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Swiss experience of atezolizumab for platinum-pretreated urinary tract carcinoma: the SAUL study in real-world practice

Cathomas Richard[a], Schardt Julian[b], Pless Miklos[c], Llado Anna[d], Mach Nicolas[e], Riklin Christian[f], Haefeli Jenny[g], Fear Simon[h], Stenner Frank[i]

[a] Department of Internal Medicine, Department of Oncology and Haematology, Kantonsspital Graubünden, Chur, Switzerland
[b] University Hospital for Medical Oncology, Inselspital Bern, Switzerland
[c] Department of Medical Oncology, Kantonsspital Winterthur, Switzerland
[d] Istitut Oncologico della Svizzera Italiana, Bellinzona, Switzerland
[e] Hôpitaux Universitaires Genève, Geneva, Switzerland
[f] Department of Medical Oncology, Luzerner Kantonsspital, Luzern, Switzerland
[g] Roche (Schweiz) AG, Reinach, Switzerland
[h] F Hoffmann-La Roche Ltd, Basel, Switzerland
[i] Universitätsspital Basel, Basel, Switzerland

Summary

AIMS OF THE STUDY: Atezolizumab is an approved therapy for urothelial carcinoma based on results from the IMvigor 210 and IMvigor211 phase II and III trials. The global SAUL study evaluated atezolizumab in a broader patient population more representative of real-world populations. Among approximately 1000 patients treated in SAUL, 25 were treated in Swiss oncology centres. We evaluated outcomes in these patients to provide a better understanding of atezolizumab treatment for urinary tract carcinoma in Swiss clinical practice.

METHODS: Eligible patients had locally advanced or metastatic urothelial or non-urothelial urinary tract carcinoma that had progressed during or after one to three prior therapies for inoperable, locally advanced or metastatic disease. Patient populations typically excluded from clinical trials (e.g., patients with renal impairment, treated central nervous system [CNS] metastases, stable controlled autoimmune disease or Eastern Cooperative Oncology Group performance status 2) were also eligible. All patients received atezolizumab 1200 mg every 3 weeks until loss of clinical benefit or unacceptable toxicity. The primary endpoint was safety. Secondary endpoints included overall survival (OS), overall response rate (ORR) and disease control rate (DCR).

RESULTS: All 25 Swiss patients had previously received a gemcitabine/platinum doublet. Disease had progressed within 12 months of platinum-based therapy in all but one patient, and 19 (76%) had received one prior line of therapy for metastatic disease. The median duration of atezolizumab therapy was six cycles (range 1–27) corresponding to 3.6 months. Five patients (20%) had received >20 cycles and four (16%) remained on treatment at the data cut-off. Grade 3 adverse events (AEs) occurred in 13 patients (52%) and were considered to be treatment-related in four patients (16%; liver enzyme increases, musculoskeletal pain, diverticulitis and autoimmune hepatitis). There was one grade 4 AE (hypercalcaemia) and no grade 5 AEs. After median follow-up of 17.3 months, median OS was 7.9 months (95% confidence interval [CI] 5.3–not evaluable), the 1-year OS rate was 47% (95% CI 27–65%), the ORR was 12% (95% CI 3–31%) and the DCR was 40% (95% CI 21–61%). Durable clinical benefit (>1 year on treatment) was observed in seven patients (28%), including one with CNS metastases and one with small-cell carcinoma.

CONCLUSIONS: Atezolizumab is an active treatment option for platinum-pretreated urinary tract carcinoma, including patients with conditions that typically exclude them from clinical trials. (Trial registration no.: NCT02928406)

Keywords: *atezolizumab, urinary tract carcinoma, PD-L1, immunotherapy, Switzerland*

Data sharing statement
Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Correspondence:
Dr Richard Cathomas, PD MD, Kantonsspital Graubünden, Departement Innere Medizin, Abteilung Onkologie und Hämatologie, Loestrasse 170, CH-7000 Chur, Richard.Cathomas[at]ks-gr.ch

