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Durability of Response to Primary Chemoablation of Low-Grade Upper Tract Urothelial Carcinoma Using UGN-101, a Mitomycin-Containing Reverse Thermal Gel: OLYMPUS Trial Final Report

Surena F. Matin, Phillip M. Pierorazio, Nir Kleinmann et al.

Correspondence: Seth P. Lerner (email: slerner@bcm.edu)

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Study Need and Importance: Kidney-sparing treatment options such as endoscopic ablation are recommended for patients with low-grade upper tract urothelial carcinoma (UTUC) whose tumors are small and favorably located. Endoscopic management, however, is associated with a high rate of local disease recurrence. We previously reported interim results from a phase 3 trial in which clinically significant disease eradication was observed following 6 weekly induction instillations of UGN-101 (a mitomycin-containing reverse thermal gel), irrespective of whether the patients' tumors were resectable at baseline. We now have followed all patients with complete response to induction therapy for at least 12 months to evaluate durability of response.

What We Found: Of 41 patients who had complete response to induction therapy with UGN-101, 23 (56%) remained in complete response after 12 months (see table). Use of monthly maintenance treatment with UGN-101 varied widely with 12 patients receiving no maintenance treatment and 29 patients receiving ≥1 maintenance instillation (median 6, range 1−11). There was no clear association between durability of response and maintenance treatment with 6/12 patients (50%) and 17/29 patients (59%) maintaining complete response; however, an increasing number of instillations of UGN-101 appeared to be associated with increased incidence of urinary adverse events.

Limitations: The primary limitations of this study are the small sample size, reflecting the rarity of low-grade UTUC, and its open-label, single-arm design, which does not permit direct comparison of the observed recurrence rate with rates of local disease recurrence in patients managed endoscopically.

Interpretations for Patient Care: Primary chemoablation with UGN-101 is a nonsurgical, kidney-sparing treatment that results in clinically significant and durable disease eradication, thereby providing an additional option for the management of patients with low-grade UTUC, including those with multifocal disease and those whose tumors are difficult to treat endoscopically.

Table. *Proportion of 41 patients with durable complete response at followup*

Time Since Primary Disease Evaluation (mos)	No. Pts with Evaluation at Followup Visit	No. Pts Maintaining Complete Response (%)
3	38	35 (85)
6	38	33 (80)
9	35	28 (68)
12	31	23 (56)

Percentage is calculated from No. of patients with complete response at primary disease evaluation visit.

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Durability of Response to Primary Chemoablation of Low-Grade Upper Tract Urothelial Carcinoma Using UGN-101, a Mitomycin-Containing Reverse Thermal Gel: OLYMPUS Trial Final Report

Surena F. Matin,[1,*,†] Phillip M. Pierorazio,[2,*] Nir Kleinmann,[3] John L. Gore,[4,‡] Ahmad Shabsigh,[5,§] Brian Hu,[6,§] Karim Chamie,[7,§] Guilherme Godoy,[8] Scott G. Hubosky,[9] Marcelino Rivera,[10] Michael O'Donnell,[11] Marcus Quek,[12] Jay D. Raman,[13,§] John J. Knoedler,[13] Douglas Scherr,[14] Christopher Weight,[15,‖] Alon Weizer,[16] Michael Woods,[12] Hristos Kaimakliotis,[17] Angela B. Smith,[18,§] Jennifer Linehan,[19,¶] Jonathan Coleman,[20] Mitchell R. Humphreys,[21] Raymond Pak,[22,**] David Lifshitz,[23] Michael Verni,[24,§] Ifat Klein,[25,§] Marina Konorty,[25,§] Dalit Strauss-Ayali,[25,§] Gil Hakim,[25,§] Elyse Seltzer,[26,§] Mark Schoenberg[26,27,§] and Seth P. Lerner[8,‡‡,§§]

[1]*Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[2]*Brady Urological Institute, The Johns Hopkins University, Baltimore, Maryland*
[3]*Department of Urology, Sheba Medical Center, Ramat Gan, Israel*
[4]*Department of Urology, University of Washington Medical Center, Seattle, Washington*
[5]*Department of Urology, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio*
[6]*Department of Urology, Loma Linda University, Loma Linda, California*
[7]*Department of Urology, UCLA, Los Angeles, California*
[8]*Scott Department of Urology, Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, Texas*
[9]*Department of Urology, Sidney Kimmel Medical College at Thomas Jefferson University Hospitals, Philadelphia, Pennsylvania*
[10]*Department of Urology, Mayo Clinic Health System, Rochester, Minnesota*
[11]*Department of Urology, University of Iowa, Iowa City, Iowa*
[12]*Department of Urology, Loyola University Medical Center, Maywood, Illinois*
[13]*Division of Urology, Pennsylvania State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania*
[14]*Department of Urology, Weill Medical College of Cornell University, New York, New York*
[15]*Cleveland Clinic, Glickman Urological and Kidney Institute, Cleveland, Ohio*
[16]*Department of Urology, University of Michigan, Ann Arbor, Michigan*
[17]*Department of Urology, Indiana University School of Medicine, Indianapolis, Indiana*
[18]*Department of Urology, University of North Carolina School of Medicine, Chapel Hill, North Carolina*
[19]*Department of Urology, John Wayne Cancer Institute, Santa Monica, California*
[20]*Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York*
[21]*Department of Urology, Mayo Clinic-Phoenix, Scottsdale, Arizona*
[22]*Department of Urology, Mayo Clinic-Jacksonville, Jacksonville, Florida*
[23]*Department of Urology, Rabin Medical Center, Tel Aviv, Israel*
[24]*Urology Center of Las Vegas, Las Vegas, Nevada*
[25]*UroGen Pharma, Ra'anana, Israel*
[26]*UroGen Pharma, Princeton, New Jersey*
[27]*Department of Urology, Albert Einstein College of Medicine, Bronx, New York*

