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Atezolizumab in Platinum-Treated Locally Advanced or Metastatic Urothelial Carcinoma: Outcomes by Prior Therapy

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Abstract

Background: Historically, patients with metastatic urothelial carcinoma (mUC) who progress after platinum-based chemotherapy have had few treatment options and uniformly poor outcomes. Atezolizumab, a programmed cell death-ligand 1 (PD-L1)–directed monoclonal antibody was recently approved in the US for cisplatin-ineligible and platinum-treated mUC based on the IMvigor210 trial.

Objective: To determine the efficacy and safety of atezolizumab by the number of prior lines of systemic therapy in a pre-treated mUC population.

Design, setting and participants: The IMvigor210 trial was a phase 2, multicenter, single-arm, two-cohort study. Enrollment of 315 patients with mUC with progression during or following platinum-based therapy occurred from May-November 2014 at 70 international sites. Key inclusion criteria included age ≥18 years, CrCl ≥30 mL/min and ECOG PS 0–1, with no maximum restriction on prior lines of therapy.

Intervention: Patients in this cohort received atezolizumab 1200 mg IV q3w until loss of clinical benefit.

Outcome measurements and statistical Analysis: Key study endpoints assessed in prior treatment subgroups included RECIST v1.1 ORR, median duration of response (mDOR), overall survival, and adverse event (AE) rates.

Results and limitations: 310 patients were efficacy and safety evaluable. Responses occurred notwithstanding the number of prior regimens; mDOR was not reached in most subgroups (median follow-up, 21 mo). No consistent OS trend or major differences in toxicity were observed by line of therapy.

Conclusions: In this cohort of the IMvigor210 study, the efficacy and safety of atezolizumab were demonstrated regardless of the number of prior regimens, suggesting that atezolizumab provides clinical benefit across multiple prior lines of therapy.

Patient summary: We evaluated the impact of different lines of therapy in a clinical study of atezolizumab in patients with mUC whose disease had progressed despite platinum-based therapy. Results showed that atezolizumab was clinically active and tolerable regardless of the number of prior treatments regimens.

1. Introduction

Platinum-based chemotherapy is the standard initial approach for treating metastatic urothelial carcinoma (mUC) (NCCN, 2017, Bellmunt, 2014). However, effective therapies for patients who progress after first-line (1L) therapy are needed, as overall survival remains short (Loerher, 1992; von der Maase, 2005; Bellmunt, 2013; NCI-SEER, 2017), cisplatin ineligibility presents a challenge, especially among elderly patients (Galsky, 2014), and progression on platinum is typically inevitable. Clinical trials using a wide variety of chemotherapies and targeted therapies have failed to significantly improve clinical outcomes, leaving a lack of effective options. In Europe, vinflunine is the only approved agent for the second-line (2L) treatment of mUC (Bellmunt, 2009), and until recently in the United States, no approved treatments were available for patients with mUC who progressed on platinum-based chemotherapy.

Atezolizumab is a humanized engineered monoclonal antibody that selectively targets anti–programmed death-ligand 1 to reinvigorate and enhance anti-cancer activity (Herbst, 2014; Powles 2014). Atezolizumab has demonstrated efficacy and safety in a range of cancers (Herbst, 2014) and was granted US Food and Drug Administration (FDA) approval in mUC for patients both in the cisplatin-ineligible and platinum-treated settings (TECENTRIQ PI, 2016). The approval in platinum-treated patients was granted following results from the phase 2 IMvigor210 study, which showed that among a population of generally heavily pre-treated patients, atezolizumab provided durable activity and tolerability in an overall population unselected for PD-L1 expression (Rosenberg, 2016).

Due to the lack of treatment options for mUC, a large proportion of patients are not treated with any 2L chemotherapy, and far fewer receive treatment beyond the second line (Pal, 2016; Pond, 2015). Furthermore, the differential impact of prior lines of therapy in patients receiving salvage chemotherapy for mUC is unclear, as patients receiving later lines of therapy have historically been under-reported or excluded from clinical trials. The platinum-treated cohort of the IMvigor210 study included patients who were considered heavily pre-treated in the metastatic setting, providing an opportunity to assess outcomes as a function of the extent of pre-treatment. Here, we describe efficacy and safety outcomes in an updated analysis based on the number of systemic treatments administered in the metastatic setting prior to study enrollment.

