original report

Phase II California Cancer Consortium Trial of Gemcitabine-Eribulin Combination in Cisplatin-Ineligible Patients With Metastatic Urothelial Carcinoma: Final Report (NCI-9653)

Sarmad Sadeghi, MD, PhD[1]; Susan G. Groshen, PhD[1]; Denice D. Tsao-Wei, MS[1]; Rahul Parikh, MBBS, PhD[2]; Amir Mortazavi, MD[3]; Tanya B. Dorff, MD[4]; Cheryl Kefauver, RN[1]; Christopher Hoimes, MD[5]; Laurence Doyle, MD[6]; David I. Quinn, MBBS, PhD[1]; Edward Newman, PhD[4]; and Primo N. Lara Jr, MD[7]

abstract

PURPOSE Patients with metastatic urothelial carcinoma are often ineligible for cisplatin-based treatments. A National Cancer Institute Cancer Therapy Evaluation Program–sponsored trial assessed the tolerability and efficacy of a gemcitabine-eribulin combination in this population.

METHODS Patients with treatment-naïve advanced or recurrent metastatic urothelial carcinoma of the bladder, ureter, or urethra not amenable to curative surgery and not candidates for cisplatin-based therapy were eligible. Cisplatin ineligibility was defined as creatinine clearance less than 60 mL/min (but ≥ 30 mL/min), grade 2 neuropathy, or grade 2 hearing loss. Treatment was gemcitabine 1,000 mg/m^2 intravenously followed by eribulin 1.4 mg/m^2, both on days 1 and 8, repeated in 21-day cycles until progression or unacceptable toxicity. A Simon two-stage phase II trial design was used to distinguish between Response Evaluation Criteria in Solid Tumors, version 1.1 objective response rates of 20% versus 50%.

RESULTS Between June 2015 and March 2017, 24 eligible patients with a median age of 73 years (range, 62 to 88 years) underwent therapy. Performance status of 0, 1, or 2 was seen in 11, 11, and two patients, respectively. Sites of disease included: lymph nodes, 16; lungs, nine; liver, seven; bladder, five; bones, two. Median number of cycles received was four (range, one to 16). Of 24 patients, 12 were confirmed responders; the observed objective response rate was 50% (95% CI, 29% to 71%). Median overall survival was 11.9 months (95% CI, 5.6 to 20.4 months), and median progression-free survival was 5.3 months (95% CI, 4.5 to 6.7 months). The most common treatment-related any-grade toxicities were fatigue (83% of patients), neutropenia (79%), anemia (63%), alopecia (50%), elevated AST (50%), and constipation, nausea, and thrombocytopenia (42% each).

CONCLUSION Gemcitabine-eribulin treatment response and survival for cisplatin-ineligible patients compare favorably to other regimens. Additional research is needed.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Urothelial carcinoma of the bladder remains one of the most challenging and lethal urologic cancers. It is the second most common genitourinary (GU) cancer next to prostate cancer, with a 2018 estimated incidence of 81,190, and has risen to be the second most deadly GU cancer, with 17,240 estimated deaths in 2018.[1] Many of these patients will have non–muscle-invasive bladder cancer at diagnosis (75% to 80%); of those with muscle invasion at diagnosis, approximately two-thirds will go on to develop regional or systemic disease. Despite improvements in surgical techniques and multimodal therapy, 5-year survival rates for patients with muscle-invasive bladder cancer remain suboptimal.[2] Virtually all deaths from bladder cancer result from muscle-invasive disease that recurs or metastasizes after local therapy.[3]

Current standard of care offers platinum-based first-line chemotherapy with regimens such as dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin and gemcitabine-cisplatin combination for patients who are deemed cisplatin eligible.[4,5] For cisplatin-ineligible patients, the de facto standard of care became gemcitabine plus carboplatin and, with the advent of immunotherapy, anti-PD1/PDL1 (programmed cell death-1 and programmed cell death ligand-1) antibodies,[6-8] although more recently the US Food and Drug Administration (FDA) has recommended against using front-line immunotherapy in patients with low expression of PDL1 immunohistochemistry biomarker

on the basis of the companion assay for the corresponding checkpoint inhibitor antibody intended for use.

