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Primary results from SAUL, a prospective multinational single-arm study of atezolizumab for locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract

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Conflict of Interest Disclosure

I have the following potential conflicts of interest to report:

- Consultancy fees/speaker honoraria from Amgen, Merck Sharp & Dohme, Clovis, Bristol-Myers Squibb, Astellas, Pfizer, Sanofi, Roche and AstraZeneca

Background

- Atezolizumab, a humanised monoclonal antibody, targets PD-L1, inhibiting its interaction with PD-1 receptors
  - Atezolizumab also blocks binding of PD-L1 to B7.1 (CD80)[1]
- Atezolizumab is approved as monotherapy for patients with locally advanced or metastatic UC[2,3]
  - After prior platinum-containing chemotherapy, or
  - Considered cisplatin ineligible and PD-L1 positive[a]
  - Ineligible for any platinum, irrespective of PD-L1 status (US only)

[a]Tumours with PD-L1 expression ≥5%. PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand 1; UC = urothelial carcinoma. [1]Butte et al. Immunity 2007; [2]EMA Tecentriq Summary of Product Characteristics; [3]FDA Tecentriq Prescribing Information

SAUL: Rationale and study design

NCT02928406

SAUL enrolled a broader patient population with pretreated locally advanced/metastatic urinary tract carcinoma, including patients with

- Non-measurable disease
- ECOG PS 0–2
- Progression on prior non-platinum treatment
- Creatinine clearance ≥15 mL/min
- Stable CNS metastases
- Steroid treatment ongoing at baseline[a]
- Autoimmune disease
- HIV positive status
- Requirement for renal dialysis

→ **Atezolizumab 1200 mg IV q3w until loss of clinical benefit, unacceptable toxicity, patient or investigator decision to withdraw from therapy or death**

Primary endpoint:

- Safety

Secondary endpoints:

- Overall survival
- Progression-free survival
- Overall response rate
- Disease control rate
- Duration of response

Between 30 Nov 2016 and 16 March 2018, 1004 patients were enrolled (997 treated) from sites in 32 countries worldwide

[a]Stable dose (for the preceding 12 weeks) and controlled autoimmune disease, or inhaled corticosteroids for COPD, or mineralocorticoids for orthostatic hypotension, or low-dose supplemental corticosteroids for adrenocortical insufficiency, or topical steroids for cutaneous

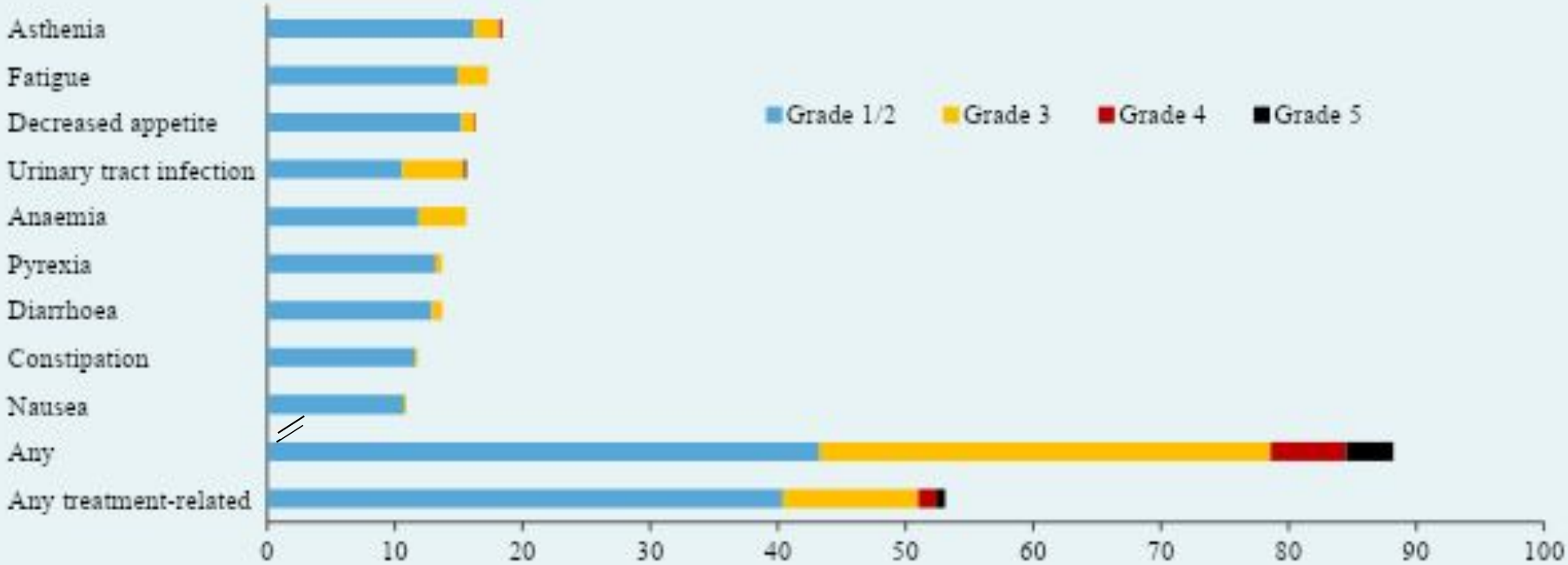
Baseline characteristics (n=997[a])

