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Upper Tract Urothelial Cancer

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Long-Term Outcomes of Primary Chemoablation of Low-Grade Upper Tract Urothelial Carcinoma With UGN-101, a Mitomycin Reverse Thermal Gel

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Study Need and Importance: Relapse of low-grade upper tract urothelial carcinoma (LG UTUC) following surgical ablation is common and often rapid. Topical adjuvant aqueous chemotherapy following local ablation has demonstrated modest benefit in this patient population, and drug dilution and rapid evacuation are postulated to be the cause of this limited efficacy. A reverse thermal gel containing mitomycin (UGN-101) that is instilled into the upper tract and converts into a semisolid gel depot at body temperature helps overcome these barriers to efficacious local therapy. This study reports the long-term follow-up (LTFU) of patients treated with UGN-101 who had an ongoing complete response (CR) at the conclusion of the pivotal OLYMPUS trial.

What We Found: Patients with LG UTUC who were treated with UGN-101 and achieved CR in the OLYMPUS trial experienced extended disease-free intervals. The median duration of response of all patients achieving CR in the OLYMPUS trial (n = 41) was 47.8 months. In the subset of patients who entered the LTFU study (n = 20), the median duration of response was not estimable (95% CI, 43.5–not estimable; Figure). Seventy-five percent of patients had no evidence of recurrence over a median follow-up of 53.3 months.

Limitations: Limitations of this study include the single-arm design of the parent study (OLYMPUS), which extends to the LTFU cohort; the small number of patients followed; and the lack of safety or quality-of-life data collection.

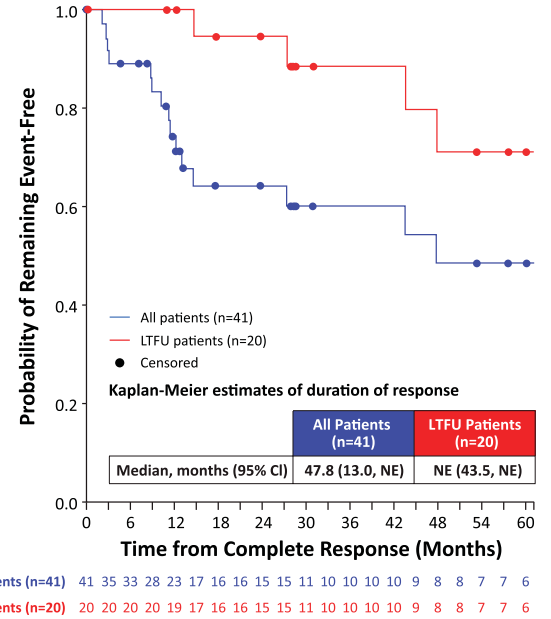

Figure. Kaplan-Meier estimation of duration of response in all patients with complete response in the OLYMPUS trial (n = 41) and the subset of patients in the long-term follow-up (LTFU) cohort analysis set (n = 20). NE indicates not estimable.

Interpretation for Patient Care: The current report provides the first description of the long-term durability of response in patients achieving CR following primary chemoablation and augments a growing body of literature that supports the use of UGN-101 as a nonsurgical, kidney-sparing primary treatment option for patients with LG UTUC.

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Long-Term Outcomes of Primary Chemoablation of Low-Grade Upper Tract Urothelial Carcinoma With UGN-101, a Mitomycin Reverse Thermal Gel

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Purpose: We evaluate long-term outcomes of primary chemoablation using a mitomycin reverse thermal gel (UGN-101) in patients with low-grade upper tract urothelial carcinoma.

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Ethics Statement: This study received Institutional Review Board approval (IRB No. TC-UT-03-P).

Author Contributions:

Conception and design: Shabsigh, Weizer, Raman, Chamie, Schoenberg, Pierorazio, Hu.

Data analysis and interpretation: Sankin, Weizer, Meads, Burger, Kaimakliotis, Raman, Schoenberg, Louie, Pierorazio, Raju.

Data acquisition: Shabsigh, Weizer, Kaimakliotis, Raman, Schoenberg, Louie, Kleinmann, Singla, Hu.

Drafting the manuscript: Burger, Raman, Schoenberg, Louie, Pierorazio, Hu.

Critical revision of the manuscript for scientific and factual content: Shabsigh, Sankin, Weizer, Meads, Burger, Kaimakliotis, Raman, Chamie, Schoenberg, Louie, Kleinmann, Singla, Pierorazio, Raju.

Statistical analysis: Burger.

Supervision: Shabsigh, Sankin, Weizer, Meads, Kaimakliotis, Raman, Chamie, Schoenberg, Louie, Kleinmann, Singla, Pierorazio, Raju, Hu.

