Efficacy and Safety of Lucitanib + Nivolumab in Patients With Advanced Gynecologic Malignancies: Phase 2 Results From the LIO-1 Study (NCT04042116; ENGOT-GYN3/AGO/LIO)

Abstract 5517

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SUMMARY

- The combination of lucitanib + nivolumab is active in the treatment of patients with advanced gynecologic malignancies, with antitumor activity seen in patients with prior PD-1 inhibitor exposure, and those without classic biomarkers of response to checkpoint inhibitor therapy
  - Notable activity was observed in patients in the clear-cell histology cohort
- Safety of the combination was manageable through effective dose titration, and consistent with previous reports for lucitanib, nivolumab, and other agents of both classes

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ACKNOWLEDGMENTS

We thank all of the LIO-1 investigators, and the LIO-1 study patients and their families and caregivers. This research was sponsored by Clovis Oncology, Inc. Medical writing support was provided by Andrew Croskery (Clovis Oncology, London, UK), and editorial support funded by Clovis Oncology was provided by Kathleen Blake (Ashfield MedComms).

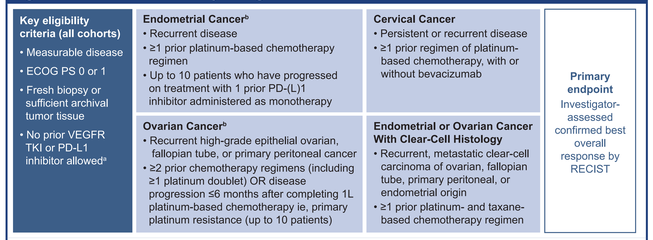
INTRODUCTION

- Lucitanib is an oral, potent tyrosine kinase inhibitor (TKI) that selectively inhibits vascular endothelial growth factor receptors 1–3 (VEGFR1–3), platelet-derived growth factor receptors alpha and beta (PDGFR α/β), and fibroblast growth factor receptors 1–3 (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 (PD-L2), releasing PD-1–mediated inhibition of the antitumor immune response[2]
- Tumor-secreted proangiogenic growth factors promote the generation of new blood vessels and mediate immunosuppression[3,4] that may dampen the effect of immune checkpoint inhibitors. Inhibiting angiogenesis with a TKI may, therefore, relieve immunosuppression and enhance the efficacy of PD-(L)1 inhibitors
- LIO-1 (NCT04042116; ENGOT-GYN3/AGO/LIO) is a 2-part open-label study assessing the efficacy and safety of the combination of lucitanib + nivolumab in patients with advanced and metastatic solid tumors
- The phase 1b part confirmed the recommended starting dose of lucitanib as 6 mg orally once daily (QD) in combination with nivolumab (480 mg intravenously [IV] every 28 days)[5]
- Here, we present phase 2 experience of the combination in patients with an advanced gynecologic solid tumor

METHODS

- Patients with an advanced gynecologic solid tumor were enrolled (endometrial cancer [EC], cervical cancer [CC], ovarian cancer [OC], or EC/OC with clear-cell histology [EOCC]). The primary objective was to evaluate the efficacy of the combination by investigator-assessed confirmed best overall response rate (**Figure 1**)
- Lucitanib was administered by safety-based individualized dose titration
  - Patients received oral lucitanib at a starting dose of 6 mg QD, escalating to 8 mg QD, and then 10 mg QD if safety-based titration criteria were met, plus IV nivolumab 480 mg every 28 days (see **Supplementary Material**)
- The data cutoff was April 14, 2022

Figure 1. LIO-1 Phase 2 Study Design Overview



[a]Unless otherwise specified; [b]Excluding clear-cell histology.
1L, first-line; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptors.