Introduction

Platinum-based chemotherapy has been the standard treatment for metastatic urothelial cancer for many years. Response rates to platinum-based treatment are fairly good, but lasting responses are rare [1]. However, treatment options have expanded rapidly in recent years with the introduction of immunotherapeutic agents into clinical practice [2]. There are now five agents targeting programmed cell death ligand 1 (PD-L1) or programmed cell death-1 (PD-1) that are approved as treatment for urothelial carcinoma after progression on platinum-based chemotherapy: avelumab, atezolizumab, durvalumab, nivolumab and pembrolizumab [3]. Atezolizumab, the first of these agents to be approved, is a humanised monoclonal antibody that

binds selectively to PD-L1. Regulatory approval of atezolizumab as second-line treatment for metastatic urothelial carcinoma was based on results from the IMvigor210 and IMvigor211 trials [4–6]. In the IMvigor211 phase III trial, median overall survival (OS) was 8.7 months and the overall response rate was 13% [6]. The subsequent single-arm SAUL study (Clinicaltrials.gov NCT02928406) evaluated atezolizumab in a broader patient population (predominantly platinum pretreated) with the aim of improving understanding of the safety and efficacy of atezolizumab in understudied populations typically excluded from trials designed with regulatory intent. This multinational study enrolled patients from 32 countries across Europe, Asia, South America, Australia and Canada. Median OS in the overall population of SAUL was 8.7 months (95% confidence interval [CI] 7.8–9.9 months). In the subgroup of 643 patients considered to be 'IMvigor211-like' (i.e., excluding special populations of patients that were ineligible for IMvigor211, such as those with Eastern Cooperative Oncology Group [ECOG] performance status 2, autoimmune disease, non-urothelial histology, etc.), median OS was 10.0 months (95% CI 8.8–11.9 months).

These results provide a robust and reassuring indication of treatment outcomes in atezolizumab-treated patients presenting in everyday practice across a wide range of healthcare systems with varying treatment practices. However, there is considerable variation in medical care between geographical regions and clinical outcomes may differ substantially between different healthcare systems with different guidelines and practices. Every year in Switzerland, approximately 1100 patients are diagnosed with invasive bladder cancer and more than 500 die from this disease [7]. Data are limited on clinical outcomes in patients receiving systemic therapy for metastatic urinary tract carcinoma in Swiss clinical practice. Therefore, we interrogated the SAUL dataset with the aim of understanding outcomes in patients treated with atezolizumab for urinary tract carcinoma in the Swiss healthcare setting, and compared these results with findings in the global population treated in the SAUL study.

Materials and methods

The design of the SAUL study has been described in detail previously [8]. In summary, eligible patients had locally advanced or metastatic measurable and/or non-measurable urothelial or non-urothelial urinary tract carcinoma, ECOG performance status ≤2 and had experienced disease progression during or following one prior platinum- or non-platinum-based treatment for inoperable, locally advanced or metastatic disease (subsequently amended in May 2017 to allow up to three prior platinum- or non-platinum-based treatments for inoperable, locally advanced or metastatic disease). Patients whose disease relapsed within 12 months of (neo)adjuvant treatment were also eligible, as were patients with treated asymptomatic central nervous system (CNS) metastases, ongoing steroid treatment at baseline, stable controlled autoimmune disease or renal impairment (creatinine clearance ≥15 ml/min). Patients received atezolizumab 1200 mg intravenously every 3 weeks until investigator-assessed loss of clinical benefit, unacceptable toxicity, patient or investigator decision to discontinue therapy or death, whichever occurred first. Patients were allowed to continue atezolizumab after meeting Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria for disease progression, providing all of the following criteria were met: evidence of clinical benefit (defined as the stabilisation or improvement of disease-related symptoms) as assessed by the investigator; absence of symptoms and signs (including worsening of laboratory values) indicating unequivocal progression of disease; no decline in ECOG performance status that could be attributed to disease progression; and absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that could not be readily managed and stabilised by protocol-allowed medical interventions before repeat dosing.

The primary endpoint was safety, defined as the nature, severity, duration, frequency and timing of adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Secondary endpoints included OS, investigator-assessed progression-free survival (PFS) (per RECIST version 1.1), overall response rate (per RECIST version 1.1), disease control rate (defined as the sum of patients achieving a complete or partial response, or stable disease for ≥4 weeks), and duration of response.