Abbreviations and Acronyms

AE = adverse event

eGFR = estimated glomerular filtration rate

PDE = primary disease evaluation

RNU = radical nephroureterectomy

TEAE = treatment-emergent adverse event

UTUC = upper tract urothelial carcinoma

Purpose: Our goal was to evaluate long-term safety and durability of response to UGN-101, a mitomycin-containing reverse thermal gel, as primary chemoablative treatment for low-grade upper tract urothelial carcinoma.

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¶ Financial interest and/or other relationship with UroGen Pharma and Intuitive Surgical.
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‡‡Correspondence: Scott Department of Urology, Dan L. Duncan Cancer Center, Baylor College of Medicine, 7200 Cambridge, Suite 10B, Houston, Texas, 77030 (telephone: 713-798-6841; FAX: 713-798-5553; email: slerner@bcm.edu)

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Materials and Methods: In this open-label, single-arm, multicenter, phase 3 trial (NCT02793128), patients ≥18 years of age with primary or recurrent biopsy-proven low-grade upper tract urothelial carcinoma received 6 once-weekly instillations of UGN-101 via retrograde catheter to the renal pelvis and calyces. Those with complete response (defined as negative ureteroscopic evaluation, negative cytology and negative for-cause biopsy) 4–6 weeks after the last instillation were eligible for up to 11 monthly maintenance instillations and were followed for ≥12 months with quarterly evaluation of response durability. Durability of complete response was determined by ureteroscopic evaluation; duration of response was estimated by the Kaplan-Meier method. Treatment-emergent adverse events (TEAEs) were monitored.

Results: Of 71 patients who initiated treatment, 41 (58%) had complete response to induction therapy and consented to long-term followup; 23/41 patients (56%) remained in complete response after 12 months (95% CI 40, 72), comprising 6/12 (50%) who did not receive any maintenance instillations and 17/29 (59%) who received ≥1 maintenance instillation. Kaplan-Meier analysis of durability was estimated as 82% (95% CI 66, 91) at 12 months. Ureteric stenosis was the most frequently reported TEAE (31/71, 44%); an increasing number of instillations appeared to be associated with increased incidence of urinary TEAEs.

Conclusions: Durability of response to UGN-101 with or without maintenance treatment is clinically meaningful, offering a kidney-sparing therapeutic alternative for patients with low-grade disease.

Key Words: urinary bladder neoplasms, mitomycin, clinical trial

Upper tract urothelial carcinoma (UTUC) is an uncommon malignancy with few standardized treatment options supported by prospective data.[1] Patients with high-grade cancer are most commonly treated with radical nephroureterectomy (RNU), while kidney-sparing options such as endoscopic ablation are recommended for patients with low-grade disease and small, favorably located tumors or patients with functionally or anatomically solitary kidneys.[1,2] Drug concentration and dwell time are both negatively affected by urine flow, limiting the benefit of aqueous topical therapies in UTUC.[3]

UGN-101 (JELMYTO® [mitomycin] for pyelocalyceal solution) is a mitomycin-containing reverse thermal gel (4 mg mitomycin per ml gel) indicated for primary chemoablative treatment of low-grade UTUC.[4] Liquid when chilled, UGN-101 is instilled via ureteral catheter or nephrostomy tube and becomes a semisolid gel at body temperature that dissolves during urine production over 4–6 hours, resulting in increased dwell time at the tumor site.[5]

We previously reported interim results from OLYMPUS, a phase 3 clinical trial that evaluated UGN-101 for treatment of low-grade UTUC.[6] The trial's primary endpoint was complete eradication of disease in the ipsilateral pyelocalyceal system (defined as negative ureteroscopic evaluation, negative cytology and negative for-cause biopsy) 4–6 weeks following 6 weekly induction instillations of UGN-101. Complete response was observed in 59% of treated patients irrespective of baseline demographic and clinical characteristics, suggesting UGN-101 may offer a kidney-sparing alternative to patients with low-grade, low-volume UTUC. At the time of database lock for the previously reported results (May 22, 2019), fewer than half of patients with complete response at the primary disease evaluation (PDE) visit had been followed for an additional 12 months to evaluate durability of response, the key secondary outcome. As of final database lock on April 30, 2020, all patients with complete response at the PDE visit had either been followed for ≥12 additional months for continued response or had discontinued participation in the study. These longer-term results are presented here.