Data Availability: The datasets generated and/or analyzed during the current study are not publicly available as the study is ongoing as part of a post-marketing commitment with the US FDA.

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Materials and Methods: Patients who participated in the OLYMPUS trial (IRB No. TC-UT-03, NCT02793128) and achieved a complete response (CR) after 6 weekly doses of UGN-101 were followed up to 12 months after initial CR. Those with CR at study completion were eligible for long-term follow-up for up to 5 years or until disease recurrence, progression, or death.

Results: Of the 71 patients enrolled in the OLYMPUS trial, 42 patients achieved CR 4 to 6 weeks after completing $\geq$ 1 instillation of UGN-101. Among the 41 patients followed after initial CR, median follow-up was 28.1 months (95% CI, 13.1-57.5), and median duration of response was 47.8 months (95% CI, 13.0–not estimable [NE]). Twenty patients (49%) had long-term follow-up (median 53.3 months [95% CI, 27.9-65.3]). Seventy-five percent of patients had no evidence of recurrence at the last follow-up, with median duration of response NE (95% CI, 43.5-NE) because of a low event rate.

Conclusions: Primary intracavitary chemoablation with UGN-101 for low-grade upper tract urothelial carcinoma is associated with favorable long-term durability.

Clinical Trial Registration No.: NCT02793128

Key Words: mitomycin, carcinoma, transitional cell, clinical trial

Renal preservation is the recommended strategy for primary treatment of patients with low-grade (LG) upper tract urothelial carcinoma (UTUC), according to the most recent guideline from the AUA.[1] Urologists have used endoscopically guided ablation extensively in this population with acceptable short-term results; however, relapse after surgical ablation is common (20%-92%) and often rapid and requires lifelong surveillance, which can be associated with complications such as ureteral stricture, perforation of the upper urinary tract, bleeding, and infection.[2-6]

The impact of topical adjuvant aqueous chemotherapy on disease recurrence after local ablation is modest, likely the result of drug dilution and rapid evacuation secondary to normal physiologic urine flow.[2] To overcome these barriers to effective local primary pharmacotherapy, we used a reverse thermal gel containing mitomycin (UGN-101, 4 mg mitomycin per mL RTGel) that is instilled into the upper tract as a liquid under chilled conditions and subsequently converts to a semisolid gel depot at body temperature, increasing local drug dwell time to 4 to 6 hours (OLYMPUS trial, NCT02793128).[7] In April 2020, the US Food and Drug Administration approved UGN-101 to treat LG UTUC. Others have independently published their real-world experience with the use of UGN-101 in a variety of clinical settings.[8-12] Long-term real-world data with a median follow-up of 22 months (IQR, 12-27) were reported for 136 cases of UTUC treated with UGN-101, including 107 cases of LG noninvasive UTUC. Recurrence-free survival at 24 months was found to be 86% in a subset of 53 cases of LG noninvasive UTUC without evidence of disease after UGN-101 induction.[13,14]

Despite these promising results, the durability of chemoablation requires better delineation. Therefore, in this report, we provide data from a non-interventional study (BL007) to follow the long-term outcomes of patients who completed the OLYMPUS trial with an ongoing complete response (CR).

MATERIALS AND METHODS

Details of the OLYMPUS trial were published in 2020.[8] Briefly, patients with primary or recurrent biopsy-proven LG UTUC involving the renal pelvis or calyces who participated in the OLYMPUS trial and achieved a CR (defined as a negative endoscopic examination and negative cytology at the primary disease evaluation and negative for-cause biopsy when done)[7] after 6 planned weekly doses of intracavitary UGN-101 were assessed for ongoing response quarterly for up to 12 months after initial CR. Patients with ongoing CR at study completion were asked to consent to the collection of long-term follow-up data as they continued with standard-of-care disease management. UroGen initiated BL007 as a mechanism to collect outcomes of interest, including duration of response (DOR), number of patients with disease recurrence or progression, and poststudy treatment course (Table 1). There was no protocol-specified intervention or treatment in the study and no protocol-specified visits or evaluations. Supervising physicians provided semiannual updates on disease status for up to 5 years or until disease recurrence, progression, or death. All patients provided written informed consent (IRB No. TC-UT-03-P) before enrollment in BL007.