RESULTS

Patients

- A total of 124 patients were enrolled: 22 in the EC cohort, 46 in the CC cohort, 33 in the OC cohort, and 23 in the EOCC cohort (**Table 1**)
  - Two patients with low-grade granulosa cell carcinoma were included in the OC cohort and all efficacy and safety analyses
  - As of the data cutoff, 31/124 (25.0%) patients are ongoing on study
- Across cohorts, 32 (25.8%) patients escalated to a maximum lucitanib dose of 8 mg, and 20 (16.1%) escalated to a maximum dose of 10 mg

Efficacy

- The primary endpoint (investigator-assessed confirmed best overall response per RECIST v1.1) is presented in **Table 2**
- Fifteen confirmed responses were ongoing at the data cutoff (4 in the EC cohort, 6 in the CC cohort, 1 in the OC cohort, and 4 in the EOCC cohort)
- Duration of confirmed responses ranged from 5.6 to 14.8+ months in the EC cohort, 1.9+ to 13.1 months in the CC cohort, 3.7 to 14.9+ months in the OC cohort, and 3.5 to 10.4+ months in the EOCC cohort
- Two of the 5 patients in the EC cohort who received a prior PD-1 inhibitor had a confirmed response
  - Neither of these had a response to their prior PD-1 inhibitor
- Of the 12 responders in the CC cohort, 5 had received prior bevacizumab
- Progression-free survival is presented in **Figure 2**

Table 1. Baseline Characteristics and Disposition

	EC (n=22)	CC (n=46)	OC (n=33)	EOCC (n=23)
Baseline Demographics and Disease Characteristics				
Age, median (range), y	66.5 (45.0–88.0)	48.5 (32.0–77.0)	65.0 (41.0–84.0)	54.0 (38.0–77.0)
ECOG PS, n (%)				
0	14 (63.6)	22 (47.8)	19 (57.6)	14 (60.9)
1	8 (36.4)	24 (52.2)	14 (42.4)	9 (39.1)
No. of prior anticancer regimens				
1	12 (54.5)	24 (52.2)	5 (15.2)	8 (34.8)
2	4 (18.2)	17 (37.0)	8 (24.2)	12 (52.2)
≥3	6 (27.3)	5 (10.9)	20 (60.6)	3 (13.0)
No. of prior platinum regimens				
1	16 (72.7)	26 (56.5)	6 (18.2)	14 (60.9)
2	5 (22.7)	17 (37.0)	17 (51.5)	8 (34.8)
≥3	1 (4.5)	3 (6.5)	10 (30.3)	1 (4.3)
Prior bevacizumab	1 (4.5)	26 (56.5)	20 (60.6)	12 (52.2)
Prior PD-1 inhibitor	5 (22.7)	NA	NA	NA
Prior radiotherapy	14 (63.6)	29 (63.0)	4 (12.1)	5 (21.7)
Prior surgery	22 (100)	32 (69.6)	32 (97.0)	21 (91.3)
Primary platinum resistance[a]	11 (50.0)	NA	9 (27.3)	10 (43.5)
Resistant to most recent platinum[a]	15 (68.2)	NA	26 (78.8)	16 (69.6)
Disposition and Dose Escalation				
Ongoing on study treatment, n (%)	5 (22.7)	17 (37.0)	2 (6.1)	7 (30.4)
Maximum lucitanib dose achieved, n (%)				
6 mg	12 (54.5)	33 (71.7)	18 (54.5)	9 (39.1)
8 mg	6 (27.3)	6 (13.0)	9 (27.3)	11 (47.8)
10 mg	4 (18.2)	7 (15.2)	6 (18.2)	3 (13.0)

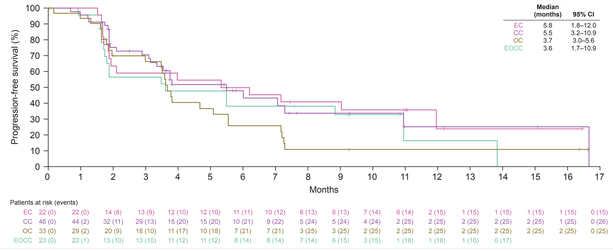
[a]Progression within <6 months.
CC, cervical cancer; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOCC, endometrial/ovarian clear-cell cancer; NA, not applicable; OC, ovarian cancer; PD-1, programmed cell death receptor 1.

