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# Atezolizumab in Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: Outcomes by Prior Number of Regimens.

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

3

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## 31 **Abstract**

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

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

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

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

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

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

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

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

## 61 **1. Introduction**

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

73

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

84

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

95

## 96 **2. Patients and Methods**

### 97 ***2.1. Patients, study design, and procedures***

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

106

107 Key eligibility criteria specific to this cohort included locally advanced or metastatic  
108 urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra (herein referred to as  
109 mUC), creatinine clearance  $\geq 30$  mL/min and Eastern Cooperative Oncology Group  
110 performance status (ECOG PS) of 0–1. Patients were required to have experienced  
111 disease progression during or following  $\geq 1$  prior platinum-based regimen for metastatic  
112 disease or in the neoadjuvant or adjuvant setting if progression occurred within 12  
113 months. There were no restrictions on maximum number of prior therapies. Patients  
114 received atezo 1200 mg IV q3w until loss of clinical benefit as defined by the treating  
115 investigator. Confirmed, objective response rates (ORRs) were assessed using  
116 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and reviewed by an  
117 independent facility (BioClinica, Princeton, NJ, USA). Central evaluation of PD-L1  
118 expression (HistoGeneX, Brussels, Belgium) was performed prospectively using the  
119 VENTANA SP142 immunohistochemistry assay (Ventana Medical Systems, Tucson,  
120 AZ, USA). Patient samples were scored as IC2/3, IC1, or IC0 based on the percentage  
121 of tumor-infiltrating immune cells (IC) with PD-L1 expression:  $\geq 5\%$ ,  $\geq 1\%$  (and  $< 5\%$ ), or  
122  $< 1\%$ , respectively. Safety was assessed using National Cancer Institute Common  
123 Terminology Criteria for Adverse Events version 4.0.

124

## 125 **2.2. Treatment definitions and assessments**

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



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

## 146 **3. Results**

### 147 **3.1 Baseline and prior treatment characteristics**

148 Overall, 310 eligible patients were included in this analysis (Table 1). The median age  
149 was 66 years, the majority (78%) were male and had visceral metastases (78%). Thirty-  
150 eight percent of patients had liver metastases, and 62% had an ECOG PS of 1. Fifty-six  
151 patients received only perioperative chemotherapy and were considered to have  
152 received atezolizumab as 1L therapy. Of 254 (82%) patients who were treated with prior  
153 therapy in the metastatic setting, 39% received 1 prior line of therapy and 43% received  
154 2 or more prior regimens (Table 1). Prior platinum-based treatments predominantly  
155 included cisplatin (in 73% of patients), and 26% of patients received prior carboplatin.  
156 Patients also received a variety of other prior therapies, most commonly chemotherapy  
157 or targeted agents (data not shown).

158

### 159 ***3.2 Atezolizumab treatment, follow-up duration and subsequent therapies*** 160 ***administered***

161 At the time of data cutoff (July 4, 2016), the median survival follow-up was 21.0 months  
162 (range, 0.2+ to 24.5) in all patients and similar across subgroups (Supplementary Table  
163 1). 310 patients had received atezolizumab for a median treatment duration of 12 weeks  
164 (range, 0-104), corresponding to a median of 5 doses. Exposure was slightly lower in  
165 the 3L subgroup, with no consistent pattern as a function of prior lines of therapy  
166 (Supplementary Table 1).

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

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

176

### 177 **3.3. Independent Review Facility–assessed RECIST v1.1 response rates and** 178 **duration**

179 The ORR across all patients was 16% (95% CI, 12%–20%) and ranged from 8% (95%  
180 CI, 1%–25%) in the 5L+ subgroup to 25% (95% CI, 14%–38%) in the 1L subgroup.

181 Complete and partial responses (CR and PR) were observed in all subgroups based on  
182 prior regimens. In addition to ORR, CR rates were also numerically higher in patients  
183 without prior treatment for mUC (1L subgroup), but no consistent trend appeared among  
184 previously treated patients across the different lines of therapy (Table 2).

