A Phase 3 study of atezolizumab as monotherapy or combined with chemotherapy vs placebo + chemotherapy in previously untreated locally advanced or metastatic urothelial carcinoma: IMvigor130

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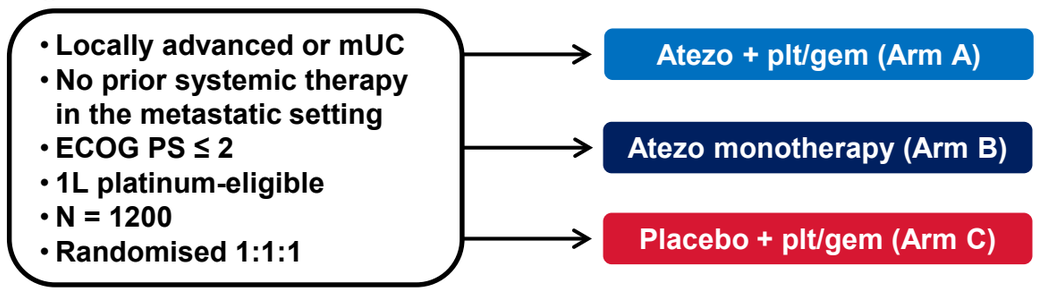
Background:

- PD-L1 and PD-1 inhibitors are the first new systemic therapies for mUC, both for 1L treatment of cisplatin-ineligible patients and for patients experiencing disease progression despite platinum-based chemotherapy (cisplatin or carboplatin plus gemcitabine; plt/gem)[1-8]
- In July 2018, the FDA and EMA revised the 1L label for atezolizumab (anti–PD-L1) and pembrolizumab (anti–PD-1) based on IDMC assessments[9-12]
- Here we report final PFS and interim OS results for IMvigor130, assessing atezolizumab in combination with plt/gem vs placebo + plt/gem in 1L mUC **(Fig. 1)**

Methods:

- **Eligibility criteria:** locally advanced or metastatic UC, no prior systemic therapy in the metastatic setting, ECOG PS ≤ 2, and 1L platinum-eligible
- **Stratification factors:** PD-L1 IC status (IC0 vs IC1 vs IC2/3), Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 and/or patients with liver metastases), investigator choice of plt/gem (cisplatin + gem or carboplatin + gem)
- Patients were randomised to Arm A (atezo + plt/gem), Arm B (atezo; added later per protocol amendment) or Arm C (placebo + plt/gem)
- **Coprimary endpoints:** investigator-assessed PFS (per RECIST 1.1) and OS (Arm A vs C, Arm B vs C)

