Post hoc analysis of outcomes according to prior chemotherapy response and platinum agent in the international SAUL study of atezolizumab for urinary tract carcinoma

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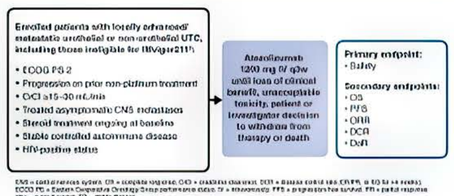
BACKGROUND

- The international single-arm prospective SAUL study (NCT02928406) evaluated the safety and efficacy of atezolizumab for platinum-pretreated locally advanced/metastatic urinary tract carcinoma (UTC).[1,2]
  - SAUL provides insight into the tolerability and effectiveness of atezolizumab in the real-world setting, enrolling a broad population of patients including understudied populations and patients with complex comorbidities.
- At the final analysis after a median follow-up of 55 months, median overall survival (OS) was 8.6 months,[2] similar to results with immunotherapy in more selected clinical trial populations.[3–5]
  - The overall response rate (ORR) to atezolizumab was 16% (95% confidence interval [CI]: 14–18%)[2]
  - The median duration of response (DoR) in responding patients was 27.8 months.[2]
- Here we report post hoc analyses exploring whether response to prior chemotherapy and type of prior platinum influenced outcomes in patients treated with atezolizumab.

PATIENTS AND METHODS

- The open-label single-arm SAUL study enrolled patients with locally advanced/metastatic urothelial or non-urothelial UTC that had progressed during or after 1–3 prior lines of therapy for advanced UTC (or within 12 months of [neo]adjuvant therapy) (Figure 1).
  - Broad eligibility criteria allowed enrolment of patients typically excluded from pivotal clinical trials of immunotherapy.
- Patients received atezolizumab until disease progression (PD) or unacceptable toxicity.
- In post hoc analyses, efficacy (ORR, DoR, OS) was assessed according to investigator-reported response to prior chemotherapy and type of prior platinum (cisplatin vs other platinum).

Figure 1. SAUL study design[1,2]



CNS = central nervous system; CR = complete response; CrCl = creatinine clearance; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; IV = intravenously; PFS = progression-free survival; PR = partial response; q3w = every 3 weeks; SD = stable disease

RESULTS

Analysis populations

- The intent-to-treat population included 1004 patients. Of these:
  - 599 (60%) had previously received at least one dose of cisplatin
  - 380 (38%) had received platinum (predominantly carboplatin) without cisplatin
  - 25 (2%) had received non-platinum agents (predominantly gemcitabine) and were excluded from the analyses according to type of prior platinum.
- Best overall response (BOR) to the previous line of chemotherapy was:
  - CR in 80 patients (8%)
  - PR in 248 patients (25%)
  - SD in 202 patients (20%)
  - PD in 320 patients (32%)
  - Missing/not evaluable (NE) in 154 patients (15%), excluded from the analyses according to response to prior chemotherapy.

Outcomes on atezolizumab

- The best outcomes on atezolizumab were seen:
  - In cisplatin-pretreated patients (Table 1 and Figure 2)
  - In patients with a CR to prior chemotherapy (Table 2 and Figure 3).
- Nevertheless, 36% of patients with PD as BOR to prior chemotherapy had a CR (3%), PR (10%) or SD (23%) on atezolizumab (Table 2 and Figure 4), irrespective of PD-L1 status (Table 3).
  - Median DoR was >2 years and the 4-year OS rate was 15% (Table 2)
  - Most of the patients responding to atezolizumab and/or with OS >4 years despite primary resistance to prior chemotherapy had ECOG performance status 0/1 and few comorbidities (Table 3)
  - Figure 5 shows an example of a patient with primary resistance to prior chemotherapy (PD as BOR) who subsequently demonstrated a CR on atezolizumab.

Figure 2. OS on atezolizumab according to type of prior platinum

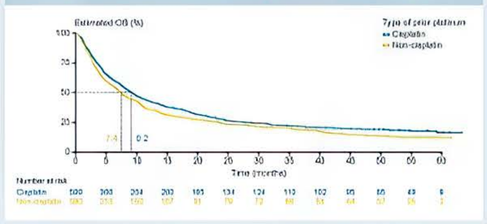


Table 1. Outcomes on atezolizumab according to type of prior platinum

Prior platinum	BOR to atezolizumab, n (%)					Median DoR, months (95% CI)	OS (95% CI)	
	CR	PR	SD	PD	NE		Median, months	4-year rate, %
All patients (n=1004)	50 (5)	108 (11)	243 (24)	396 (39)	207 (21)	27.8 (18.9–43.3)	8.6 (7.8–9.7)	17 (15–20)
Cisplatin (n=599)	35 (6)	66 (11)	140 (23)	239 (40)	119 (20)	35.2 (18.9–52.8)	9.2 (8.0–10.6)	19 (16–22)
Non-cisplatin (n=380)[a]	12 (3)	39 (10)	98 (26)	144 (38)	87 (23)	21.8 (11.0–41.9)	7.4 (6.3–8.8)	14 (10–18)

[a]377 carboplatin, 3 oxaliplatin.