Ethical approval for the study (ID 2016-01933) was obtained from the Cantonal Ethics Commission (KEK) in Bern, the Ethics Commission Northwest and Central Switzerland (EKNZ) in Basel, the Commission Cantonale d'Ethique de la Recherche sur l'être humain (CCER) in Geneva, the Comitato Etico Cantonale (CE-TI) in Ticino and the Cantonal Ethics Commission Zurich (CEC) in Zurich.

Results

Among 997 patients treated in the global SAUL study, 25 patients were treated in one of seven Swiss oncology centres (Kantonsspital Graubünden [Chur], Inselspital Bern, Istituto Oncologico della Svizzera Italiana [Bellinzona], Kantonsspital Winterthur, Universitätsspital Basel, Luzerner Kantonsspital and Hôpitaux Universitaires Genève). The enrolment period for the overall study population was 30 November 2016 to 16 March 2018; patients in the Swiss subgroup were enrolled between 6 February 2017 and 30 October 2017.

Baseline characteristics of the Swiss subgroup are shown alongside the global population in table 1. The Swiss subgroup was slightly older than the global population in terms of both median age (70 vs 68 years, respectively) and the proportion aged ≥70 years (56% vs 23%, respectively).

In the Swiss population, 16 patients (64%) were considered to be 'IMvigor211-like', eight patients (32%) represented populations typically excluded from clinical trials but of particular interest in the SAUL study, and the remaining patient had not experienced disease progression on or within 12 months of platinum-based therapy. All three patients with non-urothelial histology (non-IMvigor211-like) had small-cell carcinoma.

The majority of patients (76%) received atezolizumab as second-line therapy, with the remainder treated following only neoadjuvant or adjuvant chemotherapy (counted as 0 prior lines for the purposes of eligibility). Although pa-

tients treated in later lines were eligible for enrolment in SAUL after protocol amendment 4 in May 2017, recruitment in Switzerland was almost complete by this time. All 25 patients had previously received gemcitabine/platinum combinations (16 patients [64%] with carboplatin; nine [36%] with cisplatin). Additionally, three patients (12%) had received etoposide during their prior treatment.

Eight patients (32%) had never smoked (5/16 men [31%] and 3/9 women [33%]), 10 (40%) were former smokers (seven men [44%], three women [33%]) and seven (28%) were current smokers (four men [25%] and three women [33%]). The mean duration of smoking was 33 years (38 [range 15–60] years in men and 24 [range 5–47] years in women).

Treatment exposure

The median duration of follow-up at the data cut-off (16 September 2018) was 17.3 months (95% CI 15.4–18.1 months) in the Swiss subgroup. At this time, four patients (16%) in the Swiss subgroup remained on treatment (fig. 1). Among the 21 patients who had discontinued atezolizumab, the large majority (n = 16, 64% of all 25 patients) stopped treatment because of disease progression. Two patients (8%) discontinued because of adverse events, two (8%) at the patient's request and one (4%) on the decision of the treating physician after resection of residual disease on atezolizumab and complete response.

In the Swiss subgroup, patients had received a median of six cycles (range 1–27), corresponding to 3.6 months (range 0–17.9 months) at the time of the data cut-off. Five patients (20%) received >20 cycles.

Safety

An overview of safety results in the Swiss subgroup is provided in table 2, together with results from the global population and the subgroups corresponding to the 'IMvigor211-like' population. In the Swiss subgroup, there were no grade 5 (fatal) adverse events, one patient experienced a grade 4 adverse event (hypercalcaemia) and 13 patients (52%) experienced grade 3 adverse events (four cases of

Table 1: Baseline characteristics in the Swiss subgroup and the global population [3, 8, 9].