In the primary analysis, the DOR in the 41 patients who achieved CR in the OLYMPUS trial after UGN-101 therapy was defined as the time from initial CR to recurrence, progression, or death in either study (the OLYMPUS trial or the long-term follow-up trial, BL007). Patients were censored at the last adequate documented visit if an event (ie, recurrence, progression, or death) had not been documented. The distribution of the DOR was estimated using the Kaplan-Meier method, and CIs for the Kaplan-Meier estimates were calculated using the Brookmeyer and Crowley methods.[15,16] The median follow-up time of the DOR was estimated using the inverse Kaplan-Meier method. The statistical methods described above were repeated in the subset of 20 patients who enrolled in the BL007 study. In an exploratory analysis of the durability of

Table 1. *BL007 Objective and End Points*

Objective	End points
Obtain data on long-term outcomes in patients from the OLYMPUS study	Duration of response
	No. of patients with recurrence of disease
	No. of patients with progression to high-grade disease
	No. of patients with UTUC who underwent nephroureterectomy
	No. of deaths

Abbreviations: UTUC, upper tract urothelial carcinoma.

response, a number of predictive models appropriate for time-to-event data (ie, exponential, Weibull, and log-normal) were fit to the data. Models were assessed for goodness-of-fit characteristics as measured by log-likelihood and Akaike information criterion values, along with visual inspection of the Kaplan-Meier curve to determine reasonable fit. The Weibull model was used to estimate the proportion of patients who would remain in response beyond 8 years.[17]

RESULTS

OLYMPUS Trial

A total of 71 patients were enrolled and treated in the parent OLYMPUS trial (NCT02793128).[7] The results of OLYMPUS have been previously published.[8] Most of the patients were male (48; 68%) and White (62; 87%), with a median age of 71 years (range: 42.0-87.0 years). Most of these patients had a history of tobacco use, and nearly half had previous UTUC. Overall, the demographics and baseline characteristics of patients in BL007 were similar to those of the parent (OLYMPUS) trial (Table 2).[7]

Altogether, 42 of the 71 patients achieved CR after UGN-101 treatment, of whom 41 patients entered quarterly follow-up (1 patient withdrew consent). Subsequently, 20 of the 23 patients who remained in response 12 months after CR enrolled in the long-term follow-up trial (BL007), in which they were followed for evidence of UTUC recurrence, progression, or death by their treating physicians (Figure 1). These data are presented schematically in Figure 2.

Patients Who Achieved a CR

For the entire cohort of 41 patients achieving an initial CR in the OLYMPUS trial (58%; 95% CI, 45-69), including those followed in the long-term follow-up trial, the median duration of follow-up was 28.1 months (95% CI, 13.1-57.5) and the median DOR was 47.8 months (95% CI, 13.0–not estimable [NE]; Figure 3). One or more doses of maintenance therapy were administered to 29 patients (70.7%).

Documented events were reported in 16 of 41 patients (39%). Tumor recurrence occurred in 10 patients (24.4%), of which 3 patients were treated with endoscopic ablation (data were not available for the remaining 7 patients). Six patients (14.6%) died, 1 death was related to UTUC; no deaths were related to study treatment. In this cohort, 25 (61%) participants were censored (Table 3).

Long-Term Follow-Up Trial (BL007)

Among the 20 patients enrolled in BL007, the median DOR was NE (95% CI, 43.5-NE) based on a median duration of follow-up of 53.3 months (Figure 3). Maintenance therapy was administered to 16 patients (80%).

For those patients evaluated in the long-term follow-up study, 2 patients (10%) experienced tumor recurrence and 3 (15%) died; no deaths were related to study treatment. A total of 15 patients (75%) were censored by the conclusion of the observation period (Table 4). There were no reported progressions to high-grade disease. Two patients were reported as undergoing radical nephroureterectomy: one because

Table 2. *Summary of Baseline Characteristics (Intention-to-Treat Analysis Set)*

Summary of baseline characteristics	OLYMPUS trial N = 71	Patients with CR in OLYMPUS trial n = 41	Long-term follow-up (BL007) n = 20
Age, median (min, max), y	71 (42, 87)	74 (49, 90)	72 (50, 87)
Sex, No. (%)[a]			
Male	48 (68)	27 (66)	12 (60)
Female	23 (32)	14 (34)	8 (40)
Race, No. (%)[a]			
White	62 (87)	35 (85)	18 (90)
Black	4 (6)	3 (7)	0
Hispanic	3 (4)	2 (5)	0
Asian	2 (3)	1 (2)	0
Other	0	0	2 (10)
Unknown	0	0	0
2 Kidneys at enrollment, No. (%)	63 (89)	37 (90)	19 (95)
History of upper tract UC, No. (%)	34 (48)	20 (49)	10 (50)

Abbreviations: CR, complete response; UC, urothelial carcinoma.
[a] Percentage was calculated from the overall number of patients in the intention-to-treat analysis set.