Characteristic	
Median age, years (range)	68 (34–93)
Aged ≥80 years, n (%)	91 (9)
Male, n (%)	772 (77)
ECOG PS, n (%)	
0	427 (43)
1	469 (47)
2	101 (10)
Stage IV at initial diagnosis, n (%)	772 (77)
Prior lines for metastatic disease, n (%)	
0	382 (38)
1	543 (54)
2	52 (5)
3	20 (2)
Prior platinum, n (%)	975 (98)
PD-L1 IC 2/3, n (%[b])	264 (28)

Characteristic, n (%)	
Histological type	
Urothelial	950 (95)
Squamous cell carcinoma	18 (2)
Glandular	8 (1)
Bellini collecting duct	8 (1)
Neuroendocrine	7 (1)
Location[c]	
Bladder	744 (75)
Renal pelvis	122 (12)
Ureter	97 (10)
Urethra	10 (1)
CNS metastases	14 (1)
Renal impairment (<30 mL/min)	46 (5)
Ongoing steroid use at baseline	40 (4)
History of autoimmune disease	35 (4)
HIV positive	2 (0.2)
Renal dialysis	0

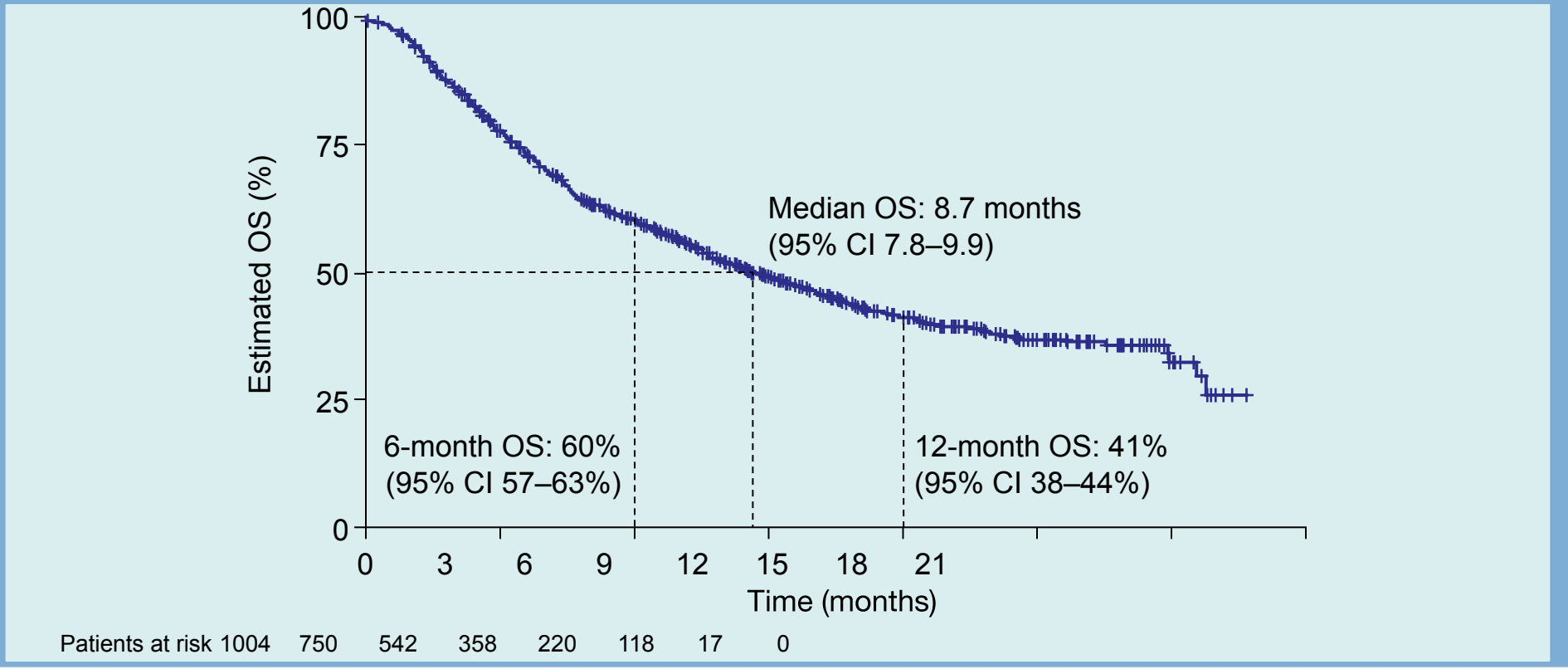
[a]7 patients enrolled but not treated; [b]Denominator = 928 patients with known PD-L1 status; [c]Other in 24 (2%)

