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Submitted by:
Jordana Wollmann, PharmD
Managed Care Medical Communications, Medical Affairs
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
Phone: (800) 821-8590
Email: genentechmedinfo-d@gene.com
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NCCN Guidelines Panel: Bladder Cancer

Dear NCCN Guideline Panel for Bladder Cancer:

Request:
We respectfully request you to consider the enclosed SAUL study on the use of Tecentriq® (atezolizumab) in pretreated urinary tract carcinoma published in *European Urology* on March 23, 2019 for inclusion into the guidelines as a reference.[1]

Key Takeaways:
SAUL was a single-arm, open-label Phase 3B study conducted to evaluate Tecentriq in patients with pretreated locally advanced or metastatic urothelial or nonurothelial urinary tract carcinoma. SAUL enrolled 1004 patients more similar to the real-world population and enrolled patients ineligible for the IMvigor211 study, including patients with:[1]

- ECOG performance status 2
- Treated asymptomatic CNS metastases
- Autoimmune disease if controlled and on stable treatment
- Concomitant corticosteroid use
- Renal impairment (i.e., creatinine clearance <30 but ≥15 mL/min with Cockcroft-Gault formula)
- Non-urothelial histology

The primary objective was to evaluate safety and secondary objectives were overall survival (OS), progression-free survival (PFS), and overall response rate (ORR). Overall, 35% of patients fell into at least one of the categories ineligible for IMvigor211. Pre-specified subgroup analyses of these patients ineligible for IMvigor211 were conducted and results are presented in Tables 3 and 4 of the enclosed manuscript. Exploratory analyses were performed for patients representing an "IMvigor211-like" more selected population. The median duration of follow-up in the SAUL study was 12.7 months, and select safety and efficacy outcomes are in Table 1.[1] Select outcomes from the IMvigor211 trial for patients treated with Tecentriq in the intention-to-treat (ITT) population are also listed in Table 1 and the duration of follow up was 17.3 months.[2] Table 1 is not intended to be a direct comparison of the trials.

Of note, data from the open-label, Phase 3 randomized IMvigor211 trial were previously submitted. Patients with metastatic urothelial carcinoma who had progressed after platinum-based chemotherapy were randomized to either Tecentriq or chemotherapy. The primary endpoint of OS was tested hierarchically in prespecified populations: IC2/3, followed by IC1/2/3, followed by the ITT population. In the IC2/3 population (n=234), there was no significant difference in OS between patients in the Tecentriq group versus the chemotherapy group (median OS 11.1 vs 10.6 months; HR 0.87, 95% CI 0.63–1.21), thus precluding further formal statistical analysis.[2]

Table 1. Select Safety and Efficacy Outcomes in SAUL (All Patients and IMvigor211-like Patients) and in the ITT population treated with Tecentriq in IMvigor211[1, 2]

Safety, %	**SAUL**[1] All Patients (n=997)	**SAUL**[1] IMvigor211-like* (n=643)	**IMvigor211 Trial**[2] ITT: Tecentriq arm (n=459)
Any AE (any Grade)	880 (88)	577 (90)	438 (95)
Treatment-related AEs Grade ≥3	530 (53) 127 (13)	355 (55) 81 (13)	319 (70) 95 (21)
AESI with Tecentriq† Grade ≥3	305 (31) 67 (7)	201 (31) 46 (7)	139 (30) 37 (8)
AE leading to treatment discontinuation	57 (6)	37 (6)	34 (7)
Median treatment duration, mo	2.8	3.5	2.8
Efficacy	**SAUL** All Patients (n=1004)	**SAUL** IMvigor211-like* (n=643)	**IMvigor211 Trial** Tecentriq arm ITT (n=467)
Median OS, mo (95% CI)	8.7 (7.8-9.9)	10.0 (8.8-11.9)	8.6 (7.8-9.6)
6-mo OS rate, % (95% CI)	60 (57-63)	65 (61-69)	NR
1-year OS rate, % (95% CI)	41 (38-44)	46 (41-50)	39.2 (34.8-43.7)
Median PFS, mo (95% CI)	2.2 (2.1-2.4)	2.3 (2.2-2.6)	2.1 (2.1-2.2)
ORR, % (95% CI) CR, % (n)	13 (11-16) 3 (29)	14 (11-17) 4 (23)	13.4 (10.5-16.9) 3 (16)

AE=adverse event; AESI=AE of special interest; CI=confidence interval; mo=months, NR=not reported; ITT=intention-to-treat population
*All patients except those in subgroups excluded from the IMvigor211 Phase 3 trial
†The full list of AESI categories with Tecentriq can be found in Supplementary Table 2

Results from the SAUL study were also presented at the European Association of Urology (EAU) 2019 Annual Meeting and the American Society of Clinical Oncology(ASCO) 2019 Annual Meeting and are enclosed for your review.[3, 4] The ASCO poster includes additional outcomes by PD-L1 status and age.

FDA Clearance:

- Tecentriq is FDA-approved for use in patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.
- Please refer to the Tecentriq prescribing information for the full FDA-approved indications and safety information, available at: https://www.gene.com/download/pdf/tecentriq_prescribing.pdf

Thank you for your consideration and I hope this information is helpful to you. If you have any questions, please contact us at the phone number and email provided above.

Respectfully submitted,
Jordana Wollmann, PharmD
US Medical Affairs, Genentech

References

1. Sternberg CN, et al. Primary Results from SAUL, a Multinational Single-arm Safety Study of Atezolizumab Therapy for Locally Advanced or Metastatic Urothelial or Nonurothelial Carcinoma of the Urinary Tract. [published online ahead of print Mar 15, 2019] *Eur Urol*. https://doi.org/10.1016/j.eururo.2019.03.015. Available at https://www.ncbi.nlm.nih.gov/pubmed/30910346.
2. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre,

open-label, phase 3 randomised controlled trial. *Lancet*. 2018 Feb 24;391(10122):748-757. Available at https://www.ncbi.nlm.nih.gov/pubmed/29268948.
3. Merseburger, et al. 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. Oral presentation at: 2019 European Association of Urology (EAU) Annual Meeting; March 2019; Barcelona, Spain.
4. Sternberg et al, et al. study of atezolizumab for locally advanced or metastatic urothelial carcinoma or non-urothelial carcinoma of the urinary tract. Poster presented at: 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; June 2019; Chicago, IL.