Characteristic		Swiss subgroup (n = 25)	Global population (n = 997)
Median age, years (range)		70 (43–81)	68 (34–93)
Age category, n (%)	≥65 years	22 (88)	620 (62)
	≥70 years	14 (56)	227 (23)
	≥75 years	7 (28)	NR
	≥80 years	1 (4)	78 (8)
Male, n (%)		16 (64)	772 (77)
Smoking history, n (%)	Current	7 (28)	167 (17)
	Former	10 (40)	503 (50)
	Never	8 (32)	327 (33)
PD-L1 expression score, n (%)*	IC 0	6 (24)	243 (24)
	IC 1	11 (44)	421 (42)
	IC 2/3	8 (32)	264 (26)
	Missing	0	69 (7)
Disease location†, n (%)	Bladder	19 (76)	744 (75)
	Renal pelvis	5 (20)	122 (12)
	Ureter	1 (4)	97 (10)
	Urethra	0	10 (1)
Stage IV at diagnosis, n (%)		17 (68)	488 (49)
Prior systemic anti-cancer therapy‡, n (%)	Total	25 (100)	NR
	Neoadjuvant	3 (12)	NR
	Adjuvant	5 (20)	NR
	Palliative	19 (76)	NR
Number of prior lines for metastatic disease§, n (%)	0	6 (24)	382 (38)
	1	19 (76)	543 (54)
	2	0	52 (5)
	3	0	20 (2)
ECOG performance status at screening, n (%)	0	13 (52)	427 (43)
	1	11 (44)	469 (47)
	2	1 (4)	101 (10)
Non-urothelial or mixed histology‖		3 (12)	47 (5)
Renal impairment (GFR <30 ml/min)		2 (8)	46 (5)
History of autoimmune disease		1 (4)	35 (4)
CNS metastases		1 (4)	14 (1)
Ongoing steroid use at baseline		0	40 (4)
HIV positive		0	2 (<1)

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; GFR = glomerular filtration rate; HIV = human immunodeficiency virus; NR = not reported; PD-L1 = programmed cell death ligand 1 * PD-L1 expression was tested using the Ventana SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ, USA). IC 0 = PD-L1 expression on <1% of tumour-infiltrating immune cells; IC 1 = PD-L1 expression on ≥1% but <5% of tumour-infiltrating immune cells; IC 2/3 = PD-L1 expression on ≥5% of tumour-infiltrating immune cells. † Reported as 'other' in 24 patients (2%) of the global population. ‡ Multiple entries possible. § Patients whose disease relapsed within 12 months of (neo)adjuvant treatment were counted (for the purposes of eligibility) as having received first-line treatment for metastatic disease. || All three patients (12%) in the Swiss subgroup and seven (1%) in the global population had neuroendocrine tumours.

urinary tract infection, two cases each of fatigue, lung infection, groin pain, musculoskeletal pain, alanine aminotransferase [ALT] increase and aspartate aminotransferase [AST] increase, and one case each of autoimmune hepatitis, asthenia, nausea, abdominal pain, oedema, cellulitis, diverticulitis, pyelonephritis, bacterial urinary tract infection, urosepsis, decreased appetite, hyponatraemia, dyspnoea, renal failure, anaemia, *Escherichia coli* infection and traumatic haemothorax). Grade 3 adverse events were considered by the local investigator to be related to atezolizumab treatment in only four patients. The treatment-related grade 3 adverse events comprised two cases of ALT and AST increase (also associated with diverticulitis in one patient), one case of autoimmune hepatitis and one of musculoskeletal pain. Three patients experienced grade 3 adverse events of special interest for atezolizumab (two cases each of ALT increase and AST increase, one case of autoimmune hepatitis). Adverse events that led to atezolizumab treatment discontinuation were ALT increase in one patient and pneumonitis in one patient.

Efficacy

At the data cut-off date, 15 patients (60%) had died, all from disease progression (with unknown other cause cited as the primary cause of death in two patients who died >30 days after the last dose of atezolizumab). Figure 1 provides details of response over time for each patient together with information on relevant baseline characteristics. Figure 2 shows OS for the Swiss subgroup (median 7.9 months, 95% CI 5.3 months – not evaluable) and the global population (median 8.7 months, 95% CI 7.8–9.9 months). In the subgroup of 16 'IMvigor211-like' Swiss patients, median OS was 18.0 months (95% CI 6.1 months – not evaluable), with treatment ongoing in three of these patients. In the subgroup of 17 patients with a PD-L1 score of IC 0/1 (PD-L1 expression on <5% of tumour-infiltrating immune cells), median OS was 7.8 months (95% CI 2.8–18.0 months); median OS could not be estimated in the eight patients with a PD-L1 immune score of IC 2/3 (PD-L1 expression on ≥5% of tumour-infiltrating immune cells).