2. Patients and Methods

2.1. Patients, study design, and procedures

The study population for this analysis included patients with mUC who were enrolled in the platinum-treated cohort of the Phase II IMvigor210 trial (ClinicalTrials.gov identifier, NCT02108652). Details on this two-cohort study and general patient populations have been reported previously (Balar, 2017; Rosenberg, 2016). The study protocol was approved by institutional review boards or independent ethics committees at participating study sites. All patients provided written informed consent before entry into the study, which was performed in accordance with the Declaration of Helsinki and International Conference of Harmonization Good Clinical Practice guidelines.

Key eligibility criteria specific to this cohort included locally advanced or metastatic urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra (herein referred to as mUC), creatinine clearance ≥30 mL/min and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1. Patients were required to have experienced disease progression during or following ≥1 prior platinum-based regimen for metastatic disease or in the neoadjuvant or adjuvant setting if progression occurred within 12 months. There were no restrictions on maximum number of prior therapies. Patients received atezo 1200 mg IV q3w until loss of clinical benefit as defined by the treating investigator. Confirmed, objective response rates (ORRs) were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and reviewed by an independent facility (BioClinica, Princeton, NJ, USA). Central evaluation of PD-L1 expression (HistoGeneX, Brussels, Belgium) was performed prospectively using the VENTANA SP142 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ, USA). Patient samples were scored as IC2/3, IC1, or IC0 based on the percentage of tumor-infiltrating immune cells (IC) with PD-L1 expression: ≥5%, ≥1% (and <5%), or <1%, respectively. Safety was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

2.2. Treatment definitions and assessments

The IMvigor210 study protocol defined atezolizumab treatment in the metastatic setting as second line and above (2L+) for patients who met the above-described inclusion criteria. For the current analysis, treatment definitions were assessed as follows:

atezolizumab treatment was considered first line (1L) when administered to patients who had only received prior platinum perioperatively. Atezolizumab treatment was considered 2L, third line (3L), fourth line (4L), or fifth line and beyond (5L+) for patients who received 1, 2, 3, or ≥4 prior regimens, respectively, specific to the metastatic setting (regardless of perioperative chemotherapy). The protocol-defined primary analysis (Rosenberg, 2016) evaluated co-primary endpoints of ORR based on centrally assessed, confirmed RECIST v1.1 and investigator-assessed immune-modified RECIST (imRECIST) (Mazieres, 2016). Secondary endpoints included duration of response (DOR) and progression-free survival (by both RECIST v1.1 per independent review facility and imRECIST per investigator assessment, overall survival (OS) and safety. In this post-hoc analysis, centrally assessed RECIST v1.1 ORR and DOR, in addition to OS and adverse event frequencies were evaluated based on the number of prior treatment regimens as defined above. DOR and OS were estimated using the Kaplan-Meier method (Kaplan,1958) and 95% confidence intervals (CIs) for median OS used a modified Brookmeyer and Crowley method (Brookmeyer, 1982). Descriptive summaries of these analyses are presented within for this single-arm study. The date of data cutoff used in this analysis was July 4, 2016.

3. Results

3.1 Baseline and prior treatment characteristics

Overall, 310 eligible patients were included in this analysis (Table 1). The median age was 66 years, the majority (78%) were male and had visceral metastases (78%). Thirty-eight percent of patients had liver metastases, and 62% had an ECOG PS of 1. Fifty-six patients received only perioperative chemotherapy and were considered to have received atezolizumab as 1L therapy. Of 254 (82%) patients who were treated with prior therapy in the metastatic setting, 39% received 1 prior line of therapy and 43% received 2 or more prior regimens (Table 1). Prior platinum-based treatments predominantly included cisplatin (in 73% of patients), and 26% of patients received prior carboplatin. Patients also received a variety of other prior therapies, most commonly chemotherapy or targeted agents (data not shown).