Most common adverse events (>10%) by grade



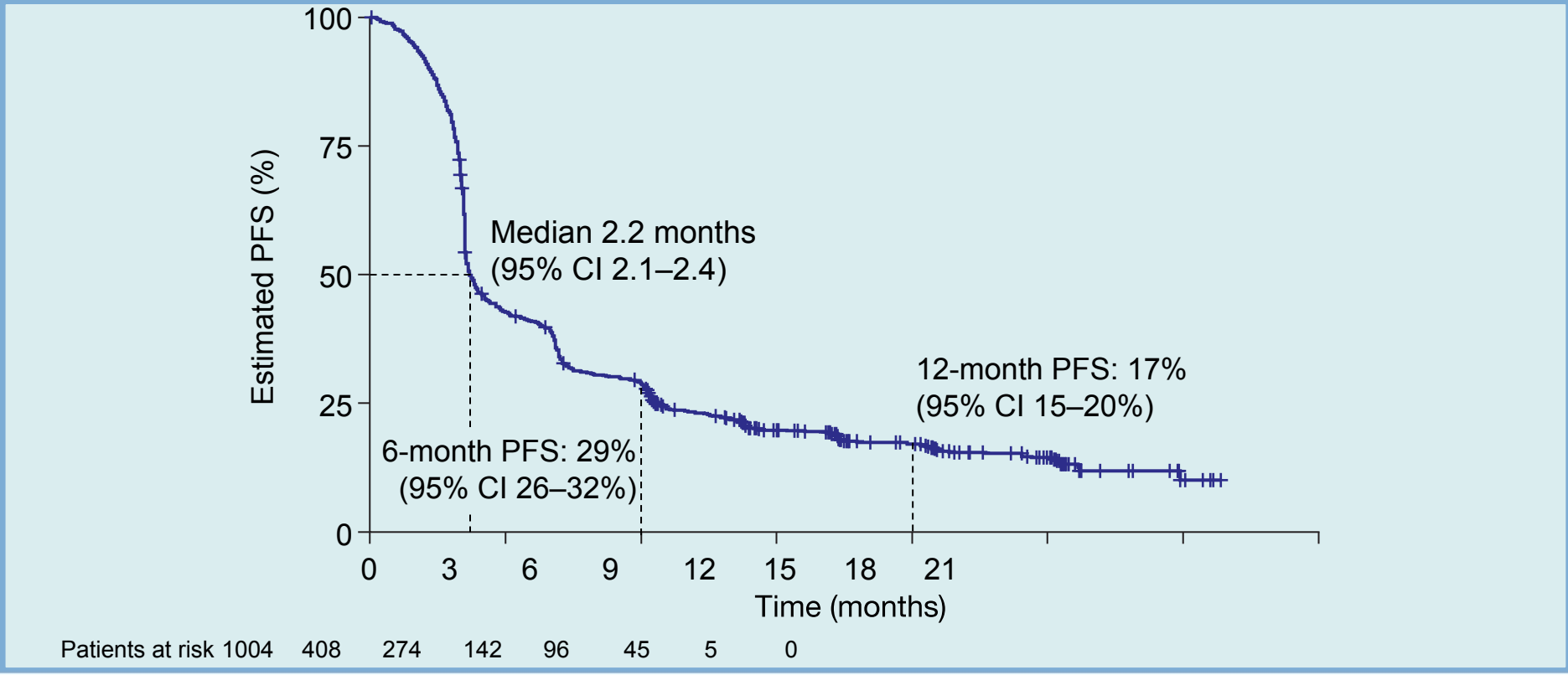
Median no. of cycles: 5 (range 1–28). Median treatment duration: 2.8 months (range 0–19 months)
Treatment-related grade 5 AEs (n=7, 0.7%): two cases of dyspnoea, one case each of colitis, intestinal perforation, respiratory failure, chronic kidney disease, drug-induced liver injury.