Eribulin is a synthetic macrocyclic ketone analog of the marine natural product halichondrin B, which acts predominantly as a microtubule inhibitor. After a positive National Cancer Institute Cancer Therapy Evaluation Program–sponsored phase II trial of single-agent eribulin in metastatic urothelial carcinoma,[9] this trial was designed to evaluate the gemcitabine-eribulin combination in patients with newly diagnosed metastatic urothelial carcinoma who are deemed ineligible for cisplatin-based chemotherapy. The trial was conducted before FDA approval of PD1/PDL1 antibodies for cisplatin-ineligible patients, in a period when gemcitabine plus carboplatin regimen or single-agent chemotherapy were the options available to this patient population, and aimed to proceed to a phase III study if a significant efficacy signal was detected. Eribulin is approved by the FDA for use in metastatic breast cancer previously treated with chemotherapy[10] and, more recently, unresectable or metastatic liposarcoma after anthracycline treatment.[11]

METHODS

The study was approved by the Central Institutional Review Board and ratified at local investigational review boards in accordance with an assurance approved by the US Department of Health and Human Services and registered at www.clinicaltrials.gov as NCT02178241. Written informed consents were obtained from each participant.

Patients

Adult (age ≥ 18 years) women and men with locally advanced unresectable or metastatic predominantly urothelial carcinoma, histologically confirmed, of the bladder, ureter, or urethra that was not amenable to curative surgical treatment were eligible provided they met the following criteria: had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; were ineligible for treatment with cisplatin, on the basis of either calculated creatinine clearance greater than or equal to 30 and less than 60 mL/min (Cockcroft-Gault), or Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or greater hearing loss, or CTCAE grade 2 or greater neuropathy; must not have received prior systemic therapy for their advanced cancer; had Zubrod performance status less than or equal to 2 (or Karnofsky performance status ≥ 60%); and had adequate organ and marrow function. Tissue from the diagnostic biopsy or prior transurethral resection of bladder tumor or cystectomy were collected and stored at a biobank for future study.

Protocol Therapy

Eribulin at a dose of 1.4 mg/m^2 was administered on an outpatient basis as an intravenous bolus over 2 to 5 minutes once a week for 2 weeks in a row (on days 1 and 8) of a 21-day cycle; gemcitabine at a dose of 1,000 mg/m^2 was administered intravenously over 30 minutes before eribulin. Doses were reduced for individual patients in subsequent cycles dependent on toxicity. There was no intrapatient dose escalation.

Treatment could continue until disease progression, intercurrent illness that prevented additional administration of treatment, treatment delay of greater than 4 weeks for any reason, unacceptable adverse event(s), general or specific changes in the patient's condition that rendered additional treatment unacceptable in the judgment of the investigator, or patient's decision. Patient follow-up took place every 3 months for up to 36 months after end of treatment, until disease progression, start of a treatment with an agent other than gemcitabine-eribulin, or death, whichever occurred first.

Response Evaluation

At study entry, patients were required to have measurable disease according to the RECIST guideline (version 1.1).[12] All patients underwent radiographic evaluation and tumor measurements at baseline and then after every two cycles (every 6 weeks). Confirmatory scans were required at 4 or more weeks after initial documentation of an objective response. Overall confirmed complete response (CR) and partial response (PR) were considered objective responses, according to RECIST version 1.1.

Toxicity Assessment

Toxicity was graded using the CTCAE, version 4.0.[13] Physical examinations and toxicity assessments were done at baseline and at the start of each cycle; laboratory tests were done at baseline and before each treatment.

