	Clinical outcomes of advanced urothelial carcinoma patients following disease progression to programmed death (PD)-1 or PD-ligand (L)-1 inhibitors: Protocol Meet-URO 1
Background	Salvage systemic therapy for metastatic urothelial carcinoma (UC) has serious unmet needs, with taxanes or vinflunine yielding a median progression-free survival (PFS) and overall survival (OS) of approximately 3 and 6 months, respectively. T-lymphocyte checkpoint inhibitors, including Programmed Death (PD)-1 and PD-ligand (L)-1 inhibitors have demonstrated promising activity as salvage systemic therapy for patients with advanced UC. Various immune checkpoint inhibitors like atezolizumab, durvalumab and avelumab, all of them being PD-L1 inhibitor, and pembrolizumab or nivolumab, both PD-1 inhibitors, have demonstrated durable responses in a subset of patients, with atezolizumab having received recent FDA conditional authorization for patients with urothelial cancer progressing during or after cisplatin based therapy.[1-8] Recent results show that the responses observed are durable and might translate into survival prolongation in some selected patients. However, the majority of patients will still progress quickly and require switching to other agents. The outcomes of advanced UC patients following discontinuation of PD-1/PD-L1 inhibitors are unclear. Specifically, it is unclear if most patients receive or not further therapy following progression on PD1/PD-L1 inhibitors, including treatment with immunotherapy beyond disease progression. Moreover, it is possible that prior PD-1/PD-L1 inhibitors augment the activity of subsequent chemotherapy To examine the evolution of post-checkpoint inhibitor therapy, as well as to assess the clinical outcomes of immunotherapy continuation beyond the evidence of disease progression, we aim to perform a nationwide, multicenter data collection to examine outcomes and the frequency of systemic therapy administered following salvage PD-1/PD-L-1 inhibitors in patients with metastatic UC. *References:* 1. Massard C, Gordon MS, Sharma S, et al. J Clin Oncol 34:3119-3125, 2016. 2. Plimack ER, Bellmunt J, Gupta S, et al. Lancet Oncol. 2017;18(2):212-220. 3. Petrylak DP, Powles T, Bellmunt J, et al. J Clin Oncol 33, 2015 (suppl; abstr 4501). 4. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Lancet 387:1909-1920, 2016. 5. Sharma P, Retz M, Siefker-Radtke A, et al. Lancet Oncol. 2017;18(3):312-322. 6. Apolo AB, Infante JR, Balmanoukian A, et al. J Clin Oncol. 2017 Apr 4. [Epub ahead of print]. 7. Hahn NM, Powles T, Massard C, et al. J Clin Oncol 35, 2017 (suppl; abstr 4525). 8. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med. 2017;376(11):1015-1026.

Objectives	The clinical objectives of the present study will be as follows: • To establish a national (Italian) registry of clinical data and outcome of patients who either continue immunotherapy beyond progression or discontinue any immunotherapy with immune checkpoint inhibitors in the context of salvage therapy (i.e. ≥ II line therapy after platinum-based chemotherapy) for advanced or metastatic UC. • This database will be both retrospective and prospective in nature. Data will be collected retrospectively with no cut-off date. • Registered outcomes will include any subsequent therapy, including continuation of immunotherapy and best supportive care only, following disease progression to immune checkpoint inhibitors. This way we will be able to test possibly meaningful survival differences as detailed in the statistical analysis section. The achievement of the study goals will allow possible meaningful advantages for the healthcare system as it is exemplified below: • The possibility to quantify how many patients with advanced UC will access salvage immunotherapy in Italy on a yearly or monthly basis. • The possibility to verify the time to treatment duration in patients receiving salvage immunotherapy, and relative costs, based on a population that will include any immunotherapeutic compound. • The possibility to quantify the volume of patients who should receive any subsequent therapy after disease progression to anti-PD-1 or PD-L1 therapy. • Finally, this study may contribute important information about the key issue of patient selection. Together with results from other ongoing studies, findings from the present study may provide regulators with the necessary information to drive informed patient selection for anti-PD-1 or PD-L1 therapy in the salvage setting of metastatic UC.
Design of the clinical project	Establishing a national platform to include post-treatment, follow-up data of all patients with metastatic UC who have discontinued anti-PD-1 or PD-L1 therapy: Clinical data will be collected from participating institutions for patients with advanced UC following prior PD-1/PD-L1 inhibitors as salvage therapy. Information about the immunotherapy compound will be blinded and investigators from participating institutions will be asked to only provide the class of agent (anti-PD-1 vs anti-PD-L1). Survival will be calculated from the date of study entry (i.e. the last date of PD-1 or PD-L1 inhibitor therapy) until death from any cause. Data collection will be collected by means of an Excel file.
Expected outcomes	This study will be one of the first ever conducted to establish a national registry of clinical data of patients with advanced UC after treatment with anti-PD-1 or PD-L1 therapy. Similar initiatives are being planned in other European countries and it will be possible in the near future to join the studies together and share data on a country level. Getting information on the outcome with any treatment after immunotherapy may allow investigators to access key information on the optimal therapeutic sequence, once multiple agents will be likely available for metastatic UC patients in the next few years. Also, recent trials of PD-1/PD-L1 inhibitors suggest a somewhat more robust extension of survival compared to time to progression in other malignancies possibly due to the use of these compounds in less heavily pretreated patient population and delayed benefits conferred by these agents. One of the

	hypotheses offered as an explanation of this observation is the potential augmentation of efficacy of post-PD-1/PD-L1 inhibitor therapy (i.e. chemotherapy in most cases) owing to the persistent delayed immune response instigated by PD-1/PD-L1 inhibitors. However, such synergism with post-PD-1/PD-L1 inhibitor agents remains to be proven.
Innovatiion	An emerging challenge is the proliferation of multiple agents with potential deep and durable benefits in subsets of patients enriched for a biomarker predicting for sensitivity. In this context, one may hypothesize that patients expressing a specific biomarker predicting for benefit from a specific targeted biologic agent should probably receive that agent before receiving PD-1/PD-L1 inhibitors. Overall, our study may offer useful insights and may highlight important emerging issues regarding the sequencing of multiple emerging agents for the treatment of advanced UC.
Challanges	This study will be the first in Europe to establish a nationwide registry of post-PD-1/PD-L1 inhibitor treatment in UC. One limitation will be that the immunotherapeutic compounds will be kept anonymized in order to comply with the purposes of the present research call.

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Meet-Uro
ITALIAN NETWORK FOR RESEARCH IN UROLOGIC-ONCOLOGY

Arruolamento centri – aggiornato al 20/09/2018

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