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Original Article

A Multicenter Phase II Study of Modified FOLFIRINOX for First-Line Treatment for Advanced Urachal Cancer (ULTIMA; KCSG GU20-03)

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Purpose This study aimed to assess the efficacy and safety of first-line modified FOLFIRINOX in patients with advanced urachal cancer.

Materials and Methods The ULTIMA trial (NCT04611724) is a single-arm, open-label, multicenter phase II study evaluating modified FOLFIRINOX (oxaliplatin 85 mg/m^2 over 2 hours, irinotecan 150 mg/m^2 over 1.5 hours, leucovorin 400 mg/m^2 over 2 hours, and 5-fluorouracil 2,400 mg/m^2 over 46 hours) plus prophylactic pegteograstim in patients with recurrent or metastatic urachal cancer every 2 weeks for up to 12 cycles, or until disease progression or unacceptable toxicity. The primary endpoint was the overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and the incidence of febrile neutropenia.

Results Between April 2021 and November 2023, 21 patients with advanced urachal cancer were enrolled across five cancer centers. The median age was 50 years (range, 28 to 68 years), with 15 male patients. The most common metastatic site was the lung (47.6%), followed by lymph nodes (38.1%) and peritoneal seeding (33.3%). Two patients and 11 patients achieved a complete and partial response, respectively, yielding an ORR of 61.9%. The study met its primary endpoint in the first stage. With a median follow-up of 23.3 months, the median PFS was 9.3 months (95% confidence interval [CI], 6.7 to 11.9), and the median OS was 19.7 months (95% CI, 14.3 to 25.1). The treatment regimen was well tolerated, with no unexpected adverse events, and no instances of febrile neutropenia or grade 4 adverse events.

Conclusion In this preliminary analysis of the ULTIMA trial, Modified FOLFIRINOX demonstrated a promising ORR and PFS in patients with advanced urachal cancer. Completing the full study is essential to confirm the potential role of this regimen in the management of advanced urachal cancer.

Key words Urachal cancer, Oxaliplatin, Irinotecan, 5-Fluorouracil

Introduction

Urachal carcinoma is a rare malignancy, accounting for less than 1% of all bladder cancers and is characterized by its aggressive clinical behavior. Patients with recurrent or metastatic disease have a poor prognosis, with an overall survival rate of less than two years [1].

Systemic therapy is indicated for advanced urachal carcinoma that is not amenable to surgical intervention. However, the rarity of this malignancy has precluded the conduct of prospective clinical trials, resulting in the absence of an established standard of care. Chemotherapy regimens for advanced urachal carcinoma have traditionally been extrapolated from treatments used for urothelial and colorectal cancers, owing to anatomical and histopathological similarities. Regimens such as MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), gemcitabine combined with platinum agents, and therapies based on 5-fluorouracil (5-FU), oxaliplatin, and irinotecan, have been employed [2-8]. Systematic reviews and case series suggest that regimens used for colorectal cancer are more effective than those used for urothelial cancer regimens in treating urachal cancer [1,3]. Nonetheless, there is a lack of prospective data to support the efficacy of these treatments in urachal carcinoma.

5-FU, oxaliplatin, and irinotecan have distinct mechanisms of action, do not have overlapping major side effects, and all show potential efficacy in urachal cancer. Therefore, there is a theoretical basis for combining these three drugs. Additionally, this combination has been shown to improve overall response and survival in metastatic colorectal cancer (FOL-

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FOLXIRI [5-fluorouracil, leucovorin, oxaliplatin, and irinotecan]) in randomized phase III trials compared to FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) with or without bevacizumab [9,10]. The modified regimen (modified FOLFIRINOX [5-fluorouracil, leucovorin, irinotecan, and oxaliplatin]), which omits bolus 5-FU and reduces the dose of irinotecan, has also been shown to be superior to gemcitabine monotherapy in metastatic pancreatic cancer, with improved tolerability. It has also been effective as adjuvant therapy after surgery for early pancreatic cancer [11,12].

This study aims to investigate the efficacy and safety of a modified FOLFIRINOX regimen in the treatment of advanced urachal cancer. This prospective phase 2 clinical trial is designed to provide data on the potential of this regimen to improve outcomes in a patient population with poor prognoses and limited treatment options.