Study Design and Statistical Methods

This was a single-arm phase II study. The primary end point was treatment efficacy evaluated by overall tumor response on the basis of the RECIST version 1.1. A Simon two-stage optimal design was used, with an α of 0.09 for a true objective response rate of 20% and β of 0.09 for a true response rate of 50%. If two or more confirmed objective responses were observed in the first seven patients, the accrual would continue to a total of 21 patients. If seven or

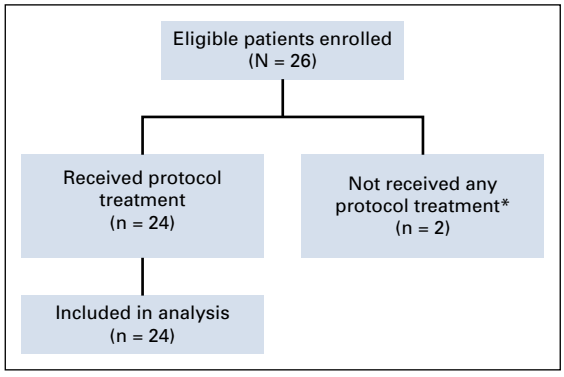

FIG 1. CONSORT diagram for the trial. (*) See Table 1.

TABLE 1. Demographics and Clinical Baseline Characteristics

Demographic or Characteristic	No. of Patients	%
Enrollment time	June 4, 2015 to March 28, 2017	
Total patients enrolled	26*	
Total eligible patients treated in study	24	100
Patients assessable for response	19	
Age at study entry, years		
< 70	11	46
≥ 70	13	54
Median (range)	73 (62-88)	
Sex		
Female	4	17
Male	20	83
Race		
White	22	92
Hispanic	1	4
Asian	1	4
Perioperative cisplatin-based chemotherapy		
Yes	5	21
No	19	79
Extent of disease		
Locally advanced	5	21
Distant metastases	19	79
Primary cancer sites		
Bladder	23	96
Ureter	1	4
Baseline site of disease involved		
Adrenal gland	1	4
Bladder	5	21
Bone	2	8
Colorectal	4	17
Kidney	2	8
Liver	7	29
Lung	9	38
Lymph node	16	67
Stomach	1	4
Muscle/soft tissue	6	25
Baseline symptoms		
Hearing loss	8	33
Grade (No. of patients)	3 (2), 2 (4), 1 (2)	
Neuropathy: sensory	3	13
Grade (No. of patients)	2 (3)	
Neuropathy: motor	1	4
Grade (No. of patients)	2 (1)	
Performance status		
0	11	46
1	11	46
2	2	8
eGFR level at baseline, mL/min		
≥ 60	6	25
< 60	18	75
Median (range)	45.9 (26.1-103.4)	

Abbreviation: eGFR, estimated glomerular filtration rate.

*Two patients who did not receive any study treatment were excluded from analysis: patient 18 was unable to receive treatment because of medication compliance related to his diabetes; patient 26 was determined to be ineligible after registration but before treatment start.

more of the 21 patients experienced a confirmed CR or PR, then this would be evidence that the true response rate of the treatment of combination of gemcitabine and eribulin is greater than 20% and not significantly less than 50%. Unacceptable toxicities were monitored on an ongoing basis, using a truncated sequential probability ratio test to establish the boundaries for acceptable toxicity rates. This monitoring boundary was based on the Wald[14] sequential probability ratio test, truncated at 21 patients with simulation to establish the operating characteristics.

The observed overall response rate was calculated as the ratio of the number of patients who experienced a confirmed CR or PR divided by the total number of eligible patients who began treatment. Clopper-Pearson 95% CIs adjusted for the interim analysis are reported. The secondary end points were progression-free survival (PFS) calculated from the date of start of treatment to the date of progression or death before progression or censored at the latest follow-up, and toxicity as graded by the CTCAE version 4. Overall survival (OS) was calculated from the date of start of treatment to death from any cause or censored at the latest follow-up. Kaplan-Meier plots were used to estimate the probabilities of PFS and OS, as well as the medians; associated CIs for PFS and OS used the Greenwood estimate for the standard error, and the CIs for the medians were based on the methods of Brookmeyer and Crowley.[15] Standard descriptive statistics were used to summarize the baseline characteristics and toxicity results.

After completion of the interim analysis, the study team considered amending the trial to continue enrollment until there were 21 evaluable patients who remained in the study long enough to have a post-treatment radiologic evaluation. Ultimately this was not done, but three additional patients had consented to treatment during this discussion period, and these three patients were treated.