185

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

191

### 192 **3.4 Overall survival**

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

198

### 199 **3.5 Safety**

200 Ninety-eight percent of patients experienced an adverse event (AE) regardless of  
201 attribution. When compared between treatment subgroups, individual AE frequencies  
202 were consistent, with rates of 98%, 98%, 99%, 98%, and 92% in the 1L, 2L, 3L 4L and  
203 5L+ settings, respectively. Seventy-one percent of patients experienced a treatment-  
204 related AE, and rates were likewise generally similar regardless of the number of lines  
205 of therapy (ranging from 58% in the 5L+ subgroup to 79% in the 1L group;  
206 Supplementary Table 2). The incidence of Grade 3–4 treatment related AEs in all  
207 patients was 18% and was similar across the different lines of therapy (ranging from  
208 15% in the 3L subgroup up to 22% in the 4L group; Table 3). The most common  
209 treatment-related Grade 3–4 AEs were fatigue, increased alanine aminotransferase and  
210 aspartate aminotransferase each occurring in  $\leq 2\%$  of all patients, with similar  
211 frequencies distributed across lines of therapy. There were no reported Grade 5  
212 treatment-related AEs in any group (Table 3).

213

## 214 **4. Discussion**

215 Critical barriers that have limited the treatment of mUC across lines of therapy include  
216 the ineligibility of many patients to receive standard-of-care cisplatin (Galsky, 2011) and  
217 the historic lack of major, broadly-applicable therapeutic advances that significantly  
218 improve efficacy outcomes. As a function of the inadequacies of current treatment  
219 options, many patients are never treated with 1L or 2L+ chemotherapy (Pal, 2015; Pal,  
220 2016). Therefore, there is very limited data on the impact of previous lines of therapy on  
221 outcomes of patients with mUC (Pond, 2015). The recent 2L approvals in mUC and  
222 paradigm-shifting advances of cancer immunotherapy will require more studies to  
223 determine best treatment practices and appropriate treatment patterns and sequencing.

224

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

238 previously treated patients with mUC who received the checkpoint inhibitor nivolumab,  
239 also recently granted FDA approval; ORR was generally similar in patients with either 0,  
240 1, 2 or 3 prior regimens for mUC, although other outcomes were not reported for these  
241 subgroups (Sharma, 2017).

242

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

254

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

261 and median follow-up duration concordant across these groups. Based on the single-  
262 arm nature of the study, we used descriptive statistics to evaluate efficacy and safety  
263 outcomes, since the interpretation of formal statistical tests would otherwise be  
264 confounded by the lack of a control arm and thus unable to distinguish between  
265 predictive treatment effects and prognostics effect across lines of therapy. Previous  
266 analyses have identified clinical and prior treatment factors that may be prognostic for  
267 survival outcomes in the 1L or 2L+ settings (Bajorin, 1999; Bellmunt, 2013; Sonpavde,  
268 2013). Pond et al. (2015) conducted a large ( $n = 710$ ) pooled analysis of 10 prospective  
269 phase II trials of salvage systemic chemotherapy, biologic agent therapy, or both, and  
270 evaluated the impact of prior lines of therapy on the prognosis of patients with advanced  
271 UC. Across studies, approximately 16% ( $n = 111$ ), 4% ( $n = 29$ ) and 2% ( $n = 12$ ) of  
272 patients received 2, 3 or  $\geq 4$  lines of prior therapy, respectively, and the number of prior  
273 lines was not found to be significantly associated with OS in either univariate or  
274 multivariate analyses, although perioperative chemo (given to 39%,  $n = 277$ ) was  
275 favorably associated with OS in univariate analyses (Pond, 2015). Collectively, these  
276 data suggest that in patients who progress despite platinum-based therapy,  
277 atezolizumab may provide clinical benefit more broadly across multiple lines of therapy.

278

## 279 **Conclusions**

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

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

286

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

290 *Study concept and design:* TBC.

291 *Acquisition of data:* TBC.

292 *Analysis and interpretation of data:* All authors/TBC.

293 *Drafting of the manuscript:* TBC.

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

295 *Statistical analysis:* Wang.

296 *Obtaining funding:* TBC.

297 *Administrative, technical, or material support:* TBC.

298 *Supervision:* TBC.

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306

## 307 **Appendix A. Supplementary data**

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

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383 **Figure Legends**

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

386 1L = first line; 2L = second line; 3L = third line; 4L = fourth line; 5L: fifth line; OS =  
387 overall survival.

388 **Tables**389 **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 (%) <sup>a</sup>	
IC2/3	100 (32.3)
IC1	107 (34.5)
IC0	103 (33.2)
Time from prior chemotherapy, n (%) <sup>b</sup>	
≤ 3 mo	121 (39.0)
Prior platinum received, n (%) <sup>b</sup>	
Cisplatin	226 (72.9)
Carboplatin	81 (26.1)
Other platinum	3 (1.0)
Prior systemic regimens for metastatic disease, n (%)	
0 (1L) <sup>c</sup>	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.  
<sup>a</sup> PD-L1 status on IC.  
<sup>b</sup> In all treatment settings.  
<sup>c</sup> Perioperative treatment setting only.  
Data cutoff date: July 4, 2016.