METHODS

The design of OLYMPUS, an open-label, single-arm, phase 3 trial of UGN-101 conducted at 24 academic centers in the U.S. and Israel (NCT02793128), has been described in detail elsewhere.[6] Briefly, eligible patients ≥18 years of age with primary or recurrent biopsy-proven low-grade UTUC were treated with 6 once-weekly instillations of UGN-101. Tumor response was evaluated at the PDE visit, 4–6 weeks after the last instillation. Patients who demonstrated complete response were offered maintenance treatment of up to 11 once-monthly instillations of UGN-101, with followup visits for evaluation of response durability at 3, 6, 9 and 12 months. The key secondary efficacy outcome was durability of response at 12 months. Safety was assessed throughout by laboratory evaluations, physical examination and adverse event (AE) monitoring. All patients provided written informed consent (IRB No. TC-UT-03-P).

Methods for sample size determination and analysis of the primary outcome have been described in detail previously.[6] The key secondary endpoint of long-term durability of response was determined for those patients who achieved complete response at the PDE visit. Durability of response was measured as ureteroscopically observed complete response at 12 months and duration of response estimated by the Kaplan-Meier method. Duration of response was defined as the time from PDE visit until disease recurrence. Patients who did not have documented disease recurrence or who died prior to recurrence

were censored at their last assessment or date of death. All statistical analyses were performed using SAS®, version 9.4 or higher (SAS, Cary, North Carolina). Safety data were summarized descriptively.

RESULTS

The study was initiated April 6, 2017 and the final data cutoff was April 30, 2020. Of 74 patients enrolled 71 received ≥1 dose of UGN-101 (comprising both the intent-to-treat and safety populations) and 61 (86%) completed the 6 planned weekly instillations. At the PDE visit, 42/71 patients (59%) achieved complete response; however, 1 patient withdrew consent prior to followup (fig. 1). Thus, the population followed for evaluation of response durability comprised 41/71 patients (58%). The median duration of followup for patients with complete response was 11.8 months (IQR 11.0, 12.7).

Baseline demographic and clinical characteristics of patients entering the maintenance phase are shown in table 1. Most patients were White, male, older than 70 years (median age 72, range 49–87) and had 2 kidneys. Maintenance regimens varied; 12/41 patients (29%) received no maintenance therapy, while 29/41 (71%) received at least 1 dose of maintenance treatment (table 2). Among the 29 patients who received any maintenance treatment, the median number of maintenance instillations was 6 (range 1–11).

Of 41 patients who achieved complete response at PDE 23 (56%) remained in complete response after 12 months (95% CI 40, 72), 8 experienced disease recurrence and 10 were unable to be evaluated. In the Kaplan-Meier analysis durability of response was estimated as 82% (95% CI 66, 91) 12 months after the PDE visit (fig. 2). The Kaplan-Meier median time to recurrence was not estimable.

Among the 23/41 patients without disease recurrence at 12 months 17/29 (59%) received ≥1 maintenance treatment and 6/12 (50%) did not receive any maintenance treatment. Exploratory subgroup analyses to evaluate treatment effect showed no individual parameter appeared to affect durability of response (table 3). Among the 4 patients with a single kidney 2 had durable response at 12 months, 1 had durable response at 9 months but did not have a 12-month evaluation and 1 had disease recurrence.