Table 2. Outcomes on atezolizumab according to BOR to prior chemotherapy

BOR on prior chemotherapy	BOR to atezolizumab, n (%)					Median DoR, months (95% CI)	OS (95% CI)	
	CR	PR	SD	PD	NE		Median, months	4-year rate, %
All patients (n=1004)	50 (5)	108 (11)	243 (24)	396 (39)	207 (21)	27.8 (18.9–43.3)	8.6 (7.8–9.7)	17 (15–20)
CR (n=80)	14 (18)	13 (16)	20 (25)	23 (29)	10 (13)	48.1 (13.2–NE)	23.3 (13.5–37.4)	31 (20–42)
PR (n=248)	10 (4)	19 (8)	60 (24)	104 (42)	55 (22)	27.3 (11.8–NE)	9.1 (7.3–10.7)	16 (12–21)
SD (n=202)	6 (3)	28 (14)	53 (26)	77 (38)	38 (19)	32.5 (11.1–45.5)	10.1 (8.0–12.0)	16 (11–22)
PD (n=320)	10 (3)	32 (10)	73 (23)	135 (42)	70 (22)	25.6 (11.7–NE)	6.5 (5.5–7.9)	15 (11–19)

Response to prior chemotherapy was missing/NE in 154 patients (15%).

Figure 3. OS according to BOR to prior chemotherapy

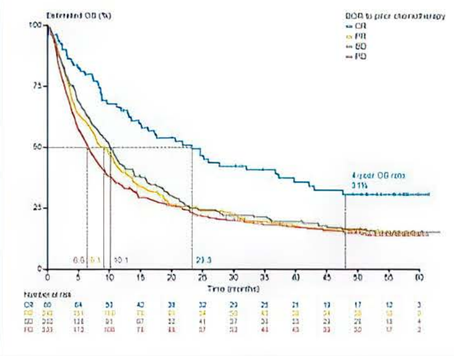


Figure 4. Response to atezolizumab according to response to prior chemotherapy

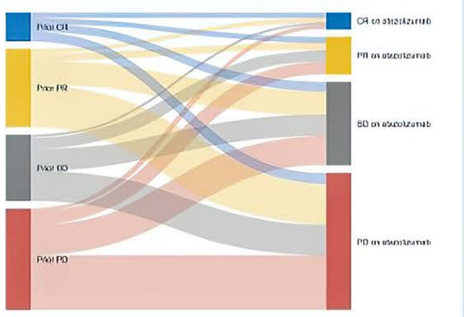


Table 3. Baseline characteristics in patients responding to atezolizumab despite PD as BOR to prior chemotherapy

Characteristic, n (%)		All treated patients (n=997)	Patients with PD as BOR to prior chemotherapy		
			CR to atezolizumab (n=10)	PR to atezolizumab (n=32)	OS >4 years with atezolizumab (n=37)
ECOG PS at screening	0	426 (43)	8 (80)	17 (53)	19 (51)
	1	471 (47)	2 (20)	14 (44)	18 (49)
	2	100 (10)	0	1 (3)	0
No. of prior treatment lines for metastatic disease*	0	360 (36)	5 (50)	13 (41)	12 (32)
	1	562 (56)	4 (40)	18 (56)	20 (54)
	2	54 (5)	1 (10)	1 (3)	4 (11)
	3	20 (2)	0	0	1 (3)
PD-L1 expression score	IC0/1	664 (67)	4 (40)	14 (44)	16 (43)
	IC2/3	264 (26)	6 (60)	16 (50)	19 (51)
	Missing	69 (7)	0	2 (6)	2 (5)
CNS metastases		14 (1)	0	0	0
CrCl <30 mL/min		46 (5)	0	2 (6)	1 (3)
History of autoimmune disease		36 (4)	0	2 (6)	0

*Missing in 1 patient in the overall population. IC0/1 = PD-L1 expression on <5% of tumour-infiltrating immune cells; IC2/3 = PD-L1 expression on ≥5% of tumour-infiltrating immune cells; PD-L1 = programmed death-ligand 1.

Figure 5. Thorax scans in a patient with a CR to atezolizumab despite PD as BOR to prior chemotherapy

CR was ongoing in November 2020, at the last scan in July 2024, the lungs remained free of disease and a small kidney nodule remained stable since the previous scan.

CONCLUSIONS

- Atezolizumab demonstrated activity irrespective of response to prior chemotherapy and type of prior platinum.
- A subset of patients progressing during prior chemotherapy (but fit enough for further therapy) experienced sustained clinical benefit with atezolizumab.
  - Patients with a CR on atezolizumab despite PD on prior chemotherapy typically had good performance status and few comorbidities.
- The main limitations of these analyses are:
  - The absence of a control group in the single-arm SAUL study or statistical methods to adjust for biases and confounding factors (preventing robust assessment of the relative impact of atezolizumab)
  - The uncertain quality of prior chemotherapy data (this analysis was not planned when the trial was initiated, thus inconsistencies and/or inaccuracies in data collection cannot be excluded)
  - Survival bias (patients who died or were too sick to receive treatment after prior chemotherapy did not enrol in SAUL, potentially skewing the results).
- Further research is needed to understand which patients may experience sustained benefit from atezolizumab despite poor response to prior chemotherapy.

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ACKNOWLEDGEMENTS & DISCLOSURES

- We thank the patients participating in the trial and their families, the investigators and staff at participating centres, the independent Data Monitoring Committee, and the study team at F. Hoffmann-La Roche Ltd.
- This study was sponsored and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.
- Medical writing support was provided by Jennifer Kelly, MA (Medi-Kelsey Ltd, Ashburne, UK), funded by F. Hoffmann-La Roche Ltd.
- Dr B Perez Valderrama reports honoraria for advisory boards from Pfizer, Astellas Pharma, BMS, Ipsen, EUSA Pharma, Merck, MSD, AstraZeneca, AAA and Recordati, invited speaker engagements for BMS, Bayer, MSD, Merck, Pfizer, Astellas Pharma, AAA and Almirall Pharma and travel/accommodation from BMS and Pfizer. For co-author disclosures, please refer to the abstract.