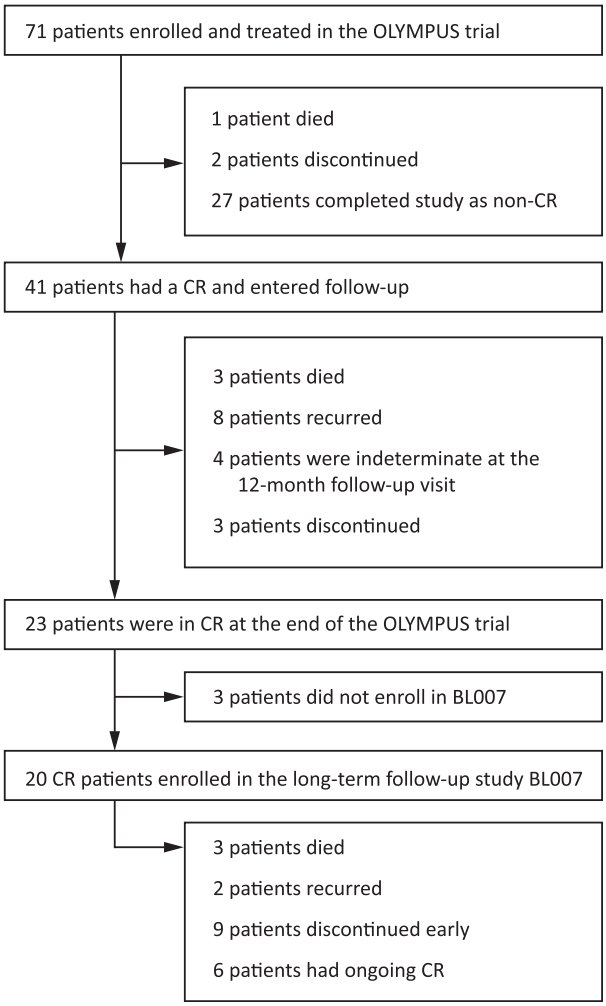


Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram for patients enrolled in BL007. CR indicates complete response.

of ureteral stricture without evidence of UTUC at the time of surgery and one because of a nonfunctioning kidney.

In the exploratory analysis of the durability of response, all models had similar goodness-of-fit characteristics. Given the similarities, the Weibull model was chosen because of its flexibility in handling various shapes of hazard functions. The exploratory results from the Weibull model indicated that the probability of remaining in response at 8 years was approximately 24% (95% CI, 9-44; Figure 4).[17]

DISCUSSION

LG UTUC follows a clinical course similar to LG nonmuscle-invasive bladder cancer (NMIBC). Despite specific molecular characteristics that may differentiate these 2 entities, the observed clinical behavior of LG UTUC and LG NMIBC suggests that local therapy to control relapse and minimize compromised organ function should be the primary objective of contemporary treatment, given the low likelihood of disease progression in either geographic location of disease.[18,19] Accordingly, the AUA recommends that urologists use organ-sparing techniques as the preferred management strategy for patients with LG UTUC when possible.[1] With the advent of advanced endoscopic instrumentation, urologists have gained significant experience with the local ablation of low-volume UTUC in the calyces, renal pelvis, and ureters.[2,4,5,20] Across retrospective studies in heterogeneous patient populations, endoscopic ablation results in an apparently safe local control of UTUC, but is associated with rates of local recurrence ranging from 20% to 92%.[2,5,6,20] In addition, new laser technology is changing the landscape of endoscopic approaches to UTUC, further confounding comparisons of data available from longitudinal series of kidney-sparing approaches to upper tract disease. In response to the high rates of local relapse with endoscopic ablation, some have advocated the use of adjuvant chemotherapy or immunotherapy in a manner reminiscent of recommendations for the treatment of patients with relapsing NMIBC.[3,21] Across small studies, treatment with adjuvant topical mitomycin C in LG UTUC resulted in local recurrence rates ranging from 20% to 53% and was generally tolerable.[3] Ultimately, because the upper tract cannot retain aqueous solutions of medication, trials of adjuvant aqueous therapies have produced mixed results and failed to consistently demonstrate a definitive therapeutic benefit. Techniques to extend dwell time and thus contact of a drug with the tumor target would potentially offer the opportunity to improve recurrence-free intervals.

In 2020, UGN-101 (Jelmyto), a reverse thermal gel containing mitomycin, was approved by the US Food and Drug Administration for the treatment of LG UTUC on the basis of an open-label single-arm trial of primary chemoablation. The pivotal trial of UGN-101 demonstrated an initial CR rate of 59% (42/71 treated patients; 95% CI, 47-71; $P < .0001$), and the Kaplan-Meier estimated probability of remaining in response for 12 months after the primary disease evaluation was 82% in those achieving CR.[7,22] The median duration of CR was NE in that analysis. The most common side effects were typically mild or moderate in severity, with the most frequent adverse event being ureteric stenosis (44%). All patients were treated by retrograde instillation of UGN-101 in the OLYMPUS trial.