TABLE 2. Treatment Outcomes

Outcome	No. of Patients	%
Total cycles of treatment completed		
1*	5	21
2-4	8	33
> 4	11	46
Median (range)	4 (1*-16)	
Best response		
Confirmed CR	1	4
Confirmed PR	11	46
SD	6	25
PD	1	4
Inevaluable	5	21
Responders, including confirmed CR/PR	12	50
90% CI		31 to 69
Off treatment/study reason		
Adverse events/ adverse effects	8	33
Complicating disease/ intercurrent illness	1	4
Death while in study	2†	8
Disease progression	6	25
Clinical deterioration (decline performance)	2	8
Received surgical resection	2	8
Shoulder fractured	1	4
Withdrawal of consent	2	8
Overall survival, months	11.9	
Median, 95% CI	5.6 to 20.4	
Progression-free survival, months	5.3	
Median, 95% CI	4.5 to 6.7	
Follow-up, months	16.8	
Median, range	1.3-16.8	

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

*One patient did not complete course 1 and withdrew consent.

†Two patients died while in the study. Causes of death were appendicitis perforated (one) and pneumonitis/bilateral pulmonary embolism (one).

RESULTS

Between June 2015 and March 2017, 26 patients were consented and enrolled; 24 patients began treatment (Fig 1). Two patients were deemed ineligible for the study during screening and before treatment. We report on the 24 patients who started treatment. Median age of the 24 patients was 73 years (range, 62 to 88 years); 20 patients were male and four were female. Eastern Cooperative Oncology Group performance status of 0, 1, or 2 was seen in 11, 11, and two patients. Five patients had received cisplatin-based chemotherapy in the perioperative setting. Sites of disease included 16 patients with lymph node involvement, nine with lung metastases, seven with liver metastases, five with bladder involvement, and two with bone metastases (Table 1).

Response and Outcome

With four confirmed PRs in the first seven patients enrolled, the trial proceeded to full accrual. The trial closed after 24 patients began treatment, with over-accrual of three patients because of administrative and logistic issues. Patients received a median of four (range, one to 16) cycles of treatment (Table 2). Of the 24 patients, five patients ended treatment before radiologic disease evaluation for reasons of intercurrent illness/infection/decline in performance status (three), adverse events (one), and patient refusal (one). Of the 19 patients who underwent disease evaluation, 14 experienced a CR or PR at the first disease evaluation, and four had stable disease. This resulted in one patient who experienced a confirmed CR, 11 who experienced a confirmed PR, six who had stable disease, and one patient who experienced progressive disease at the time of the first evaluation as their best response. Of the remaining five patients accrued, four completed cycle 1 treatment. Two of these four patients were taken off treatment because of adverse events, one because of complicating disease and the other because of deterioration. Another patient refused additional treatment before completing cycle 1 treatment. All five patients had no post-treatment imaging done. Among the seven patients with liver metastases, five experienced a confirmed partial response. The observed objective response rate was 50% (95% CI, 29% to 71%). Median duration of response was 3.1 months, with four durable responses lasting more than 6 months (Fig 2). Median survival was 11.9 months (95% CI, 5.6 to 20.4 months), and median PFS was 5.3 months (95% CI, 4.5 to 6.7 months; Fig 3).

Toxicity

All 24 patients were evaluable for toxicity; the most common treatment-related toxicities of any grade at any time were fatigue (83% of patients), neutropenia (79%), anemia (63%), alopecia (50%), elevated AST (50%), and constipation, nausea, and thrombocytopenia (42% each). The most common grade 3 or 4 toxicities were neutropenia (63% of patients) and anemia and fatigue (29% each; Table 3; Appendix Table A1, online only). Febrile neutropenia occurred in three patients (13%). There were two deaths in the study, one due to sepsis secondary to perforated appendicitis (uninvolved by tumor) and one due to pneumonitis and thromboembolism.