Materials and Methods

1. Patients

Inclusion criteria were as follows: (1) histologically confirmed adenocarcinoma of the bladder/urachal remnant clinically consistent with urachal cancer, using study-specific criteria based on those of Gopalan et al. [13] (origin in the anterior wall or dome of the bladder, predominant invasion of muscularis or deeper tissues, no obvious origin from the overlying urothelium with relatively normal-looking urothelial mucosa, and no primary adenocarcinoma elsewhere), (2) patients with locally advanced, recurrent, or metastatic disease not amenable to surgery, radiotherapy, or combined modality therapy with curative intent, (3) no prior systemic therapy for advanced urachal cancer (for recurrent disease, previous 5-FU, irinotecan, or platinum chemotherapy as neoadjuvant and/or adjuvant therapy was allowed if it ended more than 6 months before enrollment), (4) measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) ver. 1.1 criteria, (5) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, (6) age 19 years or older, (7) adequate cardiac, bone marrow, hepatic, and renal function (neutrophil count ≥ 1,500/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin ≥ 9 g/dL, total bilirubin ≤ 1.5×upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase ≤ 3×ULN, or ≤ 5×ULN in the case of liver metastasis, and creatinine clearance ≥ 30 mL/min). Exclusion criteria included: (1) age over 70, (2) grade 2 or worse peripheral neuropathy; and (3) uncontrolled central nervous system metastases.

2. Study design and treatment

ULTIMA is a single-arm, open-label, non-randomized multicenter phase II clinical trial that was conducted at 5 academic centers in Korea in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the KCSG (Korean Cancer Study Group) Protocol Review Committee institutional review boards of participating centers and registered at ClinicalTrials.gov (NCT04611724).

All patients received a modified FOLFIRINOX regimen (oxaliplatin 85 mg/m^2 over 2 hours, irinotecan 150 mg/m^2 over 1.5 hours, leucovorin 400 mg/m^2 over 2 hours, and 5-FU 2,400 mg/m^2 over 46 hours). This regimen included a reduced dose of irinotecan and excluded 5-FU bolus infusion to minimize toxicities. Prophylactic pegteograstim, which is a pegylated granulocyte-colony stimulating factor (G-CSF), 6 mg subcutaneous injection was administered on day 3. Treatment was repeated every 2 weeks for up to 12 cycles or until disease progression or unacceptable toxicity occurred. Study drugs could be administered beyond 12 cycles for subjects benefiting from the medication with manageable toxicities. Prophylactic antibiotics (levofloxacin 750 mg once daily orally from day 4 to day 7) were mandatory for the first 2 cycles, and antiemetics were prescribed at the investigator's discretion.

3. Study endpoints and statistical analysis

The primary endpoint was the overall response rate (ORR) Responses were evaluated every 6 weeks according to the RECIST ver. 1.1. After 24 weeks, response assessments were conducted every 9 weeks, and after 48 weeks, every 12 weeks. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety (particularly serious adverse events), and incidence of febrile neutropenia. Overall survival was defined as the time from the first day of modified FOLFIRINOX administration to the date of death or loss to follow-up. Progression-free survival was defined as the time from the first day of modified FOLFIRINOX administration to the date of disease progression or last follow-up. Adverse events were recorded at each visit and categorized according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0. Exploratory endpoints included the analysis of tumor tissue genomic alterations using targeted next-generation sequencing (Oncopanel v4.5 or Cancer Scan v3.1.).

4. Statistics and sample size calculation

The Kaplan-Meier method was used to evaluate PFS and OS. Frequency analysis was used for ORR and disease-control rate (using RECIST ver. 1.1), and descriptive analysis was used for safety (graded according to CTCAE ver. 4.1). Sample size was calculated using Simon's MiniMax two-stage design [14]. To test null hypothesis P0=17% [6] versus

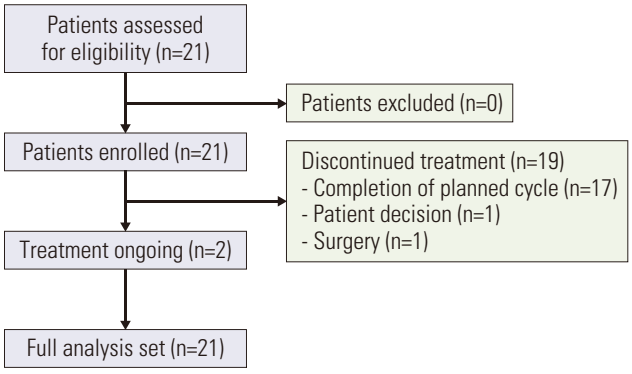

Fig. 1. Patient flowchart.

alternative hypothesis P1=36%, with α=5% and β=20%, the first stage required at least four objective responses out of 20 patients. In the second stage, accrual was planned for a total of 33 patients; if the total number of responses was less than or equal to 9, the drug would be rejected. Assuming a 5% drop-out rate, 35 patients were required. Therefore, a total of 35 patients were to be assessed, with an accrual time of 36 months and a follow-up time of 18 months.