Fig. 1

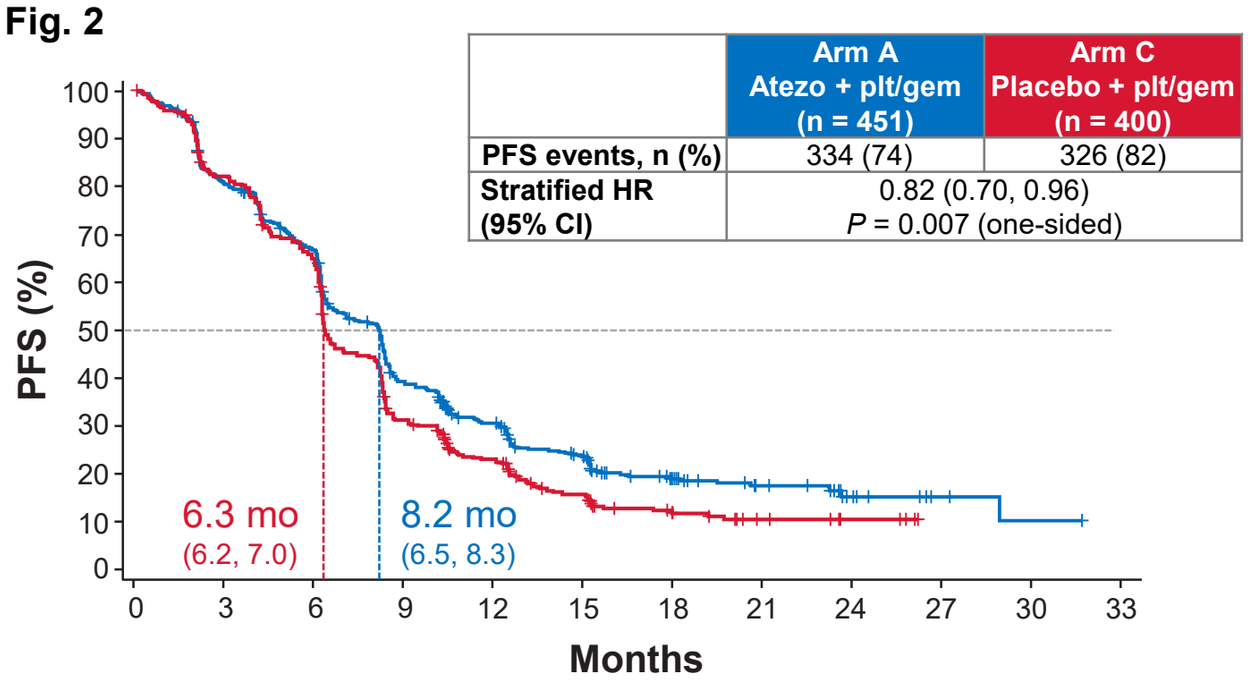


Results:

- 1213 patients were enrolled; 451 were randomly assigned to Arm A, 362 to Arm B, and 400 to Arm C (median survival follow-up for all patients was 11.8 mo)
- Median final PFS was 8.2 mo for Arm A and 6.3 mo for Arm C (hazard ratio [HR], 0.82; 95% CI, 0.70 to 0.96; 1-sided *P* = 0.007) **(Fig. 2)**
- Median interim OS was 16.0 mo for Arm A and 13.4 mo for Arm C but did not cross the prespecified efficacy boundary (HR, 0.83; 95% CI, 0.69 to 1.00, 1-sided *P* = 0.027) **(Fig. 3)**
- The rate of investigator-assessed objective response was 47% (95% CI, 43%-52%) in Arm A, 23% (19%-28%) in Arm B, and 44% (39%-49%) in Arm C and complete response was seen in 13% of patients in Arm A, 6% in Arm B, and 7% in Arm C (not shown)
- No new adverse event (AE) signals were observed, the combination safety profile was consistent with those of the individual therapeutic agents, and the safety profile was not markedly different from plt/gem alone **(Table 1)**