While BL007 was not designed to evaluate safety data, only 1 patient underwent radical nephroureterectomy without evidence of disease recurrence, indicating that the ureteral stenosis is an acute phenomenon with timing around the time of

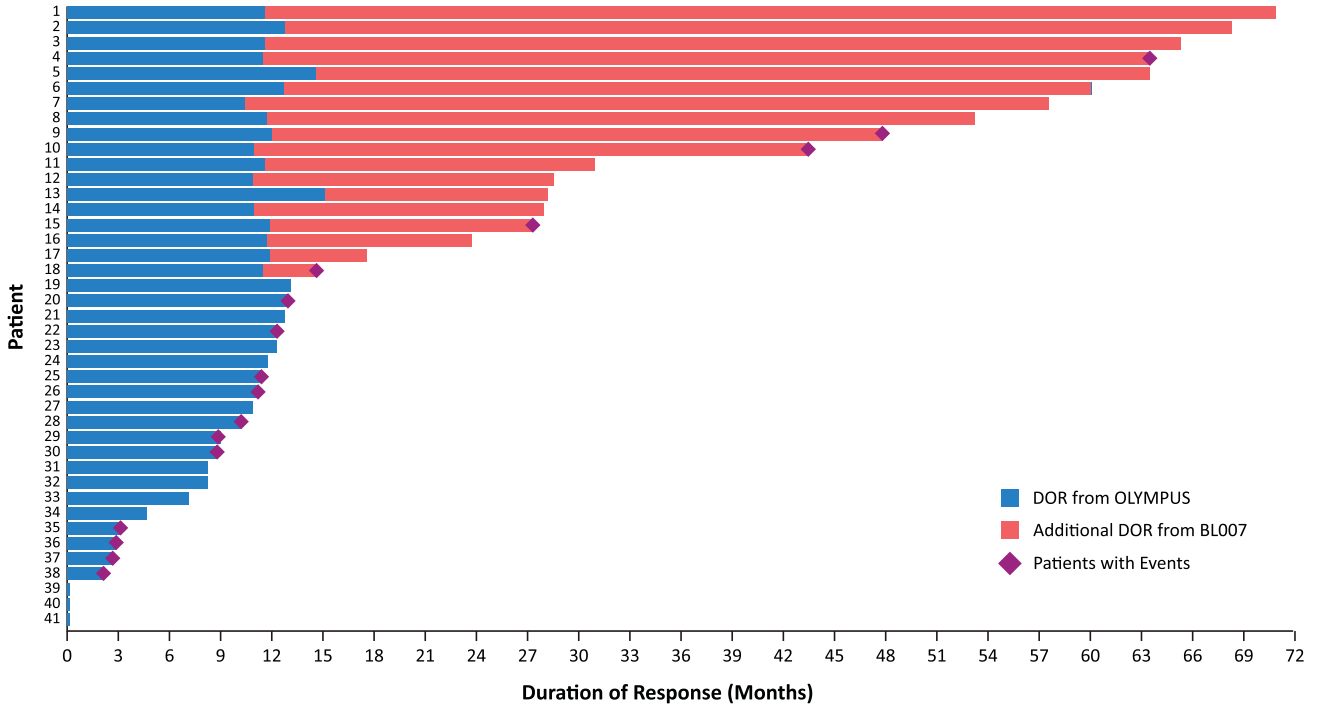
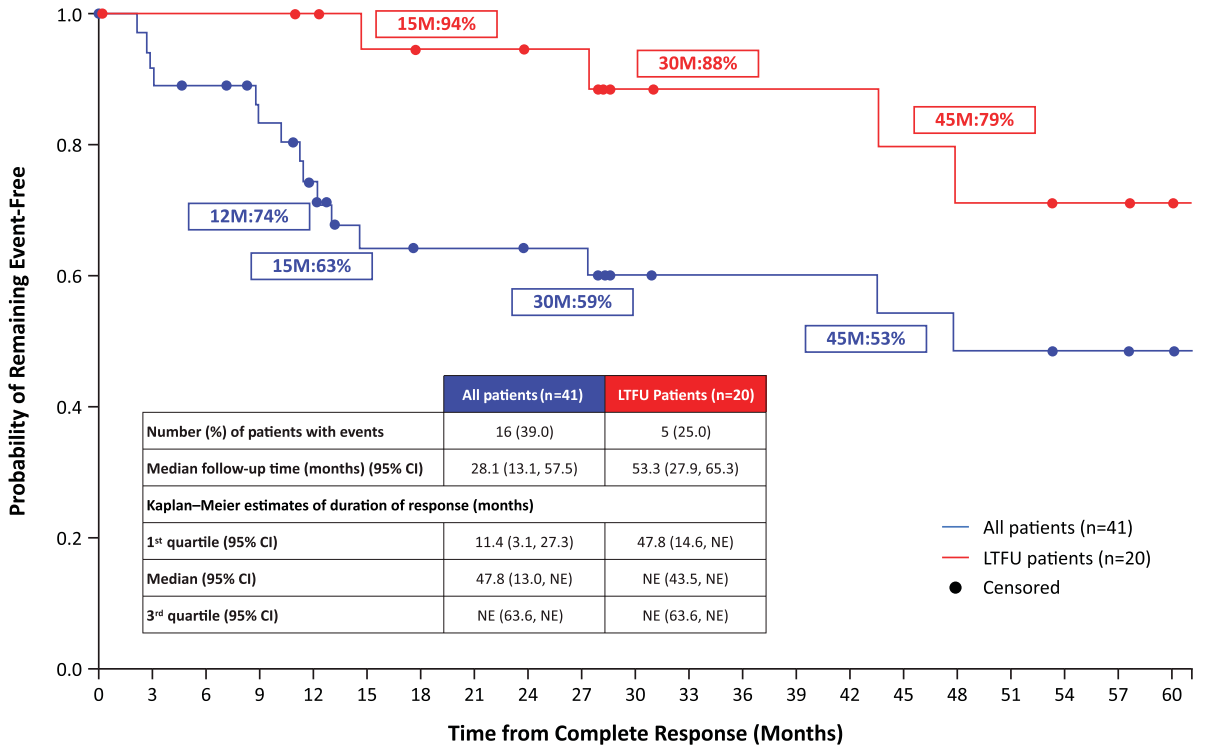