Most common treatment-related grade >2 AEs: fatigue, asthenia, colitis, hypertension (each 1%)

Overall survival (ITT population, n=1004)[a]



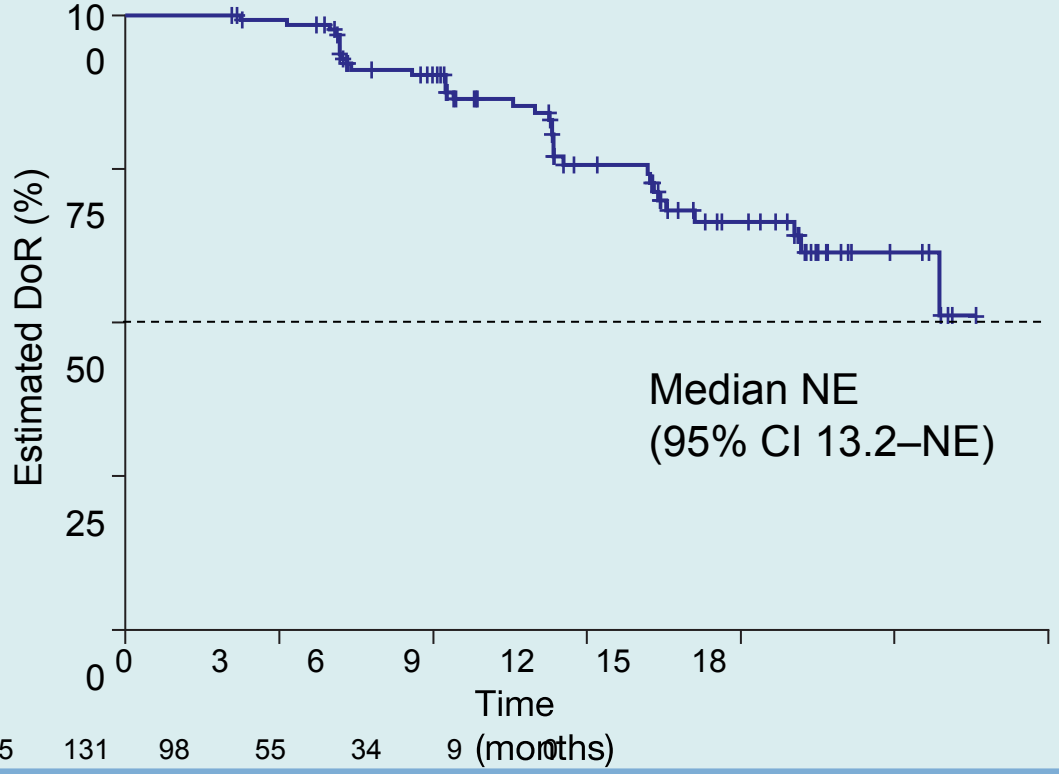
[a]Data cut-off for the protocol-specified primary analysis was 16 Sep 2018 (median follow-up: 12.7 months)