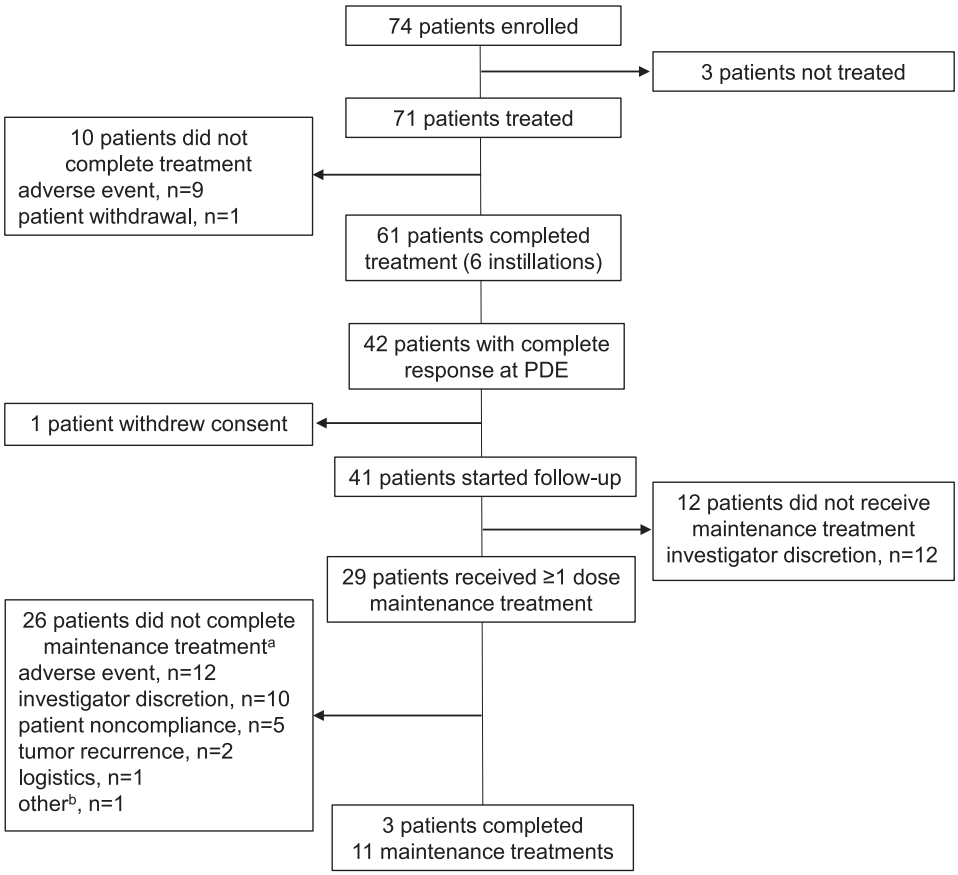

Figure 1. Patient flow diagram, modified from Kleinmann et al[6] to show final disposition of patients at the April 30, 2020 final data cutoff. *a*, more than 1 reason could be given. *b*, patient traveled out of the country.

Table 1. *Summary of baseline demographic and clinical characteristics of 41 patients with complete response at PDE*

Characteristic	Received ≥1 Maintenance Treatment	Received No Maintenance Treatment
No. pts	29	12
Mean yrs age (SD)	69.4 (9.4)	74.7 (10.8)
No. age <75 yrs (%)	20 (69)	6 (50)
No. age ≥75 yrs (%)	9 (31)	6 (50)
No. male (%)	21 (72)	6 (50)
Mean kg/m^2 body mass index (SD)	29.3 (7.0)	26.3 (5.2)
No. race or ethnicity (%)		
Caucasian	24 (83)	11 (92)
African American	2 (6.9)	1 (8.3)
Hispanic	2 (6.9)	0 (0)
Asian	1 (3.4)	0 (0)
No. 2 kidneys at enrollment (%)	27 (93)	10 (83)
No. history of UTUC (%)	17 (59)	3 (25)
No. previous transurethral resection of bladder tumors (%)	10 (34)	2 (17)
No. previous endoscopic ablative surgery (%)	14 (48)	7 (58)
No. any previous surgery related to urothelial carcinoma (%)	26 (90)	10 (83)
Mean No. of papillary tumors (SD)	2.4 (1.78)	1.9 (1.08)
Mean mm diameter of largest tumor (SD)*	12.7 (9.63)	16.9 (9.16)
Mean mm total tumor burden (SD)	17.2 (12.50)	21.2 (16.39)
No. tumor unreachable by laser (%)	15 (52)	5 (42)

* Pre-debulking. Data are summarized descriptively; no statistical analyses were performed.

Among the 8 patients with disease recurrence 3 recurrences were documented approximately 3 months after the PDE visit; the other 5 recurrences were documented at later assessments (fig. 3). Maintenance regimens varied among patients with disease recurrence. Although 2 patients with recurrences had received no maintenance, the others had received 1, 2, 3, 6, 9 and 11 maintenance instillations.

There were 8 patients who were considered to have partial response to UGN-101 at the PDE visit.

Table 2. *Number of UGN-101 maintenance instillations and number of urinary obstruction AEs during maintenance period in 41 patients with complete response at PDE*

Number of UGN-101 Maintenance Instillations	No. Pts (%)	No. Urinary Obstruction AEs
0	12 (29)	10
1	4 (10)	2
2	2 (4.9)	2
3	3 (7.3)	2
4	1 (2.4)	1
5	2 (4.9)	3
6	4 (10)	11
7	2 (4.9)	1
8	4 (10)	7
9	2 (4.9)	3
10	2 (4.9)	5
11	3 (7.3)	3

Urinary obstruction includes any TEAEs of ureteric stenosis, hydronephrosis, urinary tract obstruction, pelvi-ureteric obstruction, ureteric obstruction and obstructive uropathy.

Although not eligible for maintenance treatment, there was evidence of clinical benefit for some of these patients through modification of their treatment plans. One patient who planned to receive endoscopic ablation plus adjuvant topical agents was changed to receive only endoscopic ablation, while 2 patients who planned to undergo RNU were changed to endoscopic ablation or observation and followup every 3 months with ureteroscopy. None of the partial responders underwent RNU.

Of the 71 patients enrolled in the trial who received ≥1 instillation of UGN-101 a total of 8 (11%) eventually underwent RNU (table 4). Of these, 2 were considered complete responders; 1 received 6 maintenance instillations of UGN-101 while the other did not receive any maintenance treatment. In both cases, an AE of ureteric stenosis that did not resolve resulted in the patients' election to undergo RNU, with no cancer found at time of nephroureterectomy. The remaining 6 patients received 5 (1 patient) or 6 (5) instillations of UGN-101, but were considered nonresponders and recommended for RNU by their treating urologists.