Figure 2. Swimmer plot for 41 patients with complete response in the OLYMPUS parent trial and additional long-term follow-up for 20 patients with complete response enrolled in BL007. DOR indicates duration of response.



	All patients (n=41)	LTFU Patients (n=20)
Number (%) of patients with events	16 (39.0)	5 (25.0)
Median follow-up time (months) (95% CI)	28.1 (13.1, 57.5)	53.3 (27.9, 65.3)
Kaplan–Meier estimates of duration of response (months)		
1st quartile (95% CI)	11.4 (3.1, 27.3)	47.8 (14.6, NE)
Median (95% CI)	47.8 (13.0, NE)	NE (43.5, NE)
3rd quartile (95% CI)	NE (63.6, NE)	NE (63.6, NE)

All Patients (n=41)	41	35	33	28	23	17	16	16	15	15	11	10	10	10	10	9	8	8	7	7	6
LTFU patients (n=20)	20	20	20	20	19	17	16	16	15	15	11	10	10	10	10	9	8	8	7	7	6

Figure 3. Kaplan-Meier estimation of duration of response in all patients with complete response in the OLYMPUS trial (n = 41) and the subset of patients in the long-term follow-up (LTFU) cohort analysis set (n = 20). NE indicates not estimable.

Table 3. *Summary of the Duration of Response: Patients With Complete Response in the OLYMPUS Trial Including Those With Additional Follow-Up in BL007 (n = 41)*

	UGN-101 (n = 41)	
Patients with events, No. (%)	16	(39.0)
Recurrence of disease	10	(24.4)
Death	6	(14.6)
Patients censored, No. (%)	25	(61.0)
Early discontinuation in the parent study	5	(12.2)
Indeterminate at the end of the parent study	2	(4.9)
CR at the end of the parent study, not enrolled in BL007	3	(7.3)
Early discontinuation in long-term follow-up	9	(22.0)
Ongoing CR in long-term follow-up	6	(14.6)
Follow-up, median (95% CI), mo	28.09 (13.11-57.53)	

Abbreviations: CR, complete response.

induction therapy. There are now numerous real-world strategies described to mitigate the risks of stenosis, including antegrade instillation, biweekly instillation, and/or oral steroid administration. Some authors have advocated the antegrade instillation of UGN-101 to minimize ureteral manipulation and have reported decreased rates of ureteral stenosis with comparable rates of CR with short follow-up (<11 months). Among the studies that investigated antegrade instillation of UGN-101, CR rates ranged from 50% to 69%, with ureteral stenosis rates of less than 25%.[11,23,24]