Results

1. Patients demographics

From April 2021 to November 2023, 21 patients were enrolled across five cancer centers (Fig. 1). Since 13 patients responded in this analysis, the primary endpoint was met in the first stage, prompting the decision to report the results. Baseline characteristics indicated that the majority of patients (71%) were male, with a median age of 50 years. Most patients had an ECOG performance status of 1 (Table 1). Thirteen patients presented with initially metastatic cancer, associated with a poorer prognosis, while eight patients had recurrent disease. Two patients had previously received adjuvant chemotherapy.

Regarding metastatic sites, the lungs were the most frequent, involving 10 patients (47.6%). Other common metastatic sites included the peritoneum (7 patients, 33.3%) and lymph nodes (8 patients, 38.1%). Additionally, metastases were observed in the pelvic cavity (2 patients, 9.5%), liver (1 patient, 4.8%), bone (1 patient, 4.8%), brain (1 patient, 4.8%), and ileum (1 patient, 4.8%).

2. Treatment exposure

At the time of analysis, 19 patients had discontinued treatment, while two were still undergoing therapy, currently in their 11th and 18th cycles, respectively. A total of 17 patients completed the planned 12 cycles and discontinued treatment. One patient discontinued after 8 cycles due to an unsatisfactory response and attempted to conduct a debulking surgery, and another refused further treatment after 11 cycles due to fatigue and peripheral neuropathy. In total, 241 treatment cycles were administered, with a median of 12 cycles per patient (range, 6 to 18). Dose reductions were necessary for seven patients (33.3%), accounting for 45 cycles (18.7%). Dose delays were required in five patients (23.8%) for a total of 9 cycles (4.1%) out of 220 subsequent cycles.

Table 1. Baseline patients and disease characteristics (n=21)

Variable	No. (%)
Male sex	15 (71.4)
Age (yr), median (range)	50 (28-68)
ECOG PS 0/1	3 (14.3)/18 (85.7)
Initially metastatic disease	13 (61.9)
Recurrent disease	8 (38.1)
Prior surgery	16 (76.2)
Prior adjuvant chemotherapy (5-FU plus cisplatin)	2 (9.5)
Sites of metastases	
Lung	10 (47.6)
Lymph node	8 (38.1)
Peritoneum	7 (33.3)
Pelvic cavity	2 (9.5)
Liver	1 (4.8)
Bone	1 (4.8)
Brain	1 (4.8)

ECOG PS, Eastern Cooperative Oncology Group performance status; 5-FU, 5-fluorouracil.

3. Efficacy

1) Response

Two patients achieved a complete response (9.5%) and 11 achieved a partial response (52.4%), resulting in an ORR of 61.9% (95% confidence interval [CI], 38.4 to 82.0). Stable disease was achieved in eight patients (38.1%), with no cases of initial disease progression.

2) Progression-free survival and overall survival

After a median follow-up of 23.3 months, 15 patients had disease progression, and the median PFS was 9.3 months (95% CI, 6.7 to 11.9) (Fig. 2). With a median follow-up of 24.7 months, 10 patients had died, and the median OS was 19.7 months (95% CI, 14.3 to 25.1) (Fig. 2).

