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Start date	01 Nov 2021
End date	31 Jul 2023
Mentor / Contact	Andrea Necchi
Project Title	A personalized approach of neoadjuvant therapy, including immunotherapy and bladder preservation, for muscle-invasive urothelial bladder carcinoma (MIBC)

Rationale and Aim

After decades of therapeutic stagnation in the field of urothelial carcinoma (UC), the introduction of new agents targeting the PD-1 and PD-L1 axis has revolutionized the way we currently manage locally advanced or metastatic UC. The therapeutic area has evolved rapidly following the 2016 approval of atezolizumab from the IMvigor210 trial. Five PD-1 and PD-L1 inhibitors are now approved by the U.S. Food and Drug Administration (FDA) for treating patients with advanced UC following platinum-based chemotherapy.¹⁻⁵

Based on their documented activity in UC, coupled with the optimal toxicity profile, immune checkpoint inhibitors yield the best features for use in earlier disease stages (e.g., muscle-invasive bladder cancer [MIBC] in nonmetastatic UC). By recapitulating the therapeutic model proposed for early-stage non-small cell lung cancer,⁷ integrating short courses of immunotherapy before radical cystectomy in MIBC is poised to make a significant impact in MIBC management.

In fact, although the recommended standard of care for MIBC in patients who are eligible to receive cisplatin is neoadjuvant chemotherapy followed by radical cystectomy, the real-world adherence to this standard therapy is poor, with less than 25% of patients ultimately accessing multimodality treatment.⁸ Additionally, about 50% of the total amount of patients with UC are considered ineligible to receive cisplatin based on their renal function, performance status, and comorbidities, and a subset of patients refuse to receive any chemotherapy.⁹ Although neoadjuvant chemotherapy is active, residual high-risk disease (i.e., pT2 or higher) is still present in more than 50% of patients and represents a poor prognostic factor.¹⁰ For the patients who cannot receive cisplatin, there is no standard neoadjuvant therapy. The PURE-01 study was designed to obtain biomarker results and assess the efficacy of single-agent pembrolizumab in patients with MIBC, regardless of cisplatin eligibility.¹¹ In this study, patients with T2-4N0M0 MIBC received three courses of 200 mg pembrolizumab every 3 weeks, preceding radical cystectomy. Pembrolizumab exhibited a 42% pT0 among 50 treated patients and was safely administered. Immune-related adverse events have been reported, but they did not delay the planned surgery, and postsurgical complications were similar to those reported in the most recent literature related to either open or robot-assisted procedures. In particular, no difference in terms of intra-, peri- and postoperative complications was recorded compared with patients from the same center undergoing radical cystectomy and not receiving pembrolizumab. Similarly, intraoperative performance (e.g., number of removed lymph nodes, soft tissue surgical margins, and operative time) was not compromised by neoadjuvant immunotherapy. Notably, PD-L1 expression (defined as combined positive score \geq 10% with the 22C3 antibody) and high tumor mutational burden (TMB; assessed with the FoundationOne assay) predicted for enriched pathologic responses. The survival findings from the PURE-01 study were presented and confirmed the favorable prognostic role of the pT0 response on both Event-Free Survival (EFS) and Overall Survival (OS) after neoadjuvant pembrolizumab.

Results, Conclusions and Future Perspectives

The initial proposed project for the fellowship would use the experimental drug cetrelimab in patients with muscle-invasive bladder cancer ineligible for cisplatin. As this study was not approved by the ethics committee, the project was modified to include other two clinical trials in the same disease and scenario (perioperative treatment of MIBC).

NURE-Combo is an academic, open-label, single-arm, phase 2 study of neoadjuvant immunotherapy (anti-PD1, nivolumab) combined with nab-paclitaxel before radical cystectomy for patients with MIBC. To this date, 31 patients were enrolled in the trial. Initial results are expected to be presented in 2024, after the end of the first stage and with the results from cystectomy pathology.

A second academic study ongoing at IRCCSS is the SURE-01, a neoadjuvant phase 2, open-label, non-randomized study evaluating sacituzumab govitecan, in patients with urothelial carcinoma of the bladder who cannot receive or refuse cisplatin-based chemotherapy. This drug has very promising activity in bladder cancer and is an antibody-drug conjugate (ADC) composed of a humanized anti-Trop-2 antibody, SN-38 (a topoisomerase inhibitor), and a hydrolysable linker for SN-38 release. To this date, 14 patients were enrolled.

Objectives included in the the prolongation request:

- First analysis of SURE-01 trial, with pathological outcomes and safety analysis, expected January/2023: Not met. The trial was temporarily interrupted due to unexpected toxicity, which caused delay.
- Abstract submission for ASCO conference, February/2023: Not met. The trial was temporarily interrupted due to unexpected toxicity, which caused delay.
- Immunophenotyping initial analysis of SURE and NURE combo: Not met. Analysis will be performed only after the end of the recruitment.
- Second analysis of SURE-01 trial, with survival outcomes analysis, expected June/2023: Not met. The trial was temporarily interrupted due to unexpected toxicity, which caused delay.
- Abstract submission for ESMO conference: Not met. The trial was temporarily interrupted due to unexpected toxicity, which caused delay.
- Preparation of manuscript with initial results, expected July/2023: Not met. The trial was temporarily interrupted due to unexpected toxicity, which caused delay. I will continue working with the host institute and I will contribute with the manuscript preparation.