Safety

There were few differences in treatment emergent AEs (TEAEs), either qualitatively or quantitatively, in this final analysis compared with the interim analysis presented previously.[6] The most common TEAEs were ureteric stenosis, urinary tract infection, hematuria and flank pain, and most were considered to be related to study drug or procedure (table 5). There were differences in the incidences of individual AEs between the 29 patients who received ≥1 maintenance treatment and the 42 patients who did not receive any maintenance treatment (comprising 12 patients who were complete responders at the PDE visit but did not receive maintenance and 30 patients who were not complete responders at the PDE visit and were therefore ineligible for maintenance treatment). There appeared to be an association between the total number of UGN-101 instillations and the most commonly reported TEAEs from the renal and urinary disorders organ class. Ureteric stenosis was the most frequently reported TEAE in the safety population, occurring in 31/71 patients (44%); however, it was reported in 19/29 patients (66%) who received ≥7 instillations of UGN-101 (ie ≥1 maintenance instillation) compared with 12/42 patients (29%) who received ≤6 instillations of UGN-101. Patients with a TEAE of ureteric stenosis had completed a mean 8.0±3.2 instillations before their first reported event. TEAEs of urinary tract infection, flank pain, nausea, dysuria, abdominal pain and vomiting occurred in a higher percentage of patients who received ≥1 maintenance instillation

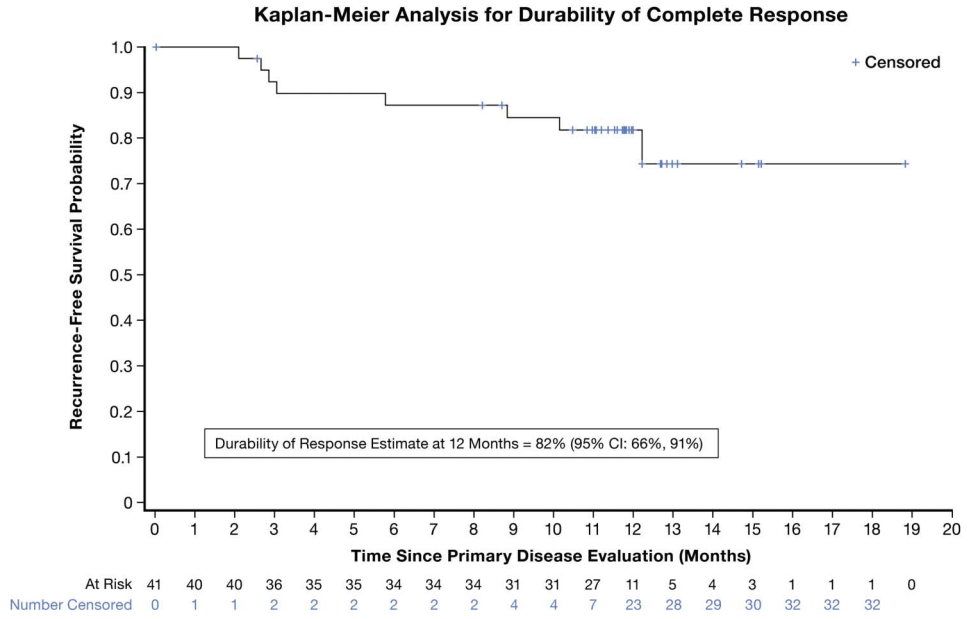

Figure 2. Kaplan-Meier analysis for durability in 41 patients with complete response at PDE during maintenance/followup.

of UGN-101, although no statistical analyses were performed.

A total of 90 urinary obstruction TEAEs (defined as ureteric stenosis, hydronephrosis, urinary tract obstruction, pelvi-ureteric obstruction, obstructive uropathy and ureteric obstruction) occurred in 41/71 patients (58%) in the safety population; however, the majority resolved

Table 3. *Subgroup analysis of durable complete response 12 months post-PDE visit (complete responder at PDE analysis set)*

		Complete Responder at PDE Analysis Set (41 pts)		
Covariate	Subgroup	Total No.	No. Durable Complete Response (%)*	95% CI
Age (yrs)	<65	10	7 (70)	(35, 93)
	65 to <75	16	10 (62)	(35, 85)
	≥75	15	6 (40)	(16, 68)
Gender	Male	27	13 (48)	(29, 68)
	Female	14	10 (71)	(42, 92)
Body mass index (kg/m^2)	≤30	27	14 (52)	(32, 71)
	>30	14	9 (64)	(35, 87)
Country	USA	31	16 (52)	(33, 70)
	Israel	10	7 (70)	(35, 93)
Pre-debulking No. of papillary lesions	1	18	12 (67)	(41, 87)
	>1	23	11 (48)	(27, 69)
Post-debulking No. of papillary lesions	1	29	18 (62)	(42, 79)
	>1	12	5 (42)	(15, 72)
Pre-debulking largest lesion diameter (mm)	≤10	20	14 (70)	(46, 88)
	>10	20	9 (45)	(23, 68)
Post-debulking largest lesion diameter (mm)	≤10	35	19 (54)	(37, 71)
	>10	6	4 (67)	(22, 96)
Pre-debulking total tumor burden (mm)	≤15	21	12 (57)	(34, 78)
	>15	16	9 (56)	(30, 80)
Post-debulking total tumor burden (mm)	≤10	25	15 (60)	(39, 79)
	>10	16	8 (50)	(25, 75)
No. treatments received	6	35	21 (60)	(42, 76)
	<6	6	2 (33)	(4, 77)
Tumor is unresectable	No	21	11 (52)	(30, 74)
	Yes	20	12 (60)	(36, 81)
Past urothelial carcinoma episodes	0	15	10 (67)	(38, 88)
	≥1	26	13 (50)	(30, 70)
Past UTUC episodes	0	21	12 (57)	(34, 78)
	≥1	20	11 (55)	(32, 77)
No. maintenance dose	0	12	6 (50)	(21, 79)
	≥1	29	17 (59)	(39, 76)

* At 12 months post-PDE.