These reports provide evidence of the efficacy and safety of UGN-101 in a variety of clinical settings, albeit with relatively short follow-up. This report provides the first description of the long-term durability of response in patients achieving CR after primary chemoablation. Of the 42 participants in the OLYMPUS trial who achieved a CR after initial primary therapy, 41 entered the initial follow-up protocol of up to 12 months and 20 entered the long-term follow-up trial (BL007). For the entire cohort of OLYMPUS patients in follow-up after primary disease evaluation revealed CR (n = 41), the median DOR was 47.8 months, and for the subset of patients in the long-term follow-up trial (BL007) who were evaluable for efficacy (n = 20), the median DOR was NE (95% CI, 43.5-NE) because of a large proportion of patients (75%) without an event as of the cutoff date. Aside from the limitations of interpreting subgroup results from a single-arm trial, the subgroup results were generally consistent with the overall estimate of efficacy for subgroups with sufficient sample size.

Table 4. *Summary of Duration of Response: Long-Term Follow-Up of BL007 Patients (n = 20)*

	UGN-101 (n = 20)	
Patients with events, No. (%)	5	(25.0)
Recurrence of disease	2	(10.0)
Death	3	(15.0)
Patients censored, No. (%)	15	(75.0)
Early discontinuation in long-term follow-up	9	(45.0)
Ongoing complete response in long-term follow-up	6	(30.0)
Follow-up, median (95% CI), mo	53.26 (27.86-65.28)	

In the Weibull model, using data observed through 5 years of follow-up, the extrapolated probability of remaining in response at 8 years was approximately 20%. While this projection extends beyond our current observation period and requires careful interpretation, it suggests the potential for sustained long-term response in some patients. However, as data mature, the concept of long-term responders could be relevant in this setting, so it would be important to understand predictive factors associated with such patients. The concept of long-term responders has been cited in various oncology settings and refers to patients who experience a prolonged positive response to therapy, significantly surpassing the median response duration typically observed in the patient population under study.[25-29] As data continue to emerge from the long-term follow-up study, it is apparent that some patients have extended response times. Importantly, these data indicate that the management of LG UTUC is a balance between estimated life expectancy and recurrence. Given an extended life expectancy of 5 years or greater, most patients and providers should consider a high probability of recurrence in that time period and may consider maintenance dosing strategies.

This study has limitations. The parent study was a single-arm trial, and that characteristic with its inherent limitations—for example, lack of a comparator arm—extends to the evaluation of the cohort that is the focus of this report. However, this limitation has to be taken into context, for example, the response rate is a key end point unique to oncology that has allowed regulators to evaluate efficacy in single-arm trials.[30] Given that cancer can be a progressive disease and tumors do not typically regress on their own, a decrease in tumor burden measured by response rate can be associated with drug activity rather than spontaneous regression of the disease or other confounding factors.[16,30] Other limitations of note include that the total number of patients followed in BL007 was small and that BL007 did not collect safety or quality-of-life data.

In an attempt to minimize bias, we report the overall durability for the entire CR cohort and for the subgroup that entered the long-term follow-up trial. In addition, the number of patients entered into the long-term follow-up trial represents approximately half of those achieving a CR in the OLYMPUS trial, so the results reported here should be viewed with appropriate caution because they are based on relatively small patient numbers and a limited number of events. Although maintenance treatment with UGN-101 was permitted per protocol in the parent study, the use was sufficiently nonuniform to prevent us from drawing definitive

