solid Tumors, version 1.1 (RECIST)
- The primary endpoints were safety and DLTs to determine the recommended phase 2 dose of the combination of lucitanib + nivolumab, and confirmed best overall response rate (ORR) by RECIST per investigator assessment
  - A key secondary endpoint was disease control rate defined as confirmed complete response (CR) or partial response (PR), or stable disease (SD) ≥16 weeks
- The phase 2 OC cohort enrolled patients with recurrent high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received ≥2 prior chemotherapy regimens (including ≥1 platinum doublet) or had disease progression ≤6 months after completing first-line platinum-based chemotherapy (up to 10 patients)
- Patients initiated treatment with lucitanib 6 mg QD + fixed-dose nivolumab
  - Those who met safety-based dose-titration criteria (**Table 1**) escalated to lucitanib 8 mg QD and then to 10 mg QD at subsequent cycles
  - Lucitanib dose could be escalated at start of cycles 2–5, provided dose-titration criteria had continued to be met since study start, and ≤2 cycles had elapsed between escalations

Table 1. Safety-Based Dose-Titration Criteria

- Blood pressure ≤150/90 mmHg
- No treatment-related adverse events grade >2
- No proteinuria >1+ (or urinary protein >1.0 g/24 h)
- No treatment-related diarrhea grade >1
- Not requiring any antihypertensive agents (or change to existing antihypertensive regimen if preexisting stable, well-controlled blood pressure at baseline)

- Lucitanib treatment could be interrupted and/or the dose could be reduced in 2-mg decrements to a minimum of 2 mg in the event of toxicity. Nivolumab dose reductions were not permitted
- We present data from the entire phase 1b cohort as well as from 24 patients enrolled to stage 1 of the phase 2 OC cohort, with a data cutoff date of March 29, 2021

RESULTS

Phase 1b

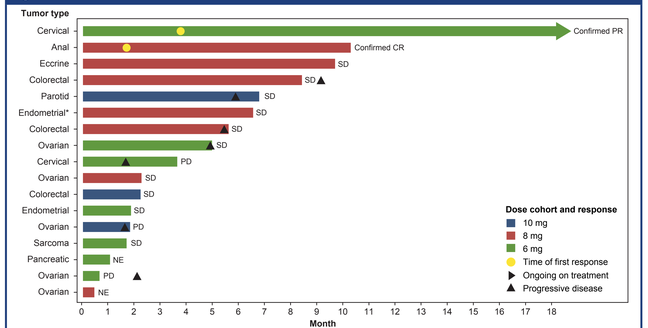
Patients

- Overall, 17 patients were treated with oral lucitanib (6 mg QD [n=7], 8 mg QD [n=7], and 10 mg QD [n=3]) + nivolumab (480 mg IV every 28 days)
  - Median (range) age was 63.0 (45.0–77.0) years; 11 (64.7%) patients had Eastern Cooperative Oncology Group performance status (ECOG PS) 1

Efficacy

- Median (range) treatment duration was 3.6 (0.5–18.4+) months
- One patient with anal cancer had a confirmed CR and remained on study for approximately 10 months; 1 patient with cervical cancer had a confirmed PR and has been ongoing on study for >19 months as of the data cutoff date (**Figure 1**)
  - 10 patients had a best overall response of SD; 3 had progressive disease (PD); and 2 were not evaluable
  - As of the data cutoff date, 1 patient remains on treatment
- Overall disease control rate was 47.1%

Figure 1. Phase 1b: Time on Lucitanib Treatment and Best Overall Response to Lucitanib + Nivolumab



Data cutoff: March 29, 2021. Patients could remain on nivolumab following discontinuation of lucitanib. *Endometrial stromal sarcoma. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Safety

- In the lucitanib 6-mg group, 1 DLT was observed: grade 3 proteinuria that improved to grade 1 but remained ongoing after study discontinuation. No DLTs were reported in the 8- or 10-mg cohorts
- Within this small group of patients, no differences in treatment-emergent adverse event (TEAE) frequencies between dose levels were apparent; see **Supplementary Material** for more detail