Among the three patients with small-cell carcinoma, one patient had a best response of stable disease, PFS of 11.9 months and OS of 13.8 months, one patient died after 1.6 months (before tumour assessment), and the remaining pa-

Figure 1: Swimmer plot of treatment duration, response and clinical outcome. The upper 16 patients represent the IMvigor211-like population. The lower eight patients represent those subgroups excluded from IMvigor211. The remaining patient did not have comorbidities or characteristics excluding them from IMvigor211 but had a treatment history atypical of that trial.CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed cell death ligand 1. IC 0/1 = PD-L1 expression on <5% of tumour-infiltrating immune cells; IC 2/3 = PD-L1 expression on ≥5% of tumour-infiltrating immune cells.

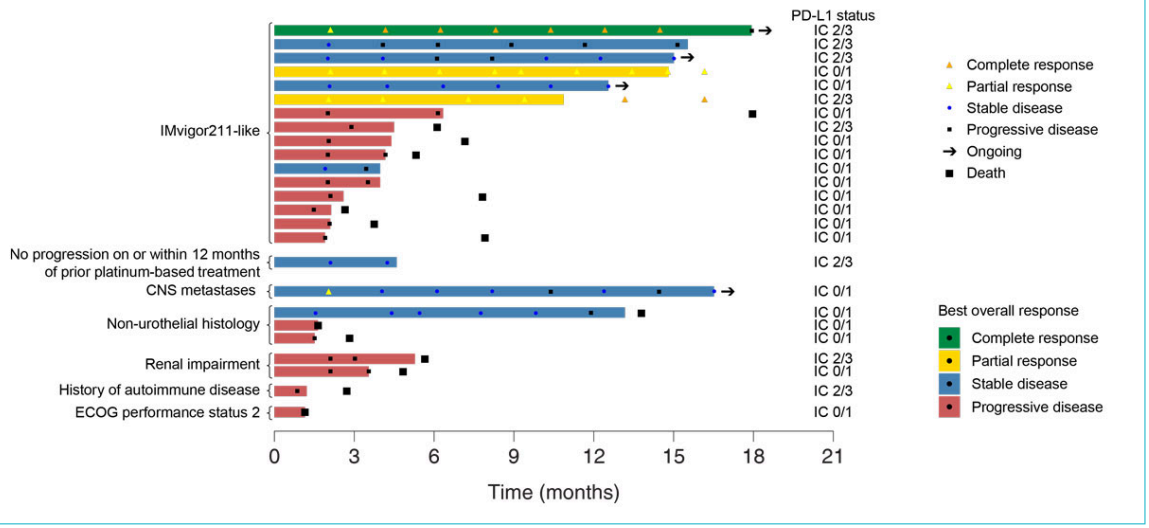

Table 2: Overview of safety by population.

AE, n (%)	Swiss subgroup (n = 25)	Global population (n = 997)	Swiss IMvigor211-like subgroup (n = 16)	Global IMvigor211-like* subgroup (n = 643)
Any grade AE	24 (96)	880 (88)	15 (94)	577 (90)
– Grade 3/4	14 (56)	431 (43)	7 (44)	261 (41)
– Grade 5	0	37 (4)	0	20 (3)
Treatment-related AE	19 (76)	530 (53)	12 (75)	355 (55)
– Grade ≥3	4 (16)	127 (13)	2 (13)	81 (13)
Serious AE	9 (36)	327 (33)	5 (31)	200 (31)
AESI	14 (56)	305 (31)	11 (69)	201 (31)
– Grade ≥3	3 (12)	67 (7)	2 (13)	46 (7)
AE leading to treatment discontinuation	2 (8)	57 (6)	2 (13)	37 (6)
Median treatment duration, months (range)	3.6 (0–17.9)	2.8 (0–19)	3.7 (0.8–17.9)	3.5 (NR)

AE = adverse event; AESI = adverse event of special interest; NR = not reported * All patients except those in subgroups excluded from the IMvigor211 phase III trial

tient had disease progression as best response, PFS of 1.5 months and OS of 2.8 months.