3.2 Atezolizumab treatment, follow-up duration and subsequent therapies administered

At the time of data cutoff (July 4, 2016), the median survival follow-up was 21.0 months (range, 0.2+ to 24.5) in all patients and similar across subgroups (Supplementary Table 1). 310 patients had received atezolizumab for a median treatment duration of 12 weeks (range, 0-104), corresponding to a median of 5 doses. Exposure was slightly lower in the 3L subgroup, with no consistent pattern as a function of prior lines of therapy (Supplementary Table 1).

At data cutoff, 14% of patients remained on treatment, and 24% of patients remained on study or follow-up. Eighty-one percent of patients treated with atezolizumab (251 of 310)

did not receive subsequent therapy, primarily due to death (*n* = 181), remaining on study treatment (*n* = 43), or other reasons (*n* = 27). Subsequent non-protocol therapies were reported during follow-up for 56 evaluable patients who experienced RECIST v1.1 PD with independent review. As with non-protocol agents received prior to atezolizumab, subsequent therapies administered varied but predominantly included chemotherapy, in addition to immunotherapy and targeted or other agents (data not shown).

3.3. Independent Review Facility–assessed RECIST v1.1 response rates and duration

The ORR across all patients was 16% (95% CI, 12%–20%) and ranged from 8% (95% CI, 1%–25%) in the 5L+ subgroup to 25% (95% CI, 14%–38%) in the 1L subgroup. Complete and partial responses (CR and PR) were observed in all subgroups based on prior regimens. In addition to ORR, CR rates were also numerically higher in patients without prior treatment for mUC (1L subgroup), but no consistent trend appeared among previously treated patients across the different lines of therapy (Table 2).

Responses were durable across lines of therapy, with ≥50% of responding patients experiencing ongoing responses, defined by the lack of death or progressive disease (PD). The median DOR was not yet reached overall and in any subgroup except in patients who received only neoadjuvant or adjuvant treatment (1L subgroups), who had a median DOR of 16.0 months (range, 2.9+–19.5+ months; Table 2).

3.4 Overall survival

The median overall survival for all patients was 7.9 months, with an event rate of 73% (Fig. 1A). Subgroups analyses suggest that patients with fewer prior lines of therapy tended to have longer median OS, 12-month and 18-month survival rates, but no consistent trend was apparent (Fig. 1A and 1B). At the time of data cut-off, event rates across lines of therapy were similar (Fig. 1A).

3.5 Safety

Ninety-eight percent of patients experienced an adverse event (AE) regardless of attribution. When compared between treatment subgroups, individual AE frequencies were consistent, with rates of 98%, 98%, 99%, 98%, and 92% in the 1L, 2L, 3L 4L and 5L+ settings, respectively. Seventy-one percent of patients experienced a treatment-related AE, and rates were likewise generally similar regardless of the number of lines of therapy (ranging from 58% in the 5L+ subgroup to 79% in the 1L group; Supplementary Table 2). The incidence of Grade 3–4 treatment related AEs in all patients was 18% and was similar across the different lines of therapy (ranging from 15% in the 3L subgroup up to 22% in the 4L group; Table 3). The most common treatment-related Grade 3–4 AEs were fatigue, increased alanine aminotransferase and aspartate aminotransferase each occurring in ≤2% of all patients, with similar frequencies distributed across lines of therapy. There were no reported Grade 5 treatment-related AEs in any group (Table 3).

4. Discussion

Critical barriers that have limited the treatment of mUC across lines of therapy include the ineligibility of many patients to receive standard-of-care cisplatin (Galsky, 2011) and the historic lack of major, broadly-applicable therapeutic advances that significantly improve efficacy outcomes. As a function of the inadequacies of current treatment options, many patients are never treated with 1L or 2L+ chemotherapy (Pal, 2015; Pal, 2016). Therefore, there is very limited data on the impact of previous lines of therapy on outcomes of patients with mUC (Pond, 2015). The recent 2L approvals in mUC and paradigm-shifting advances of cancer immunotherapy will require more studies to determine best treatment practices and appropriate treatment patterns and sequencing.