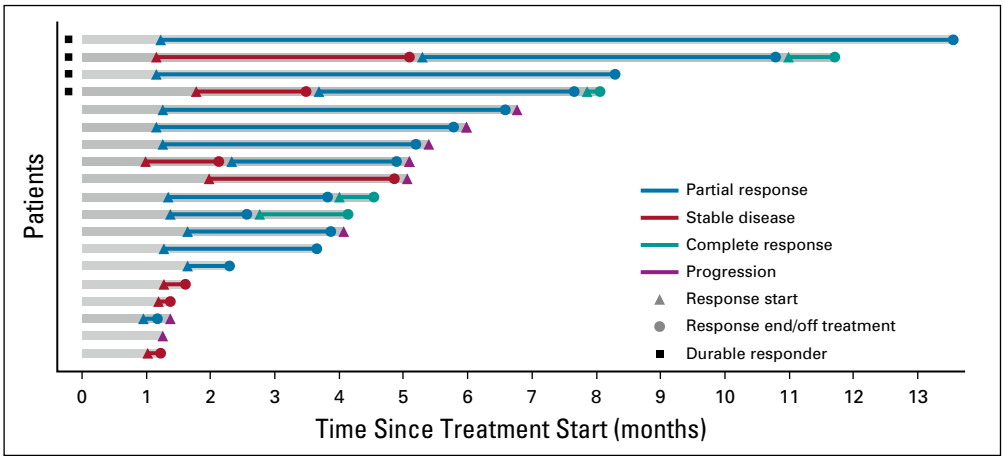

FIG 2. Swimmer plot for the 19 patients with response evaluation. A total of 24 patients were enrolled and treated; five patients discontinued treatment before the first assessment for non-progressive disease reasons. Each bar represents one patient who is evaluable for response (n = 19). A durable responder is a patient who has confirmed response for at least 6 months.

DISCUSSION

The results of this small phase II clinical trial show that the gemcitabine-eribulin combination has activity in metastatic urothelial carcinoma and is well tolerated in the cisplatin-ineligible population. The study met its primary end point even before enrolling 21 patients; enrollment continued to better characterize the toxicities, PFS, and OS, as well as to complete the trial as planned. Following Simon two-stage rules, nine (43%) of the first 21 treated patients (seven responses required) experienced a confirmed CR or PR (16 evaluable and five inevaluable). Finally, 12 (50%) of the 24 treated patients experienced a confirmed objective response.

This is the second study to demonstrate activity of eribulin in urothelial carcinoma after the phase II study of single-agent eribulin in previously treated and treatment-naïve patients.[15] These results point out that the activity may be higher compared with the single agent. The objective response rate of 50% observed in this combination study is higher compared with the trial of eribulin alone, where the overall response rate was 34.7%, albeit in mostly patients given prior therapies. The median OS and PFS also numerically favored the combination over single agent with 11.9 versus 9.5 months and 5.3 versus 4.1 months, respectively.[16] In addition, the results show that patients with liver metastases benefited from therapy with the gemcitabine-eribulin