Table 3 summarises all efficacy parameters, showing the Swiss subgroup, the global population and the IMvigor211-like subgroup within both populations. Median PFS in the Swiss subgroup after events in 21 patients (84%) was 2.1 months (95% CI 2.0–4.1 months). The 6-month PFS rate was 31% (95% CI 14–50%) and the 12-month PFS rate was 18% (95% CI 6–35%). Duration of treatment (median 3.6 months, mean 6.4 months) can be considered as an alternative measure of duration of clinical benefit because all patients continued treatment until loss of clinical benefit.

Post-progression treatment

Among the 19 patients in the Swiss subgroup in whom disease progression had been recorded at the time of data cut-off, 11 (58%) received at least one cycle of atezolizumab after RECIST-defined disease progression. Four of these patients received at least five cycles of atezolizumab, and two of them were still receiving atezolizumab at the data cut-off date.

Discussion

These are, to our knowledge, the first prospective data from a Swiss population of patients treated with an immune checkpoint inhibitor for platinum-pretreated urinary tract carcinoma. In all of the patients, disease had progressed on or after gemcitabine/platinum-containing therapy, representing a situation frequently encountered in clinical practice that remains challenging to manage. These data also provide information on outcomes in individual patients with difficult-to-treat disease, such as CNS metastases and neuroendocrine tumours (small-cell carcinoma). SAUL was designed to gain deeper insight into the safety of atezolizumab in metastatic urinary tract carcinoma and its role in special populations, rather than to compare different treatment options.

Findings among the 25 Swiss patients treated in the SAUL study are generally consistent with results in the overall population. Baseline characteristics in the Swiss subgroup were similar to those in the global population, except for slightly older age and a notable proportion of patients (12%) with small-cell carcinoma. The safety profile was consistent with the established safety profile of atezolizumab in urothelial cancer, with a low incidence of treatment-related grade ≥3 adverse events (including liver

Figure 2: Overall survival (Swiss subgroup and global population).CI = confidence interval; NE = not evaluable; OS = overall survival.

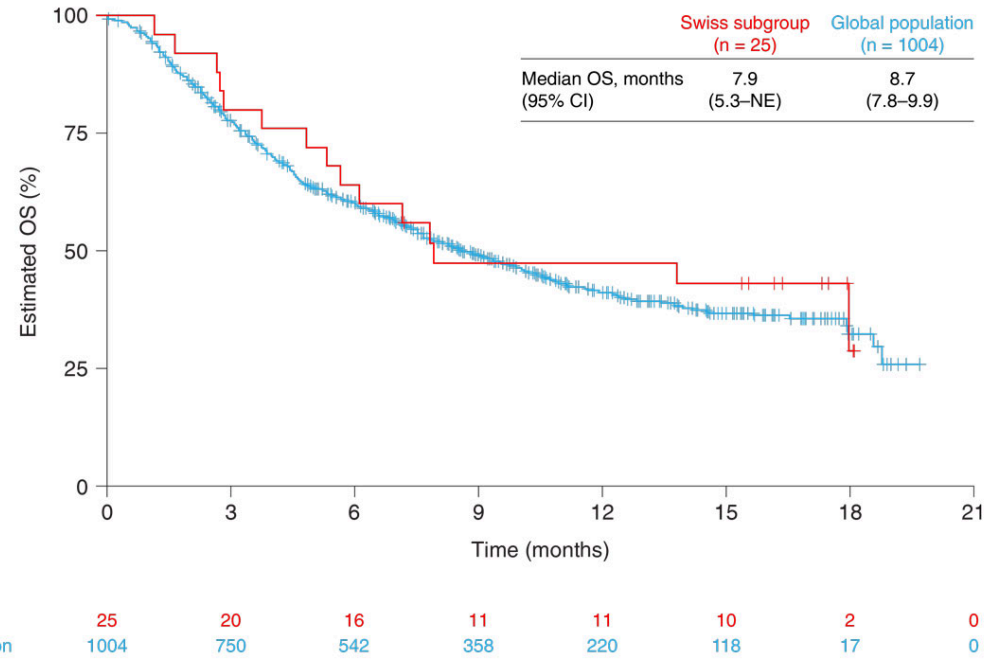

Table 3: Summary of efficacy in the Swiss subgroup and global population.

