Atezolizumab in First-Line Cisplatin–Ineligible or Platinum-Treated Locally Advanced or Metastatic Urothelial Cancer: Long-Term Efficacy From Phase II Study IMvigor210

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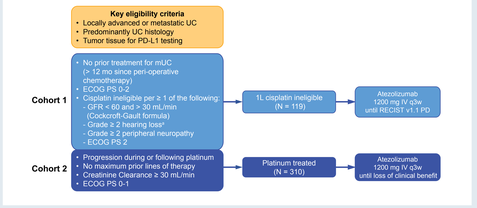
BACKGROUND

- Cisplatin-based chemotherapy is currently the standard of care in the first-line (1L) treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC)[1,2]
  - However, many patients are ineligible for cisplatin due to factors including comorbidities or poor performance status and may even go untreated entirely[3,4]
  - Historically, the preferred alternatives to cisplatin for ineligible patients have included carboplatin-based regimens,[5] which seem to result in relatively shorter survival than does cisplatin,[3] although data are limited
  - Further, despite initial responses, most patients will experience disease progression following cisplatin- or carboplatin-based regimens, and toxicities with both chemotherapies are common[5,6]
- Checkpoint inhibitors, including atezolizumab (anti–programmed death-ligand 1 [PD-L1]), are now treatment options for platinum-treated patients with mUC, and atezolizumab and pembrolizumab are approved for 1L cisplatin–ineligible patients with mUC in the United States, Europe and elsewhere[1,7,8]
  - Atezolizumab selectively targets PD-L1 to block interactions with its receptors, programmed death-1 (PD-1) and B7.1, to reinvigorate and stimulate anti-cancer immunity while leaving the PD-L2/PD-1 interaction intact[9,10]
- Phase Ia results (95 patients with previously treated mUC) demonstrated that atezolizumab was tolerable and resulted in durable responses in the long term (median follow-up, > 3 years)[11]
- IMvigor210 is a global, single-arm, 2-cohort pivotal Phase II study of atezolizumab monotherapy in mUC
  - Results from both Cohort 1 (119 cisplatin-ineligible patients with previously untreated mUC) and Cohort 2 (310 patients with previous platinum treatment) showed that atezolizumab was well tolerated and resulted in clinically meaningful efficacy[12,13]
- Here, we report long-term outcomes in both cohorts of IMvigor210, including more mature objective response rate (ORR), duration of response (DOR) and overall survival (OS) data and subgroup analyses

METHODS

- The study designs for IMvigor210 Cohort 1 and Cohort 2 (ClinicalTrials.gov identifiers NCT02951767 and NCT02108652, respectively) have been previously described[12,13]
  - Key eligibility criteria and dosing are summarized in Figure 1

Figure 1. Study Schema



PD-L1 testing per VENTANA SP142 IHC assay.
ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; IHC, immunohistochemistry; IV, intravenously; PD, progressive disease; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors.
[a]Hearing loss of 25 dB at 2 contiguous frequencies.

- Protocol-defined study objectives are summarized below
  - For both cohorts, the primary endpoint was ORR
    - In Cohort 1, RECIST v1.1–confirmed ORR was evaluated per independent review facility (IRF)
    - In Cohort 2, co-primary endpoints were confirmed IRF-assessed ORR per RECIST v1.1 (presented here) and investigator-assessed ORR per immune-modified RECIST[14]
  - Overall survival and DOR were evaluated as secondary endpoints, safety was evaluated using the National Cancer Institute's Common Terminology Criteria for Adverse Events v4 and biomarkers were evaluated as exploratory endpoints
- In this updated analysis, we evaluated ORR, DOR and OS efficacy endpoints, both in the intention-to-treat populations and in key subgroups based on clinical and treatment characteristics

RESULTS

- As of the July 12, 2017, data cutoff, 119 patients from Cohort 1 and 310 patients from Cohort 2 were evaluable
  - Key baseline characteristics are reported in Table 1