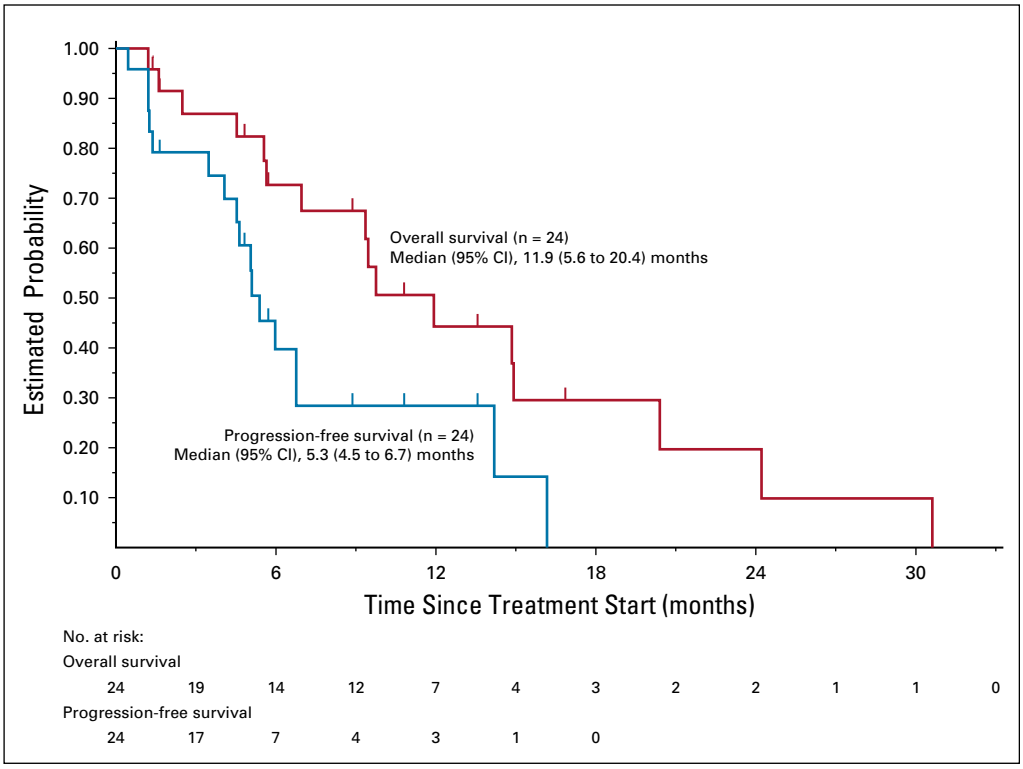

FIG 3. Kaplan-Meier curves for overall survival and progression-free survival.

TABLE 3. Most Common Treatment-Related Toxicities, Any Grade, Observed (≥ 20%)

Toxicity	No. of Patients	%
Fatigue	20	83
WBC count decreased	20	83
Neutrophil count decreased	19	79
Anemia	15	63
Alopecia	12	50
AST increased	12	50
Constipation	10	42
Edema	10	42
Lymphocyte count decreased	10	42
Nausea	10	42
Platelet count decreased	10	42
ALT increased	9	38
Anorexia	9	38
Diarrhea	9	38
Hypoalbuminemia	9	38
Hyponatremia	9	38
Generalized muscle weakness	6	25
Dehydration	5	21
Dizziness	5	21
Paresthesia	5	21
Peripheral sensory neuropathy	5	21

combination at a higher rate than expected with eribulin. However, the small sample size should moderate these inferences, and a direct comparison of the efficacy of the single agent versus the combination should be conducted and compared with the standard of care as the control arm.

The standard of care for the treatment of cisplatin-eligible patients with metastatic urothelial carcinoma remains a gemcitabine-cisplatin combination or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin regimen, with expected response rates of 46% to 50%.[5,17] For cisplatin-ineligible patients—those with creatinine clearance of less than 60 mL/min or grade 2 neuropathy or hearing loss,[18] gemcitabine and carboplatin in combination had become a standard of care, with an overall response rate of 41% and a median OS of 9.1 months.[8] In reality, gemcitabine plus carboplatin was still deemed more effective than monotherapy regimens that were tried in an effort to identify a second-line option for patients with metastatic urothelial disease or other nonplatinum doublets.

With the advent of immunotherapy, a fairly well-tolerated option became available to patients with urothelial carcinoma, quickly changing standard of care, especially for cisplatin-ineligible patients, who represent an important area of unmet need.[6,7] Immunotherapy in the first line became available as a treatment option to patients with metastatic urothelial carcinoma in April of 2017, as this trial completed accrual.

Unfortunately, immunotherapy, although an important step in the right direction, was not as effective as it was hoped to be. With objective response rates of 23% to 29%, the need for a more effective first-line and salvage option remains.[6,7,19] More recently, the FDA limited the use of pembrolizumab and atezolizumab in chemotherapy-naïve patients with low expression of PDL1 because of concerns over inferior outcomes compared with combination chemotherapy.[20]

Drug development for metastatic urothelial carcinoma continues with immunotherapy-chemotherapy combinations, immunotherapy in combination with targeted/biologic therapy, targeted therapy, and antibody drug conjugates.[21] In April of 2019, the FDA granted accelerated approval to erdafitinib to be the first targeted therapy (FGRF2 and 3) in urothelial carcinoma on the basis of the results of a phase II study, BLC2001 (ClinicalTrials.gov identifier: NCT02365597) of 87 previously treated patients with FGFR2 or 3 alterations showing a 32.2% objective response rate.[22,23] Nevertheless, it seems clear that cytotoxic therapy will continue to be part of the treatment of metastatic urothelial carcinoma and that there is still substantial unmet need in this disease.