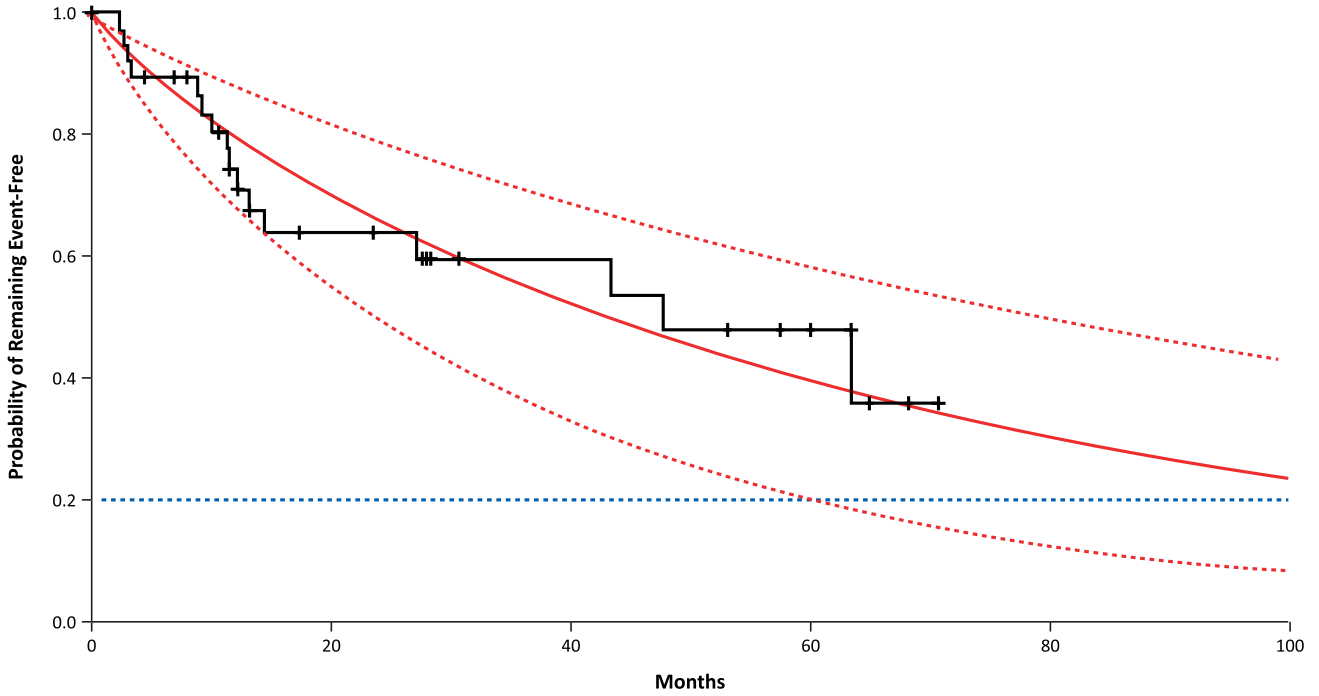


Figure 4. Weibull predicted curve and Kaplan-Meier estimation of duration of response cohort analysis set (n = 41). A Weibull curve (red lines) was fit to the data and overlaid on the Kaplan-Meier curve (black lines). CIs are displayed as dotted lines (respective colors).

conclusions about the long-term value of maintenance within the context of the durability data provided here. Despite these considerations, the durability of CR achieved after treatment with UGN-101 is noteworthy and robust. Owing to the limited nature of the information collection in BL007, we are unable to provide additional safety data regarding UGN-101 use beyond that provided in the original report.

CONCLUSIONS

Patients with LG UTUC receiving primary treatment with 6 weekly intracavitary doses of UGN-101 in the OLYMPUS trial who then entered the long-term follow-up study experienced extended disease-free intervals. The median DOR of all patients achieving CR in the OLYMPUS trial was 47.8 months. In the subset of patients entering the BL007 follow-up study, the median DOR was NE. These durability data augment a growing body of literature that supports the use of UGN-101 as primary treatment of patients with LG UTUC.

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EDITORIAL COMMENT

The authors should be commended for their current study reporting the extended follow-up of patients enrolled into the OLYMPUS trial for up to 5 years unless subjects exited the study.[1] One of the most recent Food and Drug Administration–approved kidney-sparing treatments of low-grade upper tract urothelial carcinoma is chemoablation using a reverse thermal mitomycin gel, UGN-101 marketed as Jelmyto, which was evaluated in the OLYMPUS trial.[2] This study demonstrated that 59% of patients treated with Jelmyto achieved an initial complete response, and over 55% experienced durable responses with no progression of disease during the 1-year study period.[2,3] The results of the current study with extended follow-up were quite promising with demonstration of no progression to higher-grade disease and approximately 75% of participants remaining tumor free after a median follow-up of 53.3 months.[1]

However, this study has some recognized limitations. The small sample size related to the original registration trial and stringency of enrollment could affect the reliability and reproducibility of the findings. In addition, the details regarding maintenance therapy, including timing, duration, delivery, and dosage, are not consistent across the patients in the trial, which makes it challenging to draw definitive, meaningful conclusions with a single protocol for long-term therapy.

Newer studies on Jelmyto administration have suggested that antegrade delivery through nephrostomy tube rather than retrograde ureteral catheter access may reduce inflammation-related complications

such as ureteral stricture.[4] However, using a nephrostomy tube for instillation can yield discontent with patients who may be unwilling to maintain indwelling nephrostomy tube access for a prolonged period for the multiple therapeutic instillations, followed by extended maintenance therapy which may be of positive benefit in some patients. Future studies should look more into the best ways to administer the treatment, particularly for those who garner best results with longer-term maintenance therapy.

In conclusion, despite its limitations, this study provides valuable insights into the use of intracavitary chemoablation with Jelmyto for low-grade upper tract urothelial carcinoma with longer-term follow-up, providing a durable treatment option following a reassuring initial treatment response rate.

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