Table 1. Key Baseline Characteristics

Characteristic	Cohort 1 (N = 119)	Cohort 2 (N = 310)
Age, median (range)	73 y (51-92)	66 y (32-91)
Male sex	81%	78%
ECOG PS		
0	37%	38%
1	42%	62%
2[a]	21%	0%[a]
Primary tumor site[b]		
Upper tract (renal pelvis or ureter)	28%	22%
Lower tract (bladder or urethra)	71%	77%
Metastatic sites		
Visceral[c]	66%	78%
Liver	21%	31%
Lymph node only	26%	14%
PD-L1 status on IC[d]		
IC2/3	27%	32%
IC1	40%	35%
IC0	33%	33%
Prior systemic regimens for metastatic disease		
0	98%[e]	18%[f]
1	—	38%
2	—	22%
≥ 3	—	22%
GFR[a] < 60 mL/min/1.73 m^2	71%	39%
Grade ≥ 2 hearing loss[a]	14%	—
Grade ≥ 2 peripheral neuropathy[a]	6%	—

IC, tumor-infiltrating immune cell.
[a] Refers to a criterion for cisplatin ineligibility for Cohort 1. ECOG PS 2 was not permitted for Cohort 2. [b] Patients with other tumor sites: 1 in Cohort 1 and 3 in Cohort 2. [c] Visceral metastasis defined as liver, lung, bone, any non–lymph node or soft tissue metastasis. [d] PD-L1 expression on IC: IC2/3, ≥ 5%; IC1, ≥ 1% and < 5%; IC0, < 1% per VENTANA SP142 IHC assay. [e] Two patients had recurrence < 12 mo since peri-operative chemotherapy. [f] Received platinum-based chemotherapy in the peri-operative setting only.

- In the analysis, median follow-up durations (ranges) were
  - 29.3 mo (0.2 to 35.9 mo) in Cohort 1
  - 32.9 mo (0.2+ to 35.7 mo) in Cohort 2
- Objective response rates and DORs are included in Table 2

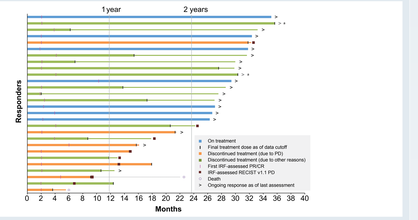
Table 2. Confirmed IRF-Assessed RECIST v1.1 ORR and DOR

Variable	Cohort 1 (N = 119)	Cohort 2 (N = 310)
ORR (95% CI)	24% (16, 32)[a]	16% (13, 21)[b]
CR rate	8%	7%
DOR, median (95% CI)	NE (30.4 mo, NE)	24.8 mo (13.8, 30.4)
Patients with ongoing response[c]	19 of 28	21 of 51

CR, complete response; NE, not estimable.
Patients with missing or unevaluable response status: [a] 19 in Cohort 1 and [b] 46 in Cohort 2. [c] No death or IRF-assessed RECIST v1.1 PD event.

- A number of patients in both cohorts, including those who discontinued treatment, experienced sustained responses
  - In Cohort 1, of the 28 responders, 7 remained on treatment (all of whom had been treated > 2 years), and 14 discontinued treatment for reasons other than PD (Figure 2)
    - In responders with tumor assessments after treatment discontinuation (n = 11), post-discontinuation DOR ranged from 1.3 to 27.1+ mo
    - Five of these patients had been off treatment for > 1 year (≤ 27 mo)

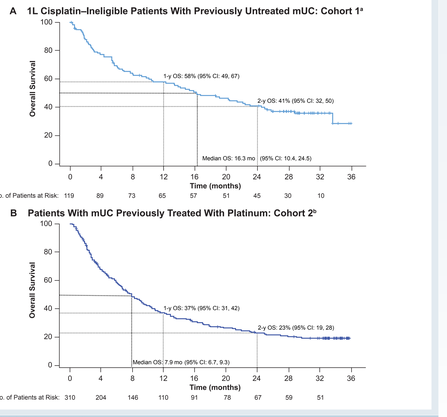
Figure 2. Duration of Treatment and Response: Cohort 1



PR, partial response.
[a] Last tumor assessment was < 20 days before final dose (ongoing response symbol does not imply timing).