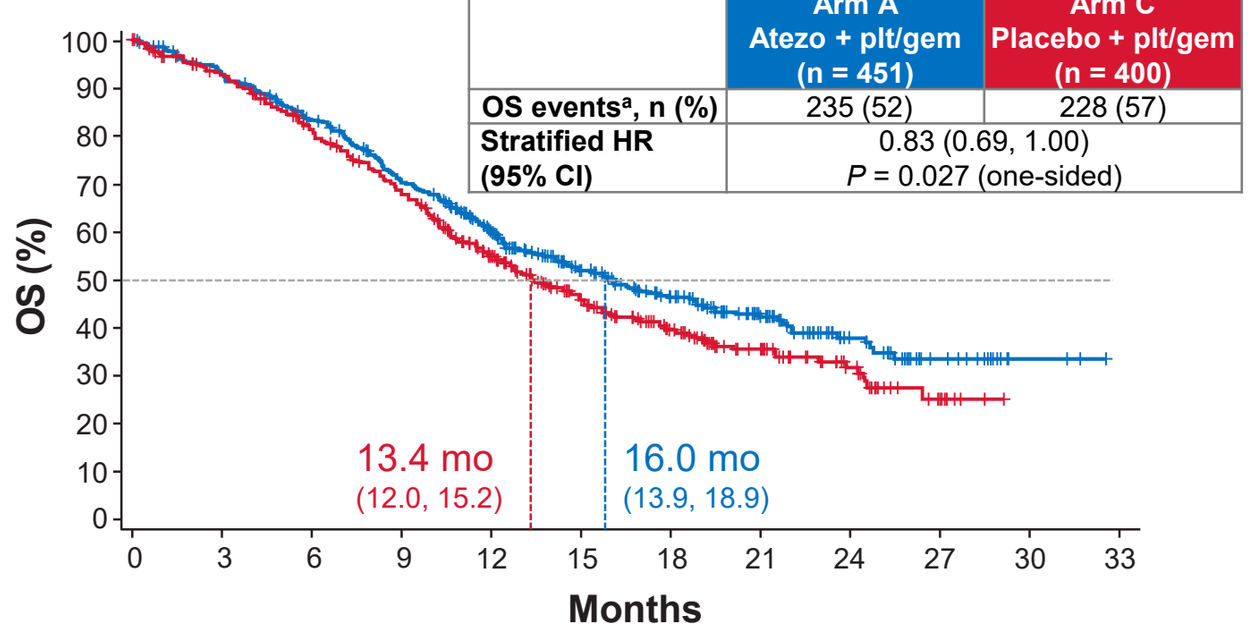
References: Grande et al. LBA14 ESMO 2019. 1. Gartrell et al. *Urol Oncol* 2017; 2. Balar et al. *Lancet* 2017; 3. Balar et al. *Lancet Oncol* 2017; 4. Powles et al. *Lancet* 2018; 5. Rosenberg et al. *Lancet* 2016; 6. Massard et al. *J Clin Oncol* 2016; 7. Sharma et al. *Lancet Oncol* 2017; 8. Apolo et al. *J Clin Oncol* 2017; 9. TECENTRIQ USPI 2019; 10. TECENTRIQ SmPC 2019; 11. KEYTRUDA USPI 2019; 12. KEYTRUDA SmPC 2019.

Fig. 2



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

Fig. 3



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)	

[a] 5% of patients from Arm A and 20% from Arm C received non-protocol immunotherapy.

Table 1

AE, n (%)	Arm A Atezo + plt/gem (n = 453)	Arm C Placebo + plt/gem (n = 390)	Arm B Atezo (n = 354)
Any grade, all cause	451 (100)	386 (99)	329 (93)
Grade 3-4	383 (85)	334 (86)	148 (42)
Grade 5	29 (6)	20 (5)	28 (8)
Any grade, treatment related	434 (96)	373 (96)	211 (60)
Grade 3-4	367 (81)	315 (81)	54 (15)
Grade 5	9 (2)	4 (1)	3 (1)
Any grade, serious	234 (52)	191 (49)	152 (43)
Treatment-related serious AEs	144 (32)	101 (26)	44 (12)
Any grade leading to any treatment discontinuation	156 (34)	132 (34)	22 (6)
Atezo or placebo	50 (11)	27 (7)	21 (6)
Cisplatin	53 (12)	52 (13)	0
Carboplatin	90 (20)	79 (20)	1 (< 1)
Gemcitabine	117 (26)	100 (26)	1 (< 1)
Any grade leading to any dose reduction or interruption	363 (80)	304 (78)	112 (32)

Conclusions:

- IMvigor130 is the first immune checkpoint inhibitor study to demonstrate an improvement in PFS over standard of care in 1L mUC
- At this interim analysis, a numerically longer OS was observed with atezolizumab + plt/gem vs placebo + plt/gem but did not cross the pre-specified interim efficacy boundary; follow-up will continue to final analysis
- Atezolizumab + plt/gem was well tolerated, with a safety profile consistent with each individual agent
- The results from IMvigor130 support atezolizumab + plt/gem as an important new treatment option for patients with untreated mUC