- Submission of the protocol prepared during the 2022 AACR/ASCO workshop (A phase 2 trial of consolidation radiotherapy in patients with metastatic hormone sensitive prostate cancer) for approval at our institution and start of enrolment, expected November/2022: Not met. After internal discussion, we decided not to continue with this protocol, due to logistic and funding issues.

Unfortunately, some of the objectives included in the prolongation request were not met. The number of enrolled patients in the academic trials was lower than expected, which cause important delays. However, during the fellowship I was directly involved with several genitourinary sponsored and academic trials, which brought me extensive experience with clinical research. Moreover, I contributed and submitted several manuscripts and conference abstracts, including publications in high impact factor journals (European Urology Oncology). Finally, I will continue working with the host institute after the end of my fellowship and I will be part of the future publications.

**List of Publications and Presentations
Resulting from the Translational
Research Project**

- T.C.D. Padua, G. Basile, M. Bandini, D. Raggi1, L. Marandino, P. Giannatempo, R. Colombo, M. Colecchia, R. Lucianò, M. Moschini, A. Briganti, F. Montorsi, A. Necchi. Three-year follow-up update and survival outcomes of the PURE-01 study. *Annals of Oncology* (2022) 33 (suppl_7): S785-S807. 10.1016/annonc/annonc1080
 - Moritz Johannes Reike, Daniele Raggi, Laura Marandino, Damiano Alfio Patanè, Emanuele Crupi, Tiago Costa de Padua, Peter C. Black, Ewan Gibb, Andrea Necchi. Distinct gene expression patterns identify patients who relapse after neoadjuvant pembrolizumab and radical cystectomy in the PURE-01 study. *J Clin Oncol* 41, 2023 (suppl 6; abstr 549)
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List of Publications and Presentations resulting from other projects during the fellowship period (if applicable)

- Tiago Costa de Padua, Greta Malena, Marco Moschini, Alberto Martini, Laura Marandino, Daniele Raggi, Alberto Briganti, Francesco Montorsi, and Andrea Necchi. Efficacy and toxicity of antibody-drug conjugates (ADCs) in the treatment of metastatic urothelial cancer (mUC): A systematic review. *Journal of Clinical Oncology* 2022 40:16_suppl, e16536-e16536
- Padua TC, Moschini M, Martini A, Pederzoli F, Nocera L, Marandino L, Raggi D, Briganti A, Montorsi F, Necchi A. Efficacy and toxicity of antibody-drug conjugates in the treatment of metastatic urothelial cancer: A scoping review. *Urol Oncol.* 2022 Aug 13:S1078-1439(22)00267-8. Epub ahead of print. PMID: 35973928.
- T.C.D. Padua, G. Basile, M. Bandini, D. Raggi¹, L. Marandino, P. Giannatempo, R. Colombo, M. Colecchia, R. Lucianò, M. Moschini, A. Briganti, F. Montorsi, A. Necchi. Three-year follow-up update and survival outcomes of the PURE-01 study. *Annals of Oncology* (2022) 33 (suppl_7): S785-S807. 10.1016/annonc/annonc1080
- Basile G, Bandini M, Gibb EA, Ross JS, Raggi D, Marandino L, Costa de Padua T, Crupi E, Colombo R, Colecchia M, Lucianò R, Nocera L, Moschini M, Briganti A, Montorsi F, Necchi A. Neoadjuvant pembrolizumab and radical cystectomy in patients with muscle-invasive urothelial bladder cancer: 3-year median follow-up update of PURE-01 trial. *Clin Cancer Res.* 2022 Oct 3:CCR-22-2158.
- Padua, Tiago; Marandino, Laura; Raggi, Daniele; Hallanger-Johnson, Julie; Kutikov, Alexander; Spiess, Philippe; Necchi, Andrea. (2022). A systematic review of published clinical trials in the systemic treatment of adrenocortical carcinoma: An initiative led on behalf of the Global Society of Rare Genitourinary Tumors. In press, *Clinical Genitourinary Cancer*. 10.1016/j.clgc.2022.10.011.
- T.C.D. Padua, L. Marandino, D. Raggi, A. Briganti, F. Montorsi, A. Necchi. Efficacy and toxicity of HER2-targeted antibody-drug conjugates (ADCs) in the treatment of metastatic urothelial cancer (mUC): A systematic review. *Annals of Oncology* (2022) 33 (suppl_9): S1485-S1494. 10.1016/annonc/annonc1124
- Tiago Costa de Padua, Laura Marandino, Damiano Alfio Patanè, Daniele Raggi, Andrea Necchi. Racial and geographical disparities in pivotal bladder cancer clinical trials. *Journal of Clinical Oncology* 41, no. 6_suppl (February 20, 2023) 454-454.
- Giorgio Brembilla, Giuseppe Basile, Marco Bandini, Daniele Raggi, Laura Marandino, Tiago Costa de Padua, Damiano Alfio Patanè, Emanuele Crupi, Andrea Del Prete, Renzo Colombo, Maurizio Colecchia, Roberta Lucianò, Marco Moschini, Jeffrey S. Ross, Alberto Briganti, Francesco Montorsi, Francesco De Cobelli, Andrea Necchi. Utility of pre- and post-pembrolizumab (Pembro) Vesical Imaging-Reporting and Data

System (VIRADS) to predict the pathological response in muscle-invasive urothelial bladder cancer (MIBC): An analysis