With immunotherapy used in the first- or second-line options for metastatic urothelial carcinoma, the post-platinum dilemma and unmet need become a postimmunotherapy unmet need. There still is a need for the development of active agents to fill this void. Although antibody drug conjugates and targeted therapies seek to address this need, the data for eribulin remain comparatively attractive and applicable to treatment-naïve and previously treated patients and make eribulin a notable candidate for development. SWOG S1937 is a three-arm phase III trial of eribulin with or without gemcitabine in postimmunotherapy or immunotherapy-ineligible patients—an important area of unmet need in this disease—compared with a dynamic standard-of-care arm that allows new regimens to be added to it as they receive FDA approval; it is expected to open in late 2019 through National Cancer Institute National Clinical Trials Network.

The combination of gemcitabine and eribulin was well tolerated and met the prespecified trial end point for activity on the basis of a 50% overall response rate in cisplatin-ineligible patients with urothelial carcinoma. Notably, the combination also demonstrated activity in liver metastases. The next step in the development of eribulin in urothelial carcinoma is a phase III study of patients previously treated with or not eligible for T-cell checkpoint therapy with agents directed at PD1 or PDL1.

AFFILIATIONS

[1]University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA
[2]University of Kansas, Lawrence, KS
[3]The Ohio State University, Columbus, OH
[4]City of Hope, Duarte, CA
[5]Case Western Reserve University, Cleveland, OH
[6]National Cancer Institute, Cancer Therapy Evaluation Program, Bethesda, MD
[7]University of California, Davis, Davis, CA

CORRESPONDING AUTHOR

Sarmad Sadeghi, MD, PhD, University of Southern California, Norris Comprehensive Cancer Center, 1441 Eastlake Ave, Suite 3440, Los Angeles, CA 90033; e-mail: sarmad.sadeghi@usc.edu.

PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.00861.

AUTHOR CONTRIBUTIONS

Conception and design: Sarmad Sadeghi, Susan G. Groshen, David I. Quinn, Edward Newman, Primo N. Lara Jr

Administrative support: Sarmad Sadeghi, Laurence Doyle, Edward Newman, Primo N. Lara Jr

Provision of study material or patients: Sarmad Sadeghi, Rahul Parikh, Amir Mortazavi, Tanya B. Dorff, Christopher Hoimes, David I. Quinn

Collection and assembly of data: Sarmad Sadeghi, Susan G. Groshen, Cheryl Kefauver

Data analysis and interpretation: Sarmad Sadeghi, Susan G. Groshen, David I. Quinn, Edward Newman, Primo N. Lara Jr

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase II California Cancer Consortium Trial of Gemcitabine-Eribulin Combination in Cisplatin-Ineligible Patients With Metastatic Urothelial Carcinoma: Final Report (NCI-9653)

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Sarmad Sadeghi
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Susan G. Groshen
Employment: Pfizer (I)

Rahul Parikh
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APPENDIX

TABLE A1. Toxicities that Occurred in 10% or More of Patients or at Least Once as a Grade 3 or Greater Adverse Event (excluding those toxicities classified as "unrelated" or "unlikely related" to study drugs)