Table 2. Confirmed Best Overall Response Rate

	EC (n=22)	CC (n=46)	OC (n=33)	EOCC (n=23)
Confirmed ORR, n (%)	**5 (22.7%)**	**12 (26.1%)**	**4 (12.1%)**	**6 (26.1%)**
[95% CI]	[7.8–45.4]	[14.3–41.1]	[3.4–28.2]	[10.2–48.4]
CR	0	2 (4.3)	0	1 (4.3)
PR	5 (22.7)	10 (21.7)	4 (12.1)	5 (21.7)
SD	8 (36.4)	19 (41.3)	18 (54.5)	7 (30.4)
PD	9 (40.9)	12 (26.1)	7 (21.2)	9 (39.1)
NE	0	3 (6.5)	4 (12.1)	1 (4.3)
DCR, n (%)	**11 (50.0%)**	**22 (47.8%)**	**11 (33.3%)**	**11 (47.8%)**
[95% CI]	[28.2–71.8]	[32.9–63.1]	[18.0–51.8]	[26.8–69.4]

CC, cervical cancer; CR, complete response; DCR, disease control rate (CR/PR/SD ≥16 weeks); EC, endometrial cancer; EOCC, endometrial/ovarian clear-cell cancer; NE, not evaluable; OC, ovarian cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 2. Progression-Free Survival



CC, cervical cancer; EC, endometrial cancer; EOCC, endometrial/ovarian clear-cell cancer; OC, ovarian cancer.

Biomarkers

- A reduction in the size of target lesions was observed across tumor types, including in some tumors without classical biomarkers of response to checkpoint inhibitors (PD-L1–negative tumors, microsatellite-stable tumors, those with low tumor mutation burden, or those without a CD8 T-cell inflamed immunophenotype) (**Figure 3**)
- Confirmed responses among patients with tumor mutation burden (TMB) <10 occurred in 1/11 patients in the EC cohort, 3/12 in the CC cohort, 6/22 in the OC cohort, and 4/17 in the EOCC cohort; confirmed responses among those with TMB ≥10 occurred in 3/5 patients in EC cohort, 3/7 in the CC cohort, and 1/3 in the OC cohort. There were no patients with TMB ≥10 in the EOCC cohort
- Among patients in the EC cohort with known microsatellite status, a confirmed response was observed in 3/14 with microsatellite stability and 2/3 with high microsatellite instability
- Among patients in the CC cohort with known PD-L1 combined positive score (CPS), a confirmed response was observed in 2/7 with CPS <1, 4/9 with CPS ≥1 and <10, and 6/12 with CPS ≥10