The phase 2 IMvigor210 study showed atezolizumab to be effective and safe among patients with mUC who progressed during or after platinum-based chemotherapy for mUC (Rosenberg, 2016). The study included heavily pre-treated patients, with 43% of patients treated with ≥ 2 regimens, mostly chemotherapy, prior to starting atezolizumab. Here, we report that the clinical benefit of atezolizumab extends to patients independently of the number of previous lines of therapy. Almost all patients in the current study who were considered to have received 1L atezolizumab were required to have experienced disease progression within 12 months of perioperative platinum-based chemotherapy (except for two patients who were enrolled due to protocol violation, see Table 2). In this subgroup without prior treatment for mUC, ORR and landmark OS rates appeared numerically higher in patients, with numerically longer mOS as well. However, no consistent trend in efficacy based on number of regimens was observed. This pattern is in agreement with data from a phase 2 study of 265

previously treated patients with mUC who received the checkpoint inhibitor nivolumab, also recently granted FDA approval; ORR was generally similar in patients with either 0, 1, 2 or 3 prior regimens for mUC, although other outcomes were not reported for these subgroups (Sharma, 2017).

The possible impacts of prior treatments on toxicities experienced by patients treated with immunotherapies in later lines of therapy are not well characterized, and the potential for increased toxicity may depend on a number of factors, including comorbidities, age, and/or prior treatment effects. In our study, atezolizumab was well tolerated, with no major differences in the rates of AEs. Safety was generally consistent across lines of therapy, and more heavily pre-treated patients did not appear to have increased toxicity. Importantly, heavily pre-treated patients had similar grade 3-4 treatment-related AEs frequencies as compared with those treated in earlier settings. Overall, the most common such toxicity was grade 3–4 fatigue that occurred in ≤3% of patients in all subgroups independent of prior treatments. Overall, these results suggest that the toxicity profile was generally consistent regardless of number of prior regimens.

To our knowledge, this study represents the largest clinical assessment of the impacts of pre-treatment on checkpoint inhibitor efficacy outcomes in mUC—and the only such analysis of safety—to date. Still, as a post-hoc analysis, this study was not designed to prospectively control for the numbers of patients enrolled in each prior regimen subgroup, or the clinical or treatment characteristics of each group, some of which contain few patients (e.g. *n* = 26 for 5L+ subgroup). Of note, exposure was consistent,

and median follow-up duration concordant across these groups. Based on the single-arm nature of the study, we used descriptive statistics to evaluate efficacy and safety outcomes, since the interpretation of formal statistical tests would otherwise be confounded by the lack of a control arm and thus unable to distinguish between predictive treatment effects and prognostics effect across lines of therapy. Previous analyses have identified clinical and prior treatment factors that may be prognostic for survival outcomes in the 1L or 2L+ settings (Bajorin, 1999; Bellmunt, 2013; Sonpavde, 2013). Pond et al. (2015) conducted a large (*n* = 710) pooled analysis of 10 prospective phase II trials of salvage systemic chemotherapy, biologic agent therapy, or both, and evaluated the impact of prior lines of therapy on the prognosis of patients with advanced UC. Across studies, approximately 16% (*n* = 111), 4% (*n* = 29) and 2% (*n* = 12) of patients received 2, 3 or ≥4 lines of prior therapy, respectively, and the number of prior lines was not found to be significantly associated with OS in either univariate or multivariate analyses, although perioperative chemo (given to 39%, *n* = 277) was favorably associated with OS in univariate analyses (Pond, 2015). Collectively, these data suggest that in patients who progress despite platinum-based therapy, atezolizumab may provide clinical benefit more broadly across multiple lines of therapy.

Conclusions

This analysis evaluated the impact of prior lines of therapy among generally heavily pre-treated patients with mUC who progressed during or after platinum-based chemotherapy and were enrolled in the IMvigor210 study. Results showed that treatment with atezolizumab conferred durable, clinically meaningful benefit

notwithstanding the number of prior lines of therapy with no observed differences in safety.

Author contributions: Jose Luis Perez-Gracia had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: TBC.

Acquisition of data: TBC.

Analysis and interpretation of data: All authors/TBC.