4. Safety

The treatment was generally well tolerated. Table 2 provides an overview of the adverse event profiles observed in

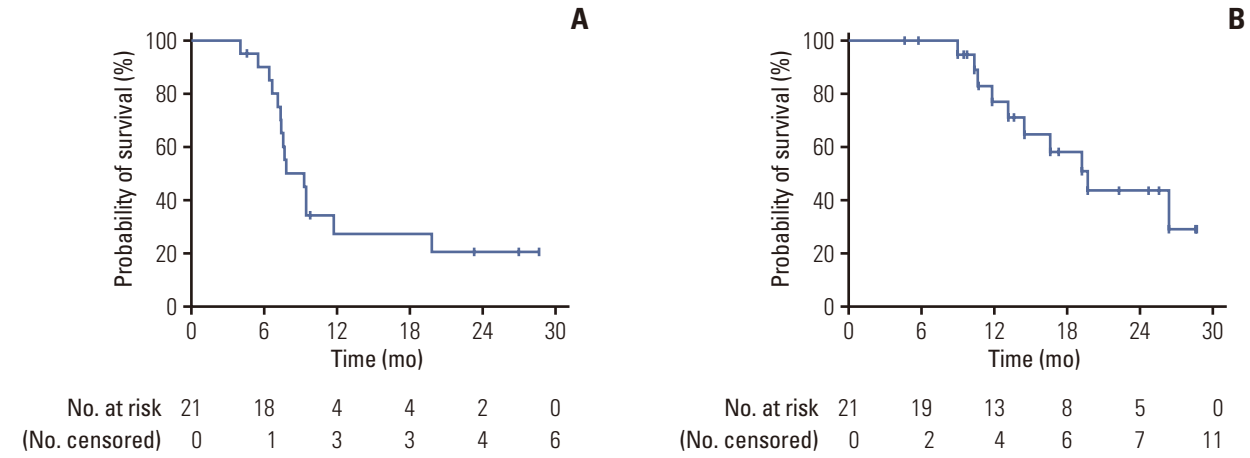

Fig. 2. Progression-free survival (dotted line) (A) and overall survival (solid line) (B).

Table 2. List of patient adverse events

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Hematological toxicity				
Leukopenia	0	0	0	0
Neutropenia	0	0	1 (4.8)	0
Anemia	0	0	2 (9.5)	0
Thrombocytopenia	0	3 (14.3)	1 (4.8)	0
Febrile neutropenia			0	0
Non-hematological toxicity				
ALT elevation	2 (9.5)	3 (14.3)	0	0
AST elevation	2 (9.5)	1 (4.8)	0	0
ALP elevation	1 (4.8)	0	0	0
Nausea	6 (28.6)	8 (38.1)	1 (4.8)	0
Vomiting	2 (9.5)	2 (9.5)	0	0
Anorexia	4 (19.0)	1 (4.8)	0	0
Diarrhea	4 (19.0)	1 (4.8)	1 (4.8)	0
Stomatitis	0	3 (14.3)	0	0
Fatigue	2 (9.5)	6 (28.6)	0	0
Peripheral neuropathy	11 (52.4)	5 (23.8)	0	0
Hiccups	4 (19.0)	1 (4.8)	0	0
Abdominal pain	2 (9.5)	2 (9.5)	1 (4.8)	0
Laryngopharyngeal dysesthesia	1 (4.8)	2 (9.5)	0	0

Values are presented as number (%). ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

the study. Notable grade 3 or worse adverse events included anemia (9.5%), thrombocytopenia (4.5%), and nausea (4.8%). Peripheral sensory neuropathy was noted in 23.8% of patients at grade 2. Importantly, there were no cases of febrile neutropenia or treatment-related mortalities.

5. Genomic aberrations

Currently, genomic data from 17 patients have been analyzed. Genomic aberrations were identified in all patients, with most exhibiting pathogenic alterations. The most common aberrations were *TP53* (90%) and *KRAS* (40%). These findings will be reported in a future publication.

Discussion

The ULTIMA trial is a landmark study as the first prospective clinical trial targeting advanced urachal cancer, a rare

Table 3. Summary of case reports or case series on chemotherapy in advanced urachal cancer (based on reports that can evaluate responses to chemotherapy)