Endpoint	Swiss subgroup (n = 25)	Global population (n = 1004)	Swiss IMvigor211-like* subgroup (n = 16)	Global population IMvigor211-like* subgroup (n = 643)
Median OS, months (95% CI)	7.9 (5.3–NE)	8.7 (7.8–9.9)	18.0 (6.1–NE)	10.0 (8.8–11.9)
6-month OS rate, % (95% CI)	64 (42–79)	60 (57–63)	81 (52–94)	65 (61–69)
1-year OS rate, % (95% CI)	47 (27–65)	41 (38–44)	56 (30–76)	46 (41–50)
Median PFS, months (95% CI)	2.1 (2.0–4.1)	2.2 (2.1–2.4)	2.5 (2.0–6.1)	2.3 (2.2–2.6)
Overall response, n (%) [95% CI]	3 (12) [3–31]	135 (13) [11–16]	3 (19) [4–46]	88 (14) [11–17]
Complete response, n (%)	1 (4)	29 (3)	1 (6)	23 (4)
Disease control rate, % (95% CI)	40 (21–61)	40 (37–43)	44 (20–70)	41 (37–45)

CI = confidence interval; NE = not evaluable; OS = overall survival; PFS = progression-free survival * All patients except those in subgroups excluded from the IMvigor211 phase III trial

enzyme elevations and one case of autoimmune hepatitis). Median OS in the Swiss subgroup was in the same range as in the global population. Median OS in the Swiss IMvigor211-like subgroup was a remarkable 18.0 months, although these results should be interpreted with particular caution given the very small sample size (n = 16). The response rate in the Swiss subgroup was 12%, consistent with the 13% rate in the global population, and in 60% of patients the best response was disease progression, highlighting the need for better patient selection or development of better therapeutic approaches (e.g., atezolizumab plus chemotherapy or novel/alternative immunotherapeutic agents). However, 20% of patients remained on treatment for >20 cycles. Furthermore, as shown in fig. 1, sustained clinical benefit was observed in several patients whose best response was stable disease, including one patient with CNS metastases and one with small-cell carcinoma. Interestingly, several patients continued atezolizumab beyond progression. Post-hoc analyses from the IMvigor210 study suggest prolonged clinical benefit from this approach [10], although this strategy has not been evaluated in a randomised trial.

Although the median OS of 18.0 months in the IMvigor211-like patients within the SAUL population is impressive, it contrasts markedly with outcomes in some of the non-IMvigor211-like patients typically excluded from clinical trials. As in the global population, the patient with ECOG performance status 2 had a very poor outcome, reflecting clinical experience and highlighting the unmet medical needs of these patients. On the other hand, the patient with CNS metastases appeared to achieve sustained disease control. Greater insight into outcomes in special populations can be gained from analyses of the global population focusing on patients with autoimmune disease [11] or upper tract carcinoma [12], and elderly patients [9].

The present analysis reports outcomes of a defined group of patients from a homogeneous health insurance system. We hypothesised that the impact of equal access to Swiss health resources would be of interest in comparison to the full cohort of patients recruited worldwide in the SAUL study. The remarkably long median OS in the IMvigor211-like patients enrolled in Switzerland may reflect the intensified specialist palliative care in the participating Swiss centres compared with some of the global centres enrolling into the SAUL study. Non-Swiss patients were enrolled from centres in Italy, Spain, Australia, Germany, Greece, the UK, the Netherlands, Hungary, Brazil, Belgium, Denmark, Romania, Poland, Austria, Canada, Ireland, Portugal, Croatia, India, Lithuania, the Czech Republic, Russia, Slovakia, Argentina, Colombia, Taiwan, Lebanon, Saudi Arabia, China, Bulgaria and Estonia. With such diversity, the likelihood of differences between countries in post-study care is high, but bias in patient selection may also contribute, with some countries favouring enrolment of patients in 'special populations' for whom there are no other options, and others treating patients who would have been eligible for typical clinical trials but do not have access to atezolizumab in their healthcare systems. Outcomes in the subgroup of patients treated in the UK have been presented [13]; others may be reported, although unlikely from countries enrolling very small numbers of patients.