Progression-free survival (ITT population, n=1004)



Response rate (ITT population) and duration of response[a]

Best response, % (95% CI)	(n=1004)
ORR	13.4 (11.4–15.7)
Complete response	2.9 (1.9–4.1)
Partial response	10.6 (8.7–12.6)
Stable disease	26.2 (23.5–29.0)
Disease control rate[b]	39.6 (36.6–42.7)



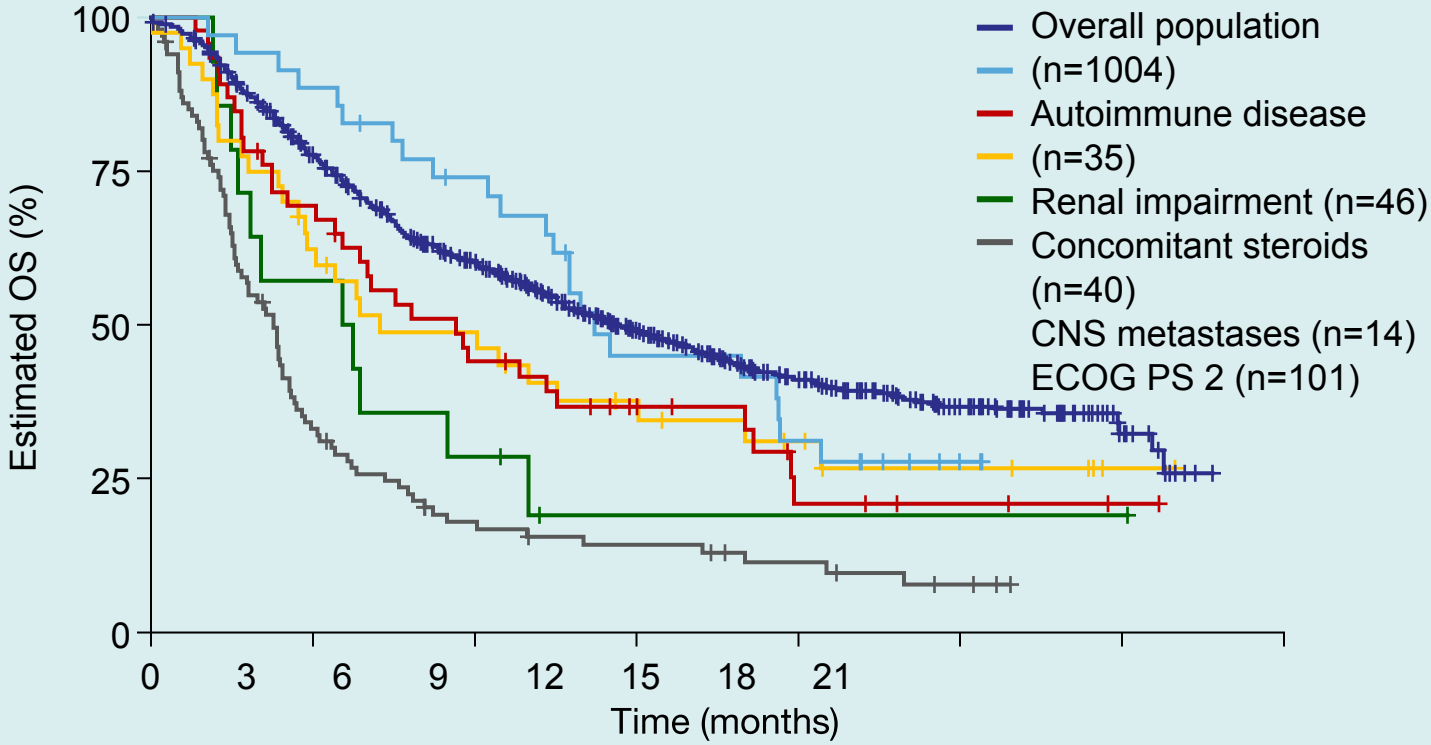
[a]RECIST v1.1. [b]Complete or partial response or stable disease for ≥4 weeks
ORR = overall response rate; DoR = duration of response; NE = not estimable