Author/Country	Year	Chemotherapy regimen	Sample size	Response	Overall survival (mo)	Comment
Moussa/USA [8]	2024	GemFLP	40	8 PR (20%), 21 SD (52.5%)	19.8	1st line, retrospective
Chen/China [7]	2021	CAPOX (n=9), paclitaxel/platinum (n=4), paclitaxel/capecitabine (n=7), GC (n=3)	24	CAPOX: 1 PR (11%), 8 SD; paclitaxel/capecitabine: 5 SD	NR	Case series
Urasaki/Japan [16]	2019	S1 (D1-D21)/cisplatin every 5 weeks	5	4 SD, 1 PD	NR	Case series
Jung/Korea [6]	2014	FP (n=2); GC (n=3), MVAC (n=1), others (n=4)	10	FP: 1 PR, 1 SD; GC: 1 SD, 2 PD; MVAC: SD	NR	Case series
Yanagihara/Japan [5]	2013	mFOLFOX6	5	1 CR (20%), 1 RR (20%), 2 SD, 1 PD	18 (DOD), 22+ (NED), 42+ (AWD), 42+ (AWD), 46+ (AWD)	Case series
Tran/Australia [17]	2010	mFOLFOX6	1	PR	NR	Case report
Miyata/Japan [18]	2011	GC	1	PR	NR	Case report
Tazi/Morocco [19]	2009	Irinotecan, 5-FU/LV bolus Q3W	1	PR	NR	Case report
Mohile/USA [4]	2008	Irinotecan 125 mg/m^2, 5-FU/LV (IFL) QW for 4 weeks then 2 week rest	1	CR	NR	Case report
Kume/Japan [20]	2006	Irinotecan 100 mg/m^2 weekly	1	PR	NR	Case report, 3rd line after failure to M-FAP and FAM
Kojima/Japan [21]	2006	S1(D1-D14)/cisplatin every 4 weeks	1	CR	NR	Case report
Siefker-Radtke/USA [3]	2003	GemFLP (n=6); 5-FU/cisplatin/IFN-a (n=3), MVAC (n=5); paclitaxel based (n=5); Ifosfamide/gemcitabine/cisplatin (n=1)	20	Emory: 2 PR (33%), 4 SD; 5-FU/cisplatin/IFN-a: 1 PR (33%), 2 SD; MVAC: 2 SD, paclitaxel based 1 PR (20%), 1 SD	20	Case series
Ichiyanagi/Japan [2]	1998	MVAC	1	1 PR	NR	Case report
Logothetis/USA [22]	1985	FAM	8	5 PR	NR	Case series, 4 patients received FAM as the 2nd line

AWD, alive with disease; CAPOX, capecitabine plus oxaliplatin; CR, complete response; DOD, died of disease; FAM, 5-FU, adriamycin and mitomycin; FP, 5-FU plus cisplatin; GC, gemcitabine plus cisplatin; GemFLP, gemcitabine, 5-FU, leucovorin, and cisplatin; IFL, irinotecan plus 5-FU plus leucovorin; IFN, interferon; LV, leucovorin; M-FAP, methotrexate plus 5-FU plus doxorubicin (adriamycin) plus cisplatin; mFOLFOX6, modified leucovorin, 5-FU, and oxaliplatin; MVAC, methotrexate plus vinblastine plus doxorubicin (adriamycin) plus cisplatin; NED, no evidence of disease; NR, not reported; PD, progressive disease; PR, partial response; QW, every week; Q3W, every 3 weeks; SD, stable disease; 5-FU, 5-fluorouracil.

and aggressive malignancy. This pioneering study assesses the efficacy and safety of a modified FOLFIRINOX regimen as first-line treatment for patients with advanced urachal cancer.

The introduction of a multidrug chemotherapy regimen comprising folinic acid (leucovorin), 5-FU, irinotecan, and oxaliplatin marked a significant advancement in the treatment of colorectal and pancreatic cancers, demonstrating substantial benefits over previous standards of care [9-12,15]. Given the similarly aggressive nature and poor prognosis of urachal cancer, the success of this regimen in other cancers supports the investigation of its applicability in advanced urachal cancer. The trial revealed a highly promising ORR of 61.9%. This response rate is particularly noteworthy when compared with other reports in the literature, which are often derived from smaller, retrospective studies and case series. Table 3 summarizes the most relevant retrospective studies or case reports, highlighting the regimens used, sample sizes, response rates, and survival outcomes. This comparative table illustrates the limited efficacy and considerable variation in response rates among the existing chemotherapy regimens for urachal cancer. Notably, no treatments have emerged as a definitive standard of care, underscoring the ongoing challenge and pressing need for more effective treatment options. The robust ORR observed in this trial indicates significant antitumor activity, positioning modified FOLFIRINOX as a potential treatment option in this patient population.

The median PFS of 9.3 months observed in this study is noteworthy, especially considering the scarcity of comparative data. Due to the rarity of urachal cancer, most existing data come from retrospective analyses or case series, where accurate measurement of PFS is challenging. Nonetheless, the PFS achieved in this trial highlights the potential for modified FOLFIRINOX to provide meaningful clinical benefits and sets a benchmark for future research in this field.