Table 3. Safety Summary

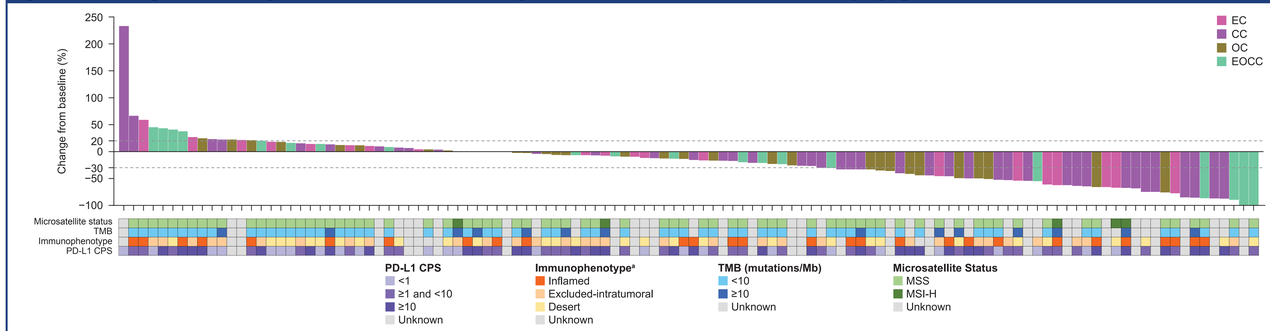
n (%)	Any causality		Treatment related[a]	
Patients with any-grade TEAE	123 (99.2)		115 (92.7)	
Patients with grade ≥3 TEAE	77 (62.1)		55 (44.4)	
Patients with serious TEAE	50 (40.3)		29 (23.4)	
Most frequently reported (≥20%) TEAEs	**Any grade**		**Grade ≥3**	
	Any causality	**Treatment related[a]**	**Any causality**	**Treatment related[a]**
Hypertension[b]	78 (62.9)	69 (55.6)	33 (26.6)	30 (24.2)
Asthenia/fatigue	67 (54.0)	55 (44.4)	4 (3.2)	4 (3.2)
Diarrhea	62 (50.0)	55 (44.4)	5 (4.0)	5 (4.0)
Nausea	49 (39.5)	39 (31.5)	0	0
Decreased appetite	39 (31.5)	34 (27.4)	0	0
Proteinuria	38 (30.6)	35 (28.2)	1 (0.8)	1 (0.8)
Hypothyroidism/increased blood thyroid stimulating hormone	40 (32.3)	37 (29.8)	1 (0.8)	1 (0.8)
Headache	37 (29.8)	20 (16.1)	1 (0.8)	1 (0.8)
Vomiting	31 (25.0)	16 (12.9)	1 (0.8)	0
Abdominal pain	30 (24.2)	7 (5.6)	2 (1.6)	1 (0.8)
Constipation	25 (20.2)	9 (7.3)	0	0

[a]Related to lucitanib and/or nivolumab; [b]Blood pressure increased, hypertension, or hypertensive crisis.
TEAE, treatment-emergent adverse event.

Safety

- Across cohorts, median duration of lucitanib and/or nivolumab treatment duration was 3.7 (range <0.1–17.5+) months
  - As of the data cutoff, 37 (29.8%) patients have remained on lucitanib and/or nivolumab treatment for ≥6 months
- Across all cohorts, the most frequently reported treatment-emergent adverse event (TEAE) was hypertension (**Table 3**)
- Of 124 patients, 50 (40.3%) met safety criteria for dose escalation at cycle 2, 63 (50.8%) were ineligible, and 11 (8.9%) did not reach cycle 2
  - The most frequently reported reasons for ineligibility for dose escalation included change to antihypertensive medication (41 [65.1%]), blood pressure >150/90 mm Hg (35 [55.6%]), grade >2 treatment-related TEAEs (17 [27.0%]), and proteinuria (11 [17.5%]) during cycle 1
- TEAEs leading to lucitanib dose reduction were reported in 21 (16.9%) patients; all were considered related to lucitanib (see **Supplementary Material**)
- TEAEs leading to discontinuation of either lucitanib and/or nivolumab were reported in 23 (18.5%) patients (see **Supplementary Material**)
  - TEAEs leading to discontinuation of lucitanib occurred in 20 (16.1%) patients, considered lucitanib related in 14 (11.3%) patients
  - TEAEs leading to discontinuation of nivolumab occurred in 15 (12.1%) patients, considered nivolumab related in 12 (9.7%) patients

Figure 3. Best Change in Sum of Target Lesions From Baseline Following Lucitanib + Nivolumab Treatment With Accompanying Biomarkers



[a]Inflamed: CD8 T-cell infiltration within the intraepithelial compartment; Excluded-intratumoral: CD8 T-cell infiltration excluded from the intraepithelial compartment but abundant in the intratumoral stroma; Desert: no to very low CD8 T-cell infiltration. Biomarker data generated from fresh tissue samples collected just prior to enrolment and from archival tissue samples collected from patients who may have undergone intervening therapy prior to enrolment.
CC, cervical cancer; CPS, combined positive score; EC, endometrial cancer; EOCC, ovarian/endometrial clear-cell cancer; MSI-H, microsatellite instability high; MSS, microsatellite stable; OC, ovarian cancer; PD-L1, programmed cell death ligand 1; TMB, tumor mutation burden.