Drafting of the manuscript: TBC.

Critical revision of the manuscript for important intellectual content: All authors/TBC.

Statistical analysis: Wang.

Obtaining funding: TBC.

Administrative, technical, or material support: TBC.

Supervision: TBC.

Other: None/TBC.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version.

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Figure Legends

Fig. 1 – Overall survival (OS) by prior regimen: (A) Median OS and landmark OS rates and (b) Kaplan-Meier curves. Data cutoff date: July 4, 2016.

1L = first line; 2L = second line; 3L = third line; 4L = fourth line; 5L: fifth line; OS = overall survival.

Tables

Table 1 – Key clinical and prior treatment characteristics at baseline

Baseline Characteristic	All Patients (*N* = 310)
Median age, yr (range)	66 (32–91)
Sex, *n* (%)	
Male	241 (77.7)
Female	69 (22.3)
ECOG PS, *n* (%)	
0	117 (37.7)
1	193 (62.3)
Primary tumor site, *n* (%)	
Bladder	233 (75.2)
Non-bladder	77 (25.8)
Metastatic site(s), *n* (%)	
Visceral	243 (78.4)
Liver	96 (31.0)
PD-L1 status, *n* (%) [a]	
IC2/3	100 (32.3)
IC1	107 (34.5)
IC0	103 (33.2)
Time from prior chemotherapy, *n* (%) [b]	
≤ 3 mo	121 (39.0)
Prior platinum received, *n* (%) [b]	
Cisplatin	226 (72.9)
Carboplatin	81 (26.1)
Other platinum	3 (1.0)
Prior systemic regimens for metastatic disease, *n* (%)	
0 (1L)[c]	56 (18.1)
1 (2L)	121 (39.0)
2 (3L)	66 (21.3)
3 (4L)	41 (13.2)
≥4 (5L+)	26 (8.4)

ECOG PS = Eastern Cooperative Oncology Group Performance Status; IC = tumor-infiltrating immune cell.
[a] PD-L1 status on IC.
[b] In all treatment settings.
[c] Perioperative treatment setting only.
Data cutoff date: July 4, 2016.

392 **Table 2 – Response rates and durations by prior regimen**

	Prior regimens for mUC					All Patients (*N* = 310) [a]
	0 (1L) (*n* = 56[f])	1 (2L) (*n* = 121)	2 (3L) (*n* = 66)	3 (4L) (*n* = 41)	≥4 (5L+) (*n* = 26)	
ORR, n(%) [a]	14 (25.0)	16 (13.2)	10 (15.2)	7 (17.1)	2 (7.7)	49 (15.8)
ORR 95% confidence interval	14.4–38.4	7.8–20.6	7.5–26.1	7.2–32.1	1.0–25.1	11.9–20.4
Response status, *n* (%) [b]						
CR	6 (10.7)	6 (5.0)	4 (6.1)	2 (4.9)	1 (3.8)	19 (6.1)
PR	8 (14.3)	10 (8.3)	6 (9.1)	5 (12.2)	1 (3.8)	30 (9.7)
SD	10 (17.9)	24 (19.8)	13 (19.7)	7 (17.1)	4 (15.4)	58 (18.7)
PD	26 (46.4)	63 (52.1)	32 (48.5)	20 (48.8)	16 (61.5)	157 (50.6)
Ongoing responses, *n* (%) [c]	7 (50.0)	9 (56.3)	8 (80.0)	6 (85.7)	2 (100.0)	32 (65.3)
Median DOR, mo [d]	16.0	not reached	not reached	not reached	not reached	not reached
DOR range [e]	2.9+–19.5+	4.2–19.4+	4.7–21.8+	2.1+–19.6+	17.6+– 22.6+	2.1+–22.6+

1L = first line; 2L = second line; 3L = third line; 4L = fourth line; 5L = fifth line; CR = complete response; DOR = duration of response; ORR = objective response rate; PR = partial response; PD = progressive disease; RECIST = Response Evaluation Criteria In Solid Tumors; SD = stable disease.

[a] Objective-response evaluable population includes 46 patients with missing/unevaluable responses.