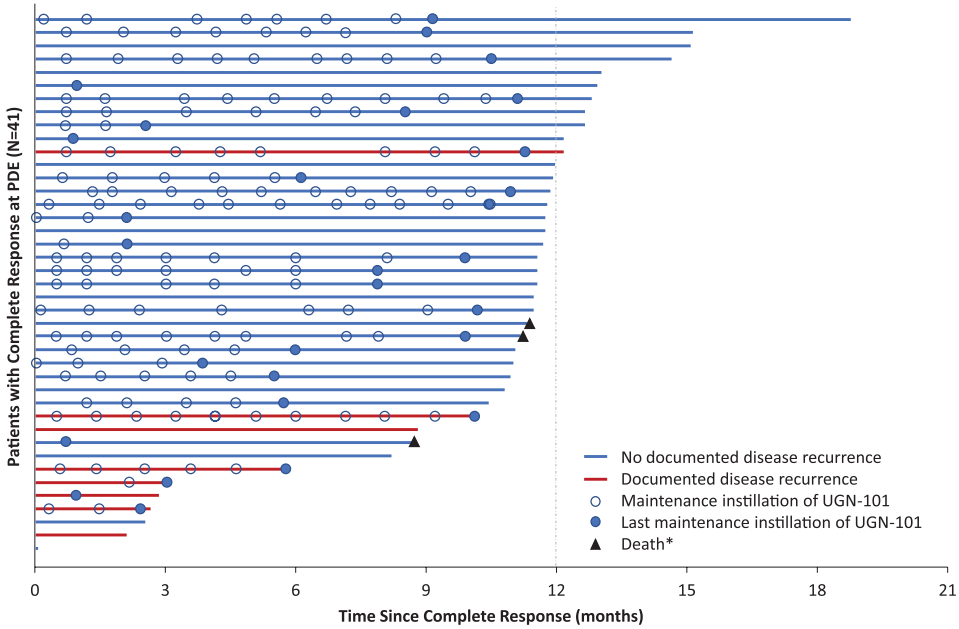

Figure 3. Swimmer plot for 41 individual patients with complete response at PDE during maintenance/followup. Among 41 patients with complete response at PDE 12 did not receive maintenance treatment, while 29 received ≥1 maintenance instillation of UGN-101. There were 8 patients with documented disease recurrence and 23 patients without disease recurrence at 12 months. Patients who did not have documented disease recurrence or who died prior to recurrence were censored at their last assessment or date of death. Asterisk indicates none of the deaths was considered related to study drug or study procedure.

without sequelae (supplementary table, https://www.jurology.com). Of 23 urinary obstruction TEAEs that occurred in 19 patients and did not resolve or resolved with sequelae 21 events occurred after ≥6 instillations of UGN-101.

Among patients with renal and urinary TEAEs (49/71, 69%), mean changes from baseline for creatinine values were generally small and transient both during the treatment and maintenance periods, and were not considered clinically relevant.

Table 4. *Demographic and clinical characteristics of patients who underwent RNU during the study or long-term followup**

Pt No.	Age	Sex	Race	No. UGN-101 Instillations		Outcome at PDE	Reason/Timing for RNU
				Induction	Maintenance		
1	50	F	Caucasian	6	6	Complete response	AE of ureteric stenosis with hydronephrosis reported 33 days after last maintenance treatment; AE did not resolve + pt elected to undergo lt RNU 166 days after last maintenance treatment. Post-RNU pathology identified no residual carcinoma.
2	68	F	Caucasian	6	0	Complete response	AE of ureteric stenosis reported 145 days after last treatment; AE did not resolve + pt elected to undergo lt RNU 290 days after last treatment. Post-RNU pathology identified no residual carcinoma.
3	63	F	Hispanic	6	0	Emergence of high-grade disease not detected at baseline	Ureteroscopy with biopsy identified large (approximately 2 cm) papillary tumor filling the renal pelvis + upper pole calyx; pt underwent rt RNU 183 days after last treatment.
4	67	M	Caucasian	6	0	Emergence of high-grade disease not detected at baseline	Ureteroscopy with biopsy identified high-grade T1 urothelial carcinoma; pt underwent rt RNU 90 days after last treatment.
5	71	M	Caucasian	6	0	Emergence of high-grade disease not detected at baseline	Ureteroscopy with biopsy identified foci of high-grade carcinoma in the background of low-grade carcinoma; pt underwent lt RNU 149 days after last treatment. Post-RNU pathology identified yp Ta papillary urothelial carcinoma.
6	78	M	Asian	6	0	No complete response	AE of ureteric stenosis reported 28 days after last treatment; cytology and biopsy identified low-grade Ta papillary urothelial carcinoma; pt underwent lt RNU 85 days after last treatment.
7	77	M	Caucasian	5	0	Emergence of high-grade disease not detected at baseline	Discontinued treatment due to urinary tract obstruction; ureteroscopy with biopsy identified superficial fragment of papillary urothelial carcinoma, predominantly low-grade with focal high-grade areas; pt underwent lt RNU 107 days after last treatment.
8	62	F	Caucasian	6	0	No complete response	Ureteroscopy evaluation indeterminate due to blood clot in upper calyx; pt underwent lt RNU 157 days after last treatment.