The modified FOLFIRINOX regimen was generally well-tolerated, with adverse events effectively managed through dose modifications and prophylactic pegteograstim. The incidence of grade 3 or worse adverse events, including anemia (9.5%), thrombocytopenia (4.5%), and nausea (4.8%), was comparable to those reported in adjuvant pancreatic cancer trials and lower than those typically observed with the standard FOLFIRINOX regimen [11,12]. Importantly, there were no cases of febrile neutropenia or treatment-related mortalities. Several factors likely contributed to the improved tolerability, including the prophylactic use of long-acting G-CSF and antibiotics, as well as the relatively young median age (50 years) and good performance status (ECOG 0-1) of the participating patients. However, while this cohort provides valuable insights, additional data on the safety and efficacy of this regimen in elderly patients with comorbidities are warranted to ensure its broader applicability.

There are several limitations to this study. First, an independent pathologic review was not conducted, preventing confirmation of the urachal cancer subtype and its potential impact on treatment effectiveness. We are planning a *post-hoc* central pathology review as well as immunohistochemical staining for available antibody-drug conjugate targets (e.g., ERBB2, nectin-4, and trop-2). Secondly, the primary endpoint of tumor response was evaluated by investigators, which may introduce bias. Thirdly, the small sample size, while sufficient for Simon's MiniMax design, limits the generalizability of the findings. From a statistical perspective, this is an unplanned interim analysis. It is difficult to ensure the completion of accrual considering the rarity of the disease, while the efficacy of modified FOLFIRINOX shown in the interim analysis deemed practice-changing. So the authors decided to report the results despite concerns of loss of precision in estimation of ORR, median PFS, and median OS. Currently, the second-stage is ongoing as originally planned, and final result will be reported after the completion of the second stage with more comprehensive data.

The ULTIMA trial represents an important step as the first prospective clinical trial in urachal cancer, providing preliminary evidence of a promising response rate and manageable safety profile for the modified FOLFIRINOX regimen. While these findings are encouraging, the study's limitations necessitate cautious interpretation. Given that these results are preliminary, completing the full study is essential to confirm the potential role of this regimen and to establish its place in the management of advanced urachal cancer.

Ethical Statement

The protocol was approved by the KCSG (Korean Cancer Study Group) Protocol Review Committee institutional review boards of participating centers and registered at ClinicalTrials.gov (NCT04611724). All patients were informed of the investigational nature of this study and provided written informed consent.

Author Contributions

Conceived and designed the analysis: Park I, Lee JL, Park K.
Collected the data: Park I, Lee JL, Yoon S, Shin SJ, Shin SH, Kim JH, Park K, Lee HJ.
Contributed data or analysis tools: Park I, Lee JL, Yoon S, Shin SJ, Shin SH, Kim JH, Park K, Lee HJ.
Performed the analysis: Park I, Lee JL.
Wrote the paper: Park I, Lee JL.
Provision of patients: Park I, Lee JL, Yoon S, Shin SJ, Shin SH, Kim JH, Park K, Lee HJ.

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Conflicts of Interest
Inkeun Park: Consulting or advisory role: Chong Kun Dang Pharmaceutical Co., Boryung Pharmaceuticals Co., Janssen Korea, and Astellas Pharma Korea. Research funding: Chong Kun Dang Pharmaceutical Co. and Boryung Pharmaceuticals Co. Jae Lyun Lee: Stock and other ownership interests: Johnson & Johnson/Janssen, Amgen, Merck, Innovent Biologics, Black Diamond Therapeutics, Karyopharm Therapeutics, and Zymeworks. Honoraria: Bristol-Myers Squibb, AstraZeneca, MSD Korea. Consulting or advisory role: Merck, AstraZeneca, Astellas Korea, Novartis, Amgen, Daiichi Sankyo/AstraZeneca. Research funding: Pfizer (inst), Janssen (inst), Novartis (inst), Bristol-Myers Squibb (inst), Roche/Genentech (inst), AstraZeneca/MedImmune (inst), MSD (inst), Bayer Schering Pharma (inst), Seagen (inst), GI Innovation (inst), Amgen (inst), Oscotec (inst), Arcus Biosciences (inst), Eutilex (inst), LG Chem (inst), Merck KGaA (inst), Loxo/Lilly (inst). All remaining authors have declared no conflicts of interest.

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