- In Cohort 2, of 51 responders, 12 discontinued treatment for reasons other than PD
  - In responders with tumor assessments after treatment discontinuation (n = 8), post-discontinuation DOR ranged from 0.6+ to 15.4 mo
- Overall survival is shown in Figures 3 and 4

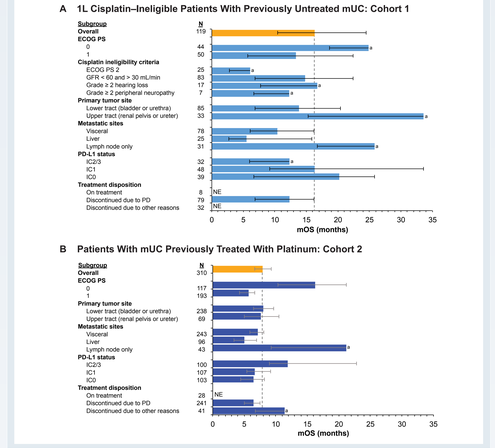
Figure 3. Kaplan-Meier Plots of OS



Plus (+) symbols indicate censored values.
[a]As of data cutoff, 73 of 119 patients had experienced an OS event (death). [b] As of data cutoff, 242 of 310 patients had experienced an OS event (death).

- Since the primary analysis, the median OS in Cohort 1 increased over time
  - After a median follow-up of 14.4 mo, median OS was 14.8 mo[15] and after 29.3 mo (this analysis), median OS was 16.3 mo
- In Cohort 2, median OS appeared stable and was comparable to the primary analysis[16]
- OS subgroup analyses are shown in Figure 4

Figure 4. Median OS in Subgroups Based on Clinical Characteristics and Response



Error bars represent 95% CIs. Median durations that are not estimable are indicated as NE.
mOS, median overall survival.
[a] Upper 95% CI is NE.

- In Cohort 1, patients with poor prognostic factors such as visceral or liver metastases or ECOG PS 2 tended to have shorter median OS
- In Cohort 2, patients with liver metastases also tended to have shorter OS, whereas the effect of any visceral metastatic site was less apparent
- In Cohort 2, patients with PD-L1 IC2/3 status tended to have longer OS than those with PD-L1 IC0 or IC1 status (IC2/3 mOS, 11.9 mo [95% CI: 9.0, 22.8]; IC0/1 mOS, 6.7 mo [95% CI: 5.4, 8.0]). In Cohort 1, an association between higher PD-L1 IC2/3 status and longer OS was not seen (IC2/3 mOS, 12.3 mo [95% CI: 6.0, NE]; IC0/1 mOS, 19.1 mo [95% CI: 10.4, 25.2])
- We also evaluated ORR, DOR and median OS in elderly patients (age ≥ 80 years) from Cohort 1 (Table 3) to inform outcomes in a population that tends to be underrepresented in clinical trials and treated with non-cisplatin therapies due to age-associated comorbidities[4,17]

Table 3. Outcomes in Elderly Patients (age ≥ 80 years): Cohort 1

Variable	Cohort 1 (n = 25)
ORR (95% CI)	28% (12, 49)
CR rate	12%
DOR (95% CI)	NE (20.2 mo, NE)
OS, median (95% CI)	21.4 mo (6.3, NE)

- Patients aged ≥ 80 years in Cohort 1 had a noteworthy CR rate and median OS

CONCLUSIONS

- With > 2.5 years of median follow-up, ORR and OS in previously treated patients (Cohort 2) were in line with prior data
  - Taken together with median DOR, which is now estimable for this cohort, data were consistent with Phase III results (IMvigor211)[18]
- With > 2 years of median follow-up, responses to 1L atezolizumab in cisplatin-ineligible patients with mUC (Cohort 1) appeared durable (median DOR not yet reached), resulting in continued improvement in OS since the primary analysis
- In Cohort 1, patients aged ≥ 80 years experienced a clinically meaningful benefit with atezolizumab, with median DOR also not yet reached in this subgroup
- These data warrant further investigation in a broader population of patients with mUC in the 1L setting. The randomized Phase III trial, IMvigor130, is ongoing (ClinicalTrials.gov identifier, NCT02807636)

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