[b] Responses were assessed using RECIST v1.1 per independent review.

[c] No death or PD at data cutoff.

[d] In patients with an objective response.

[e] Censored values are indicated with a plus symbol.

[f] Neoadjuvant or adjuvant chemotherapy only in patients with disease progression within 12 mo of chemotherapy (n = 54) or those with progression at or after 12 mo of chemotherapy (n = 2; enrolled into cohort 2 due to protocol violation).

Data cutoff date: July 4, 2016.

393

Table 3. Grade 3–4 treatment-related adverse events (AEs) by prior regimen

AE, n (%) [a]	Prior regimens for mUC					All Patients (*N* = 310)
	0 (1L) (*n* = 56)	1 (2L) (*n* = 121)	2 (3L) (*n* = 66)	3 (4L) (*n* = 41)	≥4 (5L+) (*n* = 26)	
All Grade 3–4 AEs	13 (23%)	19 (16%)	10 (15%)	9 (22%)	5 (19%)	56 (18%)
Fatigue	0 (0%)	2 (2%)	2 (3%)	1 (2%)	0 (0%)	5 (2%)
AST increased	1 (2%)	1 (1%)	1 (2%)	1 (2%)	0 (0%)	4 (1%)
ALT increased	1 (2%)	0 (0%)	2 (3%)	1 (2%)	0 (0%)	4 (1%)
Pneumonitis	2 (4%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	3 (1%)
Lymphocyte count decreased	1 (2%)	1 (1%)	1 (2%)	0 (0%)	0 (0%)	3 (1%)
Hypertension	1 (2%)	1 (1%)	1 (2%)	0 (0%)	0 (0%)	3 (1%)
Colitis	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	2 (1%)
Decreased appetite	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Arthralgia	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (4%)	2 (1%)
Dyspnea	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Anemia	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Hypotension	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	2 (1%)

1L = first line; 2L = second line; 3L = third line; 4L = fourth line; 5L = fifth line; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

[a] Occurring in ≥ 2 patients [1%] overall). Multiple occurrences of the same event were counted once at highest grade.

Data cutoff date: July 4, 1016.