Phase 2 OC Cohort

Patients

- Baseline characteristics are presented in **Table 2**

Table 2. Phase 2 OC Cohort: Baseline Characteristics

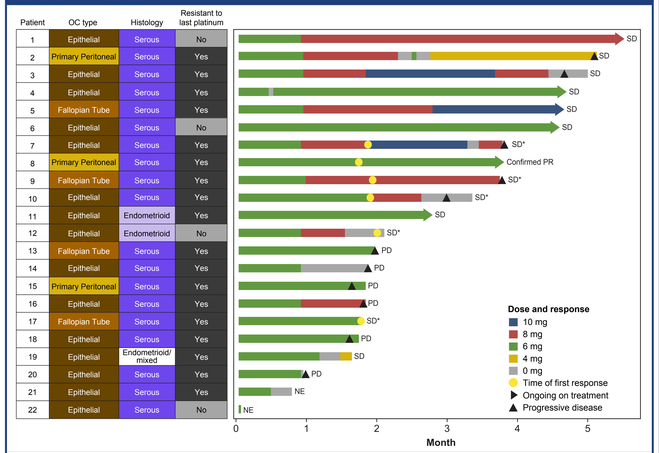
	n=24
Age, median (range), y	67.5 (42.0–84.0)
ECOG PS, n (%)	
0	16 (66.7)
1	8 (33.3)
Type of ovarian primary cancer, n (%)	
Epithelial	15 (62.5)
Fallopian tube	4 (16.7)
Primary peritoneal	3 (12.5)
Low-grade granulosa cell	2 (8.3)
Histological classification, n (%)	
Serous	19 (79.2)
Endometrioid	2 (8.3)
Mixed/other	3 (12.5)
Prior anticancer regimens, n (%)	
1	5 (20.8)
2	2 (8.3)
≥3	17 (70.8)
Primary platinum resistance, n (%)	7 (29.2)
Time to progression from last platinum, n (%)	
<1 month	10 (41.7)
≥1 to <6 months	10 (41.7)
≥6 months	4 (16.7)
Prior bevacizumab, n (%)	13 (54.2)
Prior PARP inhibitor, n (%)	11 (45.8)

Data cutoff: March 29, 2021.
ECOG PS, Eastern Cooperative Oncology Group performance status; OC, ovarian cancer; PARP, poly(ADP-ribose) polymerase.

Efficacy

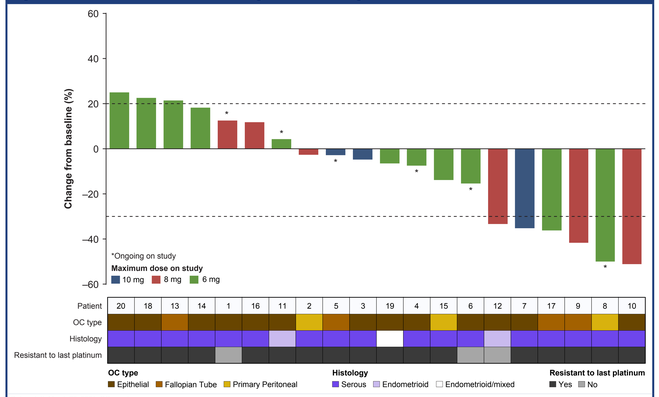
- The efficacy population comprised 22 patients with high-grade OC; 2 patients with low-grade granulosa cell carcinoma (LGGC) were excluded from the efficacy analysis
- Of 19/22 patients who completed ≥1 cycle, 9 escalated to the 8-mg lucitanib dose. Of these, 3 patients subsequently escalated to 10 mg
- As of the data cutoff date, 1 patient with a confirmed PR has been ongoing on study for >4 months (**Figure 2**, **Figure 3**)
  - 5 patients experienced an initial PR but subsequently discontinued study treatment due to PD (n=3) or a TEAE (n=2) without a confirmatory scan; 8 additional patients had a best overall response of SD, 6 patients had PD, and 2 patients were not evaluable
  - 6 (27.3%) patients are continuing to receive treatment with lucitanib + nivolumab
- Both patients with LGGC had a best overall response of SD as of the data cutoff date. One patient discontinued after 6 cycles due to PD, while the other remains on study

Figure 2. Phase 2 OC Cohort: Time on Lucitanib Treatment and Best Overall Response to Lucitanib + Nivolumab



Data cutoff: March 29, 2021. Patients could remain on nivolumab following discontinuation of lucitanib. *Unconfirmed PR. NE, not evaluable; OC, ovarian cancer; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. Phase 2 OC Cohort: Best Change in Sum of Target Lesions From Baseline



Data cutoff: March 29, 2021. OC, ovarian cancer.

Safety

- The phase 2 OC safety population comprised 24 patients who received lucitanib + nivolumab
- Treatment is ongoing with median (range) treatment duration of 2.7 (0.1–6.7+) months
- The most frequent any-grade TEAEs were consistent with the phase 1b experience: fatigue (n=13, 54.2%), hypertension (n=12, 50.0%), nausea (n=8, 33.3%), diarrhea (n=7, 29.2%), headache (n=7, 29.2%), and proteinuria (n=7, 29.2%); see **Supplementary Material** for more detail
  - 10 (41.7%) patients reported a grade ≥3 TEAE, with the most frequently reported being hypertension (n=5, 20.8%)
  - Hypertension was generally manageable with use of antihypertensive medication
  - 3 (12.5%) patients reported a TEAE leading to discontinuation of study treatment (hypertension and angina pectoris; large intestine perforation; diarrhea and fatigue)
  - 5 (20.8%) patients reported serious TEAEs considered related to lucitanib, nivolumab, or the combination; hypertension was the only serious TEAE considered related to study treatment that occurred in >1 patient