The relatively early enrolment of the Swiss patients compared with the rest of the population may also contribute to slight differences in OS, not only because of the longer median follow-up but also because of the increased opportunity for further lines of therapy, which may influence OS. On the other hand, with such small patient numbers and overlapping CIs, we should not overinterpret any numerical differences that may arise by chance. The protocol did not specify particular treatments after progression and therefore post-study treatment may reflect differences in standard of care between countries. Further insight may emerge at the final analysis, expected 4 years after enrolment of the last patient in the global population.

To date, efforts to identify those patients most likely to derive long-term benefit from atezolizumab – or from checkpoint inhibitors more generally – have unfortunately been largely unsuccessful. PD-L1 status appears to be important: in SAUL, patients with a PD-L1 immunohistochemistry score of IC 2/3 showed longer OS (median 11.6 months) than those with a score of IC 0/1 (median 7.9 months) [9], although in a single-arm study, prognostic and predictive effects cannot be differentiated. In the IMvigor211 trial, median OS was longer in the PD-L1 IC 2/3 subgroup than in the intention-to-treat population in both the atezolizumab arm and the chemotherapy arm [6]. The very small sample size and low event rate in the present Swiss subgroup analysis prevent meaningful interpretation of outcome according to PD-L1 status. It is critical to continue efforts to identify robust and reliable biomarkers for immunotherapeutic agents, not only to identify patients most suited to treatment, but also to spare those unlikely to respond from ineffective treatment.

In conclusion, atezolizumab is an active treatment option for platinum-pretreated patients with metastatic urothelial carcinoma in Switzerland, even in difficult-to-treat scenarios such as CNS metastases. Experience from this real-world population is consistent with results from controlled clinical trials in more selected populations. On the basis of our present knowledge, it is reasonable to offer second-line atezolizumab to all patients with metastatic urothelial carcinoma whose disease relapses after first-line platinum-based chemotherapy. In Switzerland, alternative registered options (not available at the time of the SAUL study) now include pembrolizumab, atezolizumab and nivolumab, as well as re-exposure to platinum/gemcitabine if patients were responding and had PFS of ≥6 months after initial therapy with these agents. Further options include vinflunine and taxanes, but these are proven to be inferior to immunotherapy. Median OS with vinflunine was 6.9 months in the phase III trial versus best supportive care [14]. No head-to-head trial has compared the different immunotherapy options. The SAUL study and also the Swiss cohort of SAUL suggest that all subgroups of patients can derive clinical benefit from atezolizumab, regardless of pre-existing adverse clinical features that often tend to bias our routine treatment selection. Inclusion of populations typically excluded from clinical trials and for whom there are little or no data in the literature provides important new information on the role of atezolizumab in clinical practice.

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Potential competing interests

RC has served on advisory boards for Roche, MSD, Bristol-Myers Squibb, Janssen, Astellas, Amgen, Pfizer, Novartis, Bayer and AstraZeneca, and has received speaker honoraria from Debiopharm, Bristol-Myers Squibb, Astellas and Janssen. JS has served on advisory boards for Roche, MSD, Bristol-Myers Squibb, Astellas, Pfizer, Novartis, Bayer and AstraZeneca, has received speaker honoraria from Bristol-Myers Squibb and has received research funding from AstraZeneca. MP has served on advisory Boards for AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, Eisei, MSD, Novartis, Pfizer, Roche, Takeda and Merck, received travel grants from AstraZeneca, BMS, Boehringer Ingelheim, Roche, Takeda and Vifor, and speakers fee from Janssen. NM has served on advisory boards for Amgen, AstraZeneca, Bristol-Myers Squibb, Merck, and MSD. JH is an employee of Roche Pharma (Schweiz) AG, Basel, Switzerland, and holds shares in Roche. SF is employed by Hayes (Schweiz) AG on behalf of F Hoffmann-La Roche, Switzerland. FS has received an honorarium from Roche for an advisory board and travel. AL and CR have nothing to disclose.

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