Safety overview in subgroups of special interest

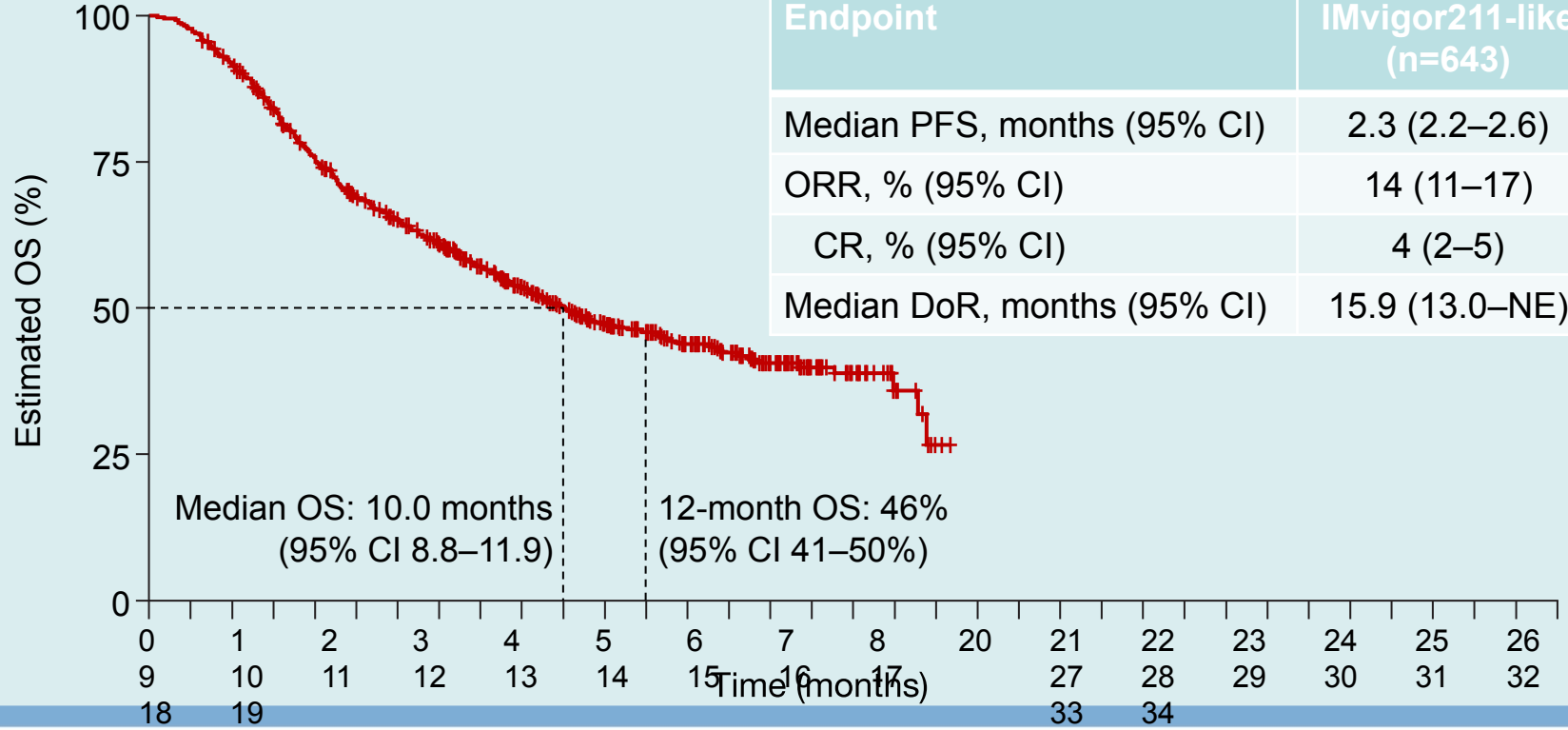
AE, n (%)	All (n=997)	CNS metastases (n=14)	Renal impairment (n=46)	Autoimmune disease (n=35)	Concomitant steroid (n=40)	ECOG PS 2 (n=101)[a]	IMvigor211-like (n=643)[b]
Any grade	880 (88)	12 (86)	37 (80)	32 (91)	38 (95)	77 (76)	577 (90)
Grade 3/4	431 (43)	7 (50)	20 (43)	17 (49)	23 (58)	50 (50)	261 (41)
Grade 5	37 (4)	0	4 (9)[c]	3 (9)[c]	3 (8)[c]	7 (7)[d]	20 (3)[e]
Treatment-related	530 (53)	6 (43)	18 (39)	24 (69)	22 (55)	35 (35)	355 (55)
Grade ≥3	127 (13)	2 (14)[c]	3 (7)[c]	9 (26)	4 (10)[c]	13 (13)	81 (13)
AE of special interest	305 (31)	5 (36)	7 (15)	16 (46)	14 (35)	20 (20)	201 (31)
Grade ≥3	67 (7)	0	1 (2)	5 (14)	2 (5)	5 (5)	46 (7)
Leading to treatment discontinuation	57 (6)	0	3 (7)	3 (9)	2 (5)	3 (3)	37 (6)
Median treatment duration, months	2.8	1.4	3.0	5.6	1.4	0.7	3.5