* As reported through December 18, 2019 among 71 patients enrolled in the study who received ≥1 instillation of UGN-101. Post-RNU pathology reported if available.

Table 5. *TEAEs occurring in ≥10 patients, safety population (71)*

	No. Pts with ≤6 Instillations of UGN-101 (%)	No. Pts with ≥7 Instillations of UGN-101 (%)
Pts	42	29
Any TEAE	38 (90)	29 (100)
Serious AE	18 (43)	10 (34)
TEAE leading to death	3 (7.1)	2 (6.9)
TEAE related to study drug	26 (62)	26 (90)
TEAE related to study procedure	27 (64)	28 (97)
Ureteric stenosis	12 (29)	19 (66)
Urinary tract infection	11 (26)	12 (41)
Hematuria	13 (31)	10 (34)
Flank pain	9 (21)	13 (45)
Nausea	7 (17)	11 (38)
Dysuria	7 (17)	9 (31)
Abdominal pain	4 (9.5)	10 (34)
Vomiting	6 (14)	8 (31)
Renal impairment	7 (17)	7 (24)
Hydronephrosis	7 (17)	6 (21)
Fatigue	6 (14)	5 (17)
Anemia	5 (12)	5 (17)
Back pain	5 (12)	5 (17)
Pollakiuria	3 (7.1)	7 (24)

Data are summarized descriptively according to the Medical Dictionary for Regulatory Activities, version 19.1. No statistical analyses were performed.

Similarly, mean changes for estimated glomerular filtration rate (eGFR) were not considered clinically relevant during the treatment period; however, mean changes were considered moderate (decreases of ≥10 ml/minute/1.73 m^2) for some visits during the maintenance period, but interpretation of clinical relevance is limited by the small number of patients. Among 3/4 patients with a single kidney there were generally small and clinically insignificant changes in creatinine levels and eGFR; 1 patient experienced significant, nonreversible decline in eGFR.

With further followup, 2 more patients died (from hypotension/septic shock/pneumonia in a 79-year-old male and metastatic urothelial carcinoma in an 83-year-old male) in addition to the 3 deaths previously reported.[6] There was no evidence of recurrent primary UTUC in the patient whose cause of death was cancer; the patient had achieved 6 months of durable complete response and was diagnosed with metastatic disease approximately 4.5 months after the last dose of study medication. None of the deaths was considered related to study drug or study procedure.

DISCUSSION

The previous interim report of the efficacy and safety of UGN-101 in primary chemoablation of low-grade UTUC demonstrated that a substantial proportion of patients (59%) achieved complete response following 6 weekly instillations, and suggested the response may be durable.[6] The current study, in which the cohort of patients who achieved complete response and entered maintenance treatment and followup, confirms that durability of response to UGN-101 is clinically meaningful. In the Kaplan-Meier analysis, durability was estimated to be 82% at 12 months followup. Because there were few documented recurrences of UTUC in this analysis, the median time to recurrence could not be estimated. From trial initiation (April 6, 2017) through final database lock (April 30, 2020) 23/71 patients (32%) have had no recurrence in the treated kidney and remain alive. The durable response to UGN-101 observed in this study is encouraging, especially considering that some patients' lesions were deemed unresectable at baseline. Even among patients who achieved partial but not complete response there was evidence of clinical benefit in the modification of treatment plans to less invasive options; however, this observation must be interpreted cautiously given the small number of patients involved.

Direct comparison of the recurrence rate in this study and local recurrence rates in UTUC patients treated endoscopically is not possible given the retrospective nature of published series with heterogeneous patient populations and lengths of followup. However, a meta-analysis of predominantly low- and intermediate-grade UTUC patients treated endoscopically found a local recurrence rate of 53% in 20 series among 736 patients whose followup ranged from 14–73 months.[7] In a prospective series of 66 low-grade UTUC patients a 77% rate of local recurrence at a mean of 12 months was observed,[8] but mean tumor size was 23 mm, greater than the maximum allowable tumor size of 15 mm in the current study.

Although patients who achieved complete response after induction therapy were eligible for up to 11 monthly maintenance treatments with UGN-101, use of maintenance was inconsistent. Twelve patients received no maintenance while just 3/41 (7%) received the maximum number of instillations allowed. There was no clear association between durability of response and any number of maintenance treatments with UGN-101. At 12 months followup durable complete response was observed in 59% of patients who had received any amount of maintenance treatment compared with 50% of patients who did not receive any maintenance treatment. Given the variability in maintenance treatment across the cohort of patients and the high estimate of durable response, it is not possible to draw conclusions about the value of maintenance therapy in sustaining complete response.