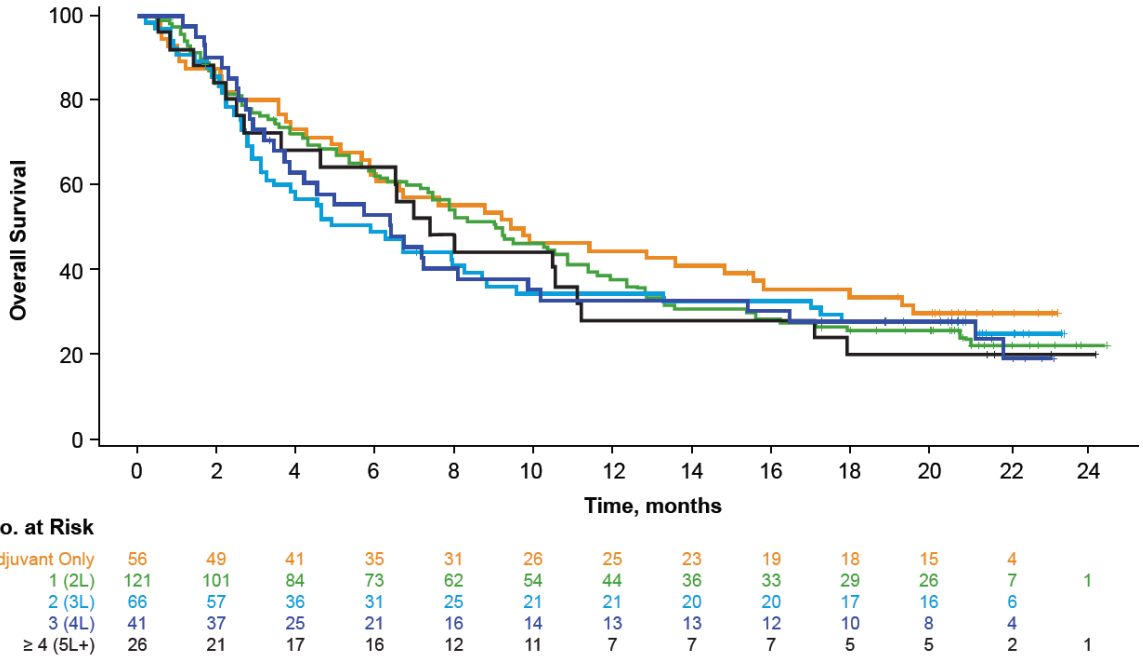
Figures

Figure 1 – Overall survival by prior regimen

(A) Median and landmark overall survival

	Prior Regimens for mUC					All Patients (*N* = 310)
	0 (1L) (*n* = 56)	1 (2L) (*n* = 121)	2 (3L) (*n* = 66)	3 (4L) (*n* = 41)	≥4 (5L+) (*n* = 26)	
Median OS, mo	9.6	9.0	5.9	6.4	7.4	7.9
95% CI	5.9–15.8	7.3–11.3	3.3–8.7	3.8–10.2	4.6–11.2	6.7–9.3
12-mo OS rate, %	45	38	34	33	28	37
95% CI	32–58	29–47	23–46	18–47	10–46	31–42
18-mo OS rate, %	34	26	28	28	20	27
95% CI	21–46	18–34	17–39	14–42	4–36	22–32
OS events, n (%)	39 (70)	89 (74)	47 (71)	31 (76)	20 (77)	226 (73)

(B) Kaplan-Meier overall survival curves



Appendix A. Supplementary data

Supplementary tables

Supplementary Table 1 – Exposure and follow-up durations by prior regimen

	Prior Regimens for mUC					All Patients (*N* = 310)
	0 (1L) (*n* = 56)	1 (2L) (*n* = 121)	2 (3L) (*n* = 66)	3 (4L) (*n* = 41)	≥4 (5L+) (*n* = 26)	
Median treatment duration, wk	15.5	12.1	7.3	12.3	11.4	12.3
Range	0–100	0–104	0–101	0–100	0–100	0–104
Median number of doses, n	6.0	5.0	3.0	5.0	4.5	5.0
Range	1–34	1–35	1–34	1–34	1–32	1–35
Median follow-up duration, mo	20.7	20.7	21.3	22.1	21.8	21.0
Range	0.6+–23.2	0.5+–24.5	0.2+–23.4	1.2+–23.1	0.5+–24.2	0.2+–24.5

1L = first line; 2L = second line; 3L = third line; 4L = fourth line; 5L = fifth line.
Data cutoff date: July 4, 2016.

406 **Supplementary Table 2 – All grade treatment-related adverse events (AEs) by**

407 **prior regimen**

AE, n (%) [a]	Prior Regimens for mUC					All Patients (*N* = 310)
	0 (1L) (*n* = 56)	1 (2L) (*n* = 121)	2 (3L) (*n* = 66)	3 (4L) (*n* = 41)	≥4 (5L+) (*n* = 26)	
All Grade AEs	44 (79%)	91 (75%)	43 (65%)	27 (66%)	15 (58%)	220 (71%)
Fatigue	19 (34)	38 (31)	23 (35)	11 (27)	4 (15)	95 (31)
Nausea	11 (20)	14 (12)	12 (18)	3 (7)	2 (8)	42 (14)
Pruritus	9 (16)	15 (12)	7 (11)	5 (12)	1 (4)	37 (12)
Decreased appetite	4 (7)	15 (12)	9 (14)	4 (10)	3 (12)	35 (11)
Pyrexia	6 (11)	15 (12)	5 (8)	2 (5)	0 (0)	28 (9)
Diarrhea	5 (9)	10 (8)	6 (9)	4 (10)	1 (4)	26 (8)
Vomiting	1 (2)	7 (6)	8 (12)	2 (5)	2 (8)	20 (7)

1L = first line; 2L = second line; 3L = third line; 4L = fourth line; 5L = fifth line; AE = adverse event.
[a] Occurring in ≥ 10% of patients in any subgroup. Multiple occurrences of the same event were counted once at highest grade.
Data cutoff date: July 4, 2016.

408