[a]Green boxes show percentages for which 95% CIs do not overlap with 95% CIs for the overall population or other subgroups shown. [b]All patients except subgroups excluded from IMvigor211. [c]No treatment-related deaths. [d]3 (3%) treatment-related deaths (dyspnoea, respiratory failure, drug-induced liver injury). [e]3 (0.5%) treatment-related deaths (colitis, intestinal perforation, dyspnoea)

Overall survival in subgroups of special interest



Efficacy in 'IMvigor211-like[a]' population (n=643)

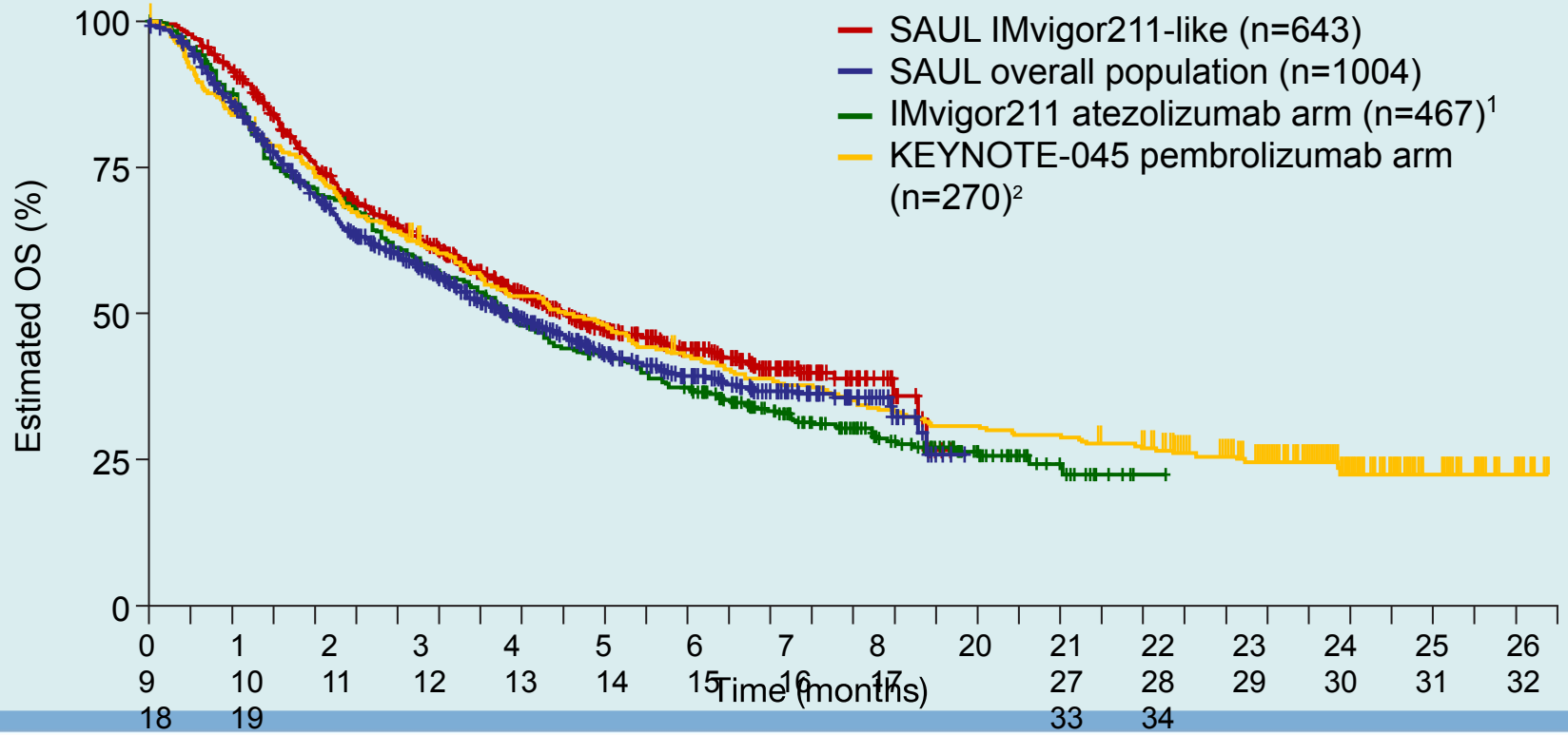


Endpoint	IMvigor211-like (n=643)
Median PFS, months (95% CI)	2.3 (2.2–2.6)
ORR, % (95% CI)	14 (11–17)
CR, % (95% CI)	4 (2–5)
Median DoR, months (95% CI)	15.9 (13.0–NE)

CR = complete response; NE = not estimable

[a]Defined as the SAUL ITT population MINUS populations excluded from IMvigor211

Overall survival in SAUL in the context of randomised phase III trials – indirect comparison[a]



[1]Powles et al. Lancet 2018 (median follow-up 17.3 months).
[2]Fradet et al. ASCO 2018 (median follow-up 27.7 months).
[a]In the absence of a direct comparison, the indirect cross-trial comparison is

Conclusions

- **SAUL is the largest prospective clinical trial of immunotherapy in advanced urinary tract carcinoma**
- **Atezolizumab is a tolerable and effective treatment, even in complex comorbid populations**
- **Efficacy overall and in the IMvigor211-like subgroup is consistent with previous pivotal anti-PD-L1/PD-1 UC trials. Median OS in SAUL was:**
  - 10.0 months in the IMvigor211-like population (n=643)
  - 8.7 months in the ITT population (n=1004)
- **These results support use of atezolizumab in urinary tract carcinoma, including in patients with limited treatment options**

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