Conversely, this analysis provides some evidence that maintenance therapy and an increasing

number of UGN-101 instillations are associated with increased incidence and severity of ureteric stenosis and incidence of urinary obstruction events that do not resolve or resolve with sequelae. Indeed, the incidence of ureteric stenosis may help explain the variability in the number of maintenance instillations patients received. Given the nature of UGN-101 delivery directly to the target organ, it can be difficult to differentiate between relationship of AEs to study drug and relationship to study procedure, particularly in the case of renal and urinary TEAEs. A detailed discussion of treatment-related morbidity that may occur as a result of multiple instillations of UGN-101 for the management of low-grade UTUC has been presented previously, including AEs of special interest (ie renal and urinary disorders, immune system disorders, and blood and lymphatic system disorders).[6]

TEAEs in this final analysis did not differ qualitatively from the interim analysis previously presented,[6] although there were some differences in the incidences of TEAEs between patients who received $\leq$6 instillations of UGN-101 (induction only) and patients who received $\geq$7 instillations ($\geq$1 maintenance instillation), reflecting the increased risk of AEs associated with increased exposure to mitomycin and an increased number of procedures. Two additional deaths occurred during the extended followup, but neither was considered related to study drug or treatment.

There are limitations to the current study. The small size of the study population reflects the rarity of low-grade UTUC and may limit the generalizability of the findings regarding durability of complete response. Additionally, the lack of a control group may introduce bias, in that benefits and harms may be over or under assessed; however, there are no other nonsurgical ablative therapies with which UGN-101 could be compared.

CONCLUSIONS

Instillation of UGN-101 once weekly for 6 weeks has been shown to be effective and clinically meaningful for primary chemoablation of low-grade UTUC. Results from this final analysis suggest durability of response in a majority of patients for up to 12 months following induction therapy, with or without maintenance treatment. No new safety signals were identified and the overall safety profile in this analysis was consistent with the known safety profile of endoscopic administration of intravesical mitomycin. Based on results to date, the benefit-risk profile of UGN-101 for induction treatment of low-grade UTUC appears favorable, and suggests that kidney-sparing endoscopic treatment can be augmented in patients with multifocal disease and those whose tumors are difficult to treat endoscopically. The use of maintenance treatment for patients achieving complete response requires full consideration of the potential benefits and risks associated with maintenance therapy.

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EDITORIAL COMMENT

While the incidence of low-grade upper tract urothelial carcinoma (UTUC) remains relatively low, it is essential to recognize that it will commonly have adverse outcomes with high rates of relapse and intensity of care.[1] Moreover, clinical management of UTUC can be challenging given limitations of endoscopic biopsy and efficacy of current ablative alternatives for the treatment of low-grade disease.[2] Against this backdrop, the innovative use of a mitomycin-containing thermal gel (UGN-101 [JELMYTO®]) for chemoablation of UTUC was recently studied in a phase 3 trial which showed an encouraging 60% complete response rate following endoscopic instillations of UGN-101 for low-volume, low-grade disease (reference 6 in article).

Matin et al report on durability of response at 12 months amongst patients who experienced complete ablation following an induction course of UGN-101. The study also allowed for monthly instillations with UGN-101, with 71% of the followup cohort receiving at least 1 dose of maintenance therapy. Importantly, 56% of the patients remained in complete response and 32% have had no recurrence in the treated kidney at the 12-month mark. Moreover, maintenance therapy did not seem to be linked to durability of response.

The authors should be applauded for this landmark work. Several questions remain unanswered and should be further addressed. One major concern is the incidence of unresolved obstructive uropathy, which seemed to be associated with repeated instillations and/or endoscopic interventions. We should not only be fully counseling patients on possible need for further interventions but also further study the ideal regimen schedule and actual role of maintenance therapy. Another key next step in moving forward is to determine whether further instillations and surveillance would be well tolerated in clinic under local anesthesia to potentially reduce total cost of therapy. Effective implementation is of paramount importance for successful dissemination and to make this revolutionary therapy fully available to patients suffering from UTUC.

Rodrigo Rodrigues Pessoa[1]
[1]*Division of Urology*
University of Colorado
Aurora, Colorado

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REPLY BY AUTHORS

We agree and fully support the need to counsel patients on the risk of ureteral strictures and resulting hydronephrosis. Most of these events appear to be transient and manageable with a treatment holiday, and if needed ureteral stenting. If persistent, oral tapered steroids may help resolve, though this is based on a small number of patients. Reverse thermal mitomycin-containing gel (UGN-101) is approved for administration via a percutaneous nephrostomy tube which may reduce the risk of treatment-associated ureteral stenosis, but this risk is present with repeated instrumentation with or without UGN-101. Many of the investigators in the OLYMPUS trial performed ureteral catheterization and instillations in the outpatient clinic, which was generally well tolerated. Given that there was no difference in durability with or without maintenance instillations, the decision to proceed with maintenance therapy is up to the treating urologist and patient, as UGN-101 is approved for induction and up to 11 monthly instillations.