391

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

	Prior regimens for mUC					All Patients (N = 310) <sup>a</sup>
	0 (1L) (n = 56) <sup>f</sup>	1 (2L) (n = 121)	2 (3L) (n = 66)	3 (4L) (n = 41)	≥4 (5L+) (n = 26)	
ORR, n(%) <sup>a</sup>	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 (%) <sup>b</sup>						
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 (%) <sup>c</sup>	7 (50.0)	9 (56.3)	8 (80.0)	6 (85.7)	2 (100.0)	32 (65.3)
Median DOR, mo <sup>d</sup>	16.0	not reached	not reached	not reached	not reached	not reached
DOR range <sup>e</sup>	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.

<sup>a</sup> Objective-response evaluable population includes 46 patients with missing/unevaluable responses.

<sup>b</sup> Responses were assessed using RECIST v1.1 per independent review.

<sup>c</sup> No death or PD at data cutoff.

<sup>d</sup> In patients with an objective response.

<sup>e</sup> Censored values are indicated with a plus symbol.

<sup>f</sup> 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



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

AE, n (%) <sup>a</sup>	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.  
<sup>a</sup> Occurring in ≥ 2 patients [1%] overall). Multiple occurrences of the same event were counted once at highest grade.  
 Data cutoff date: July 4, 1016.

395

396 **Figures**

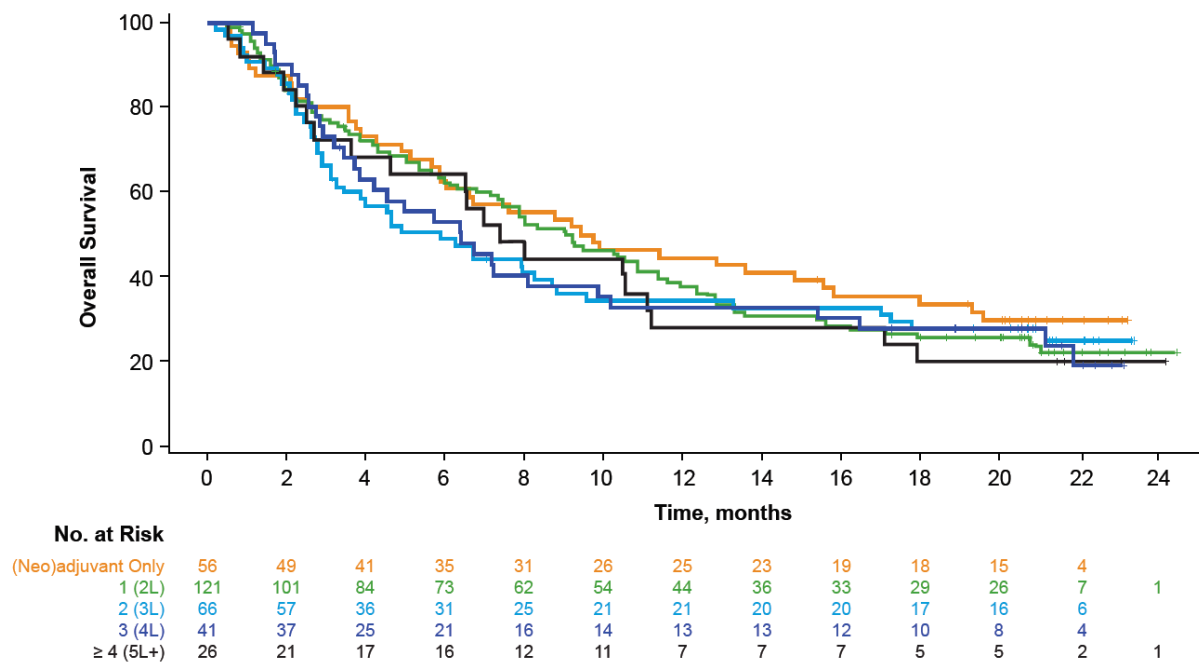
397 **Figure 1 – Overall survival by prior regimen**

398 **(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)

399

400 **(B) Kaplan-Meier overall survival curves**



401

402 **Appendix A. Supplementary data**

403 **Supplementary tables**

404 **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.						

405

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

AE, n (%) <sup>a</sup>	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.  
<sup>a</sup> 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