	Patients with Maximum Grade of Toxicity Experience		
Toxicity	**Any Grade**	**Grade 1 or 2**	**Grade 3 or 4**
Blood and lymphatic system disorders			
Anemia	15 (63)	8 (33)	7 (29)
Febrile neutropenia	3 (13)	0 (0)	3 (13)
Thrombotic microangiopathy	1 (4)	0 (0)	1 (4)
Cardiac disorders			
Chest pain, cardiac	1 (4)	0 (0)	1 (4)
Heart failure	1 (4)	0 (0)	1 (4)
GI disorders			
Colitis	1 (4)	0 (0)	1 (4)
Constipation	10 (42)	10 (42)	0 (0)
Diarrhea	9 (38)	7 (29)	2 (8)
Dry mouth	4 (17)	4 (17)	0 (0)
Mucositis oral	4 (17)	2 (8)	2 (8)
Nausea	10 (42)	7 (29)	3 (13)
Vomiting	4 (17)	2 (8)	2 (8)
General disorders and administration site conditions			
Edema	10 (42)	9 (38)	1 (4)
Fatigue	20 (83)	13 (54)	7 (29)
Fever	4 (17)	4 (17)	0 (0)
Infections and infestations			
Appendicitis perforated*	1 (4)	0 (0)	1 (4)
Lung infection	1 (4)	0 (0)	1 (4)
Sepsis	1 (4)	0 (0)	1 (4)
Upper respiratory infection	1 (4)	0 (0)	1 (4)
Urinary tract infection	3 (13)	1 (4)	2 (8)
Investigations, cardiac			
Electrocardiogram QT corrected interval prolonged	3 (13)	2 (8)	1 (4)
Investigations, constitutional symptoms			
Weight loss	4 (17)	4 (17)	0 (0)
Investigations, hematologic			
Lymphocyte count decreased	10 (42)	4 (17)	6 (25)
Neutrophil count decreased	19 (79)	4 (17)	15 (63)
Platelet count decreased	10 (42)	7 (29)	3 (13)
WBC count decreased	20 (83)	7 (29)	13 (54)
Investigations, hemorrhage			
INR increased	2 (8)	1 (4)	1 (4)
Investigations, hepatic			
ALT increased	9 (38)	9 (38)	0 (0)
AST increased	12 (50)	11 (46)	1 (4)

(continued on following page)

TABLE A1. Toxicities that Occurred in 10% or More of Patients or at Least Once as a Grade 3 or Greater Adverse Event (excluding those toxicities classified as "unrelated" or "unlikely related" to study drugs) (continued)

	Patients with Maximum Grade of Toxicity Experience		
Toxicity	**Any Grade**	**Grade 1 or 2**	**Grade 3 or 4**
Investigations, renal			
Creatinine increased	4 (17)	4 (17)	0 (0)
Metabolism and nutrition disorders			
Anorexia	9 (38)	9 (38)	0 (0)
Dehydration	5 (21)	3 (13)	2 (8)
Hyperglycemia	1 (4)	0 (0)	1 (4)
Hypoalbuminemia	9 (38)	8 (33)	1 (4)
Hypocalcemia	4 (17)	4 (17)	0 (0)
Hypokalemia	4 (17)	4 (17)	0 (0)
Hypomagnesemia	3 (13)	3 (13)	0 (0)
Hyponatremia	9 (38)	7 (29)	2 (8)
Hypophosphatemia	4 (17)	4 (17)	0 (0)
Musculoskeletal and connective tissue disorders			
Generalized muscle weakness	6 (25)	5 (21)	1 (4)
Grip weakness	1 (4)	0 (0)	1 (4)
Pain in extremity	4 (17)	3 (13)	1 (4)
Nervous system disorders			
Dizziness	5 (21)	5 (21)	0 (0)
Dysgeusia	4 (17)	4 (17)	0 (0)
Paresthesia	5 (21)	4 (17)	1 (4)
Nervous system disorders			
Peripheral sensory neuropathy	5 (21)	5 (21)	0 (0)
Psychiatric disorders			
Insomnia	3 (13)	3 (13)	0 (0)
Respiratory, thoracic and mediastinal disorders			
Dyspnea	1 (4)	0 (0)	1 (4)
Pneumonitis	1 (4)	0 (0)	1 (4)
Sore throat	3 (13)	3 (13)	0 (0)
Skin and subcutaneous tissue disorders			
Alopecia	12 (50)	12 (50)	0 (0)
Vascular disorders			
Hypotension	3 (13)	2 (8)	1 (4)
Thromboembolic event	1 (4)	0 (0)	1 (4)

NOTE. Data presented as No. (%).
Abbreviation: INR, international normalized ratio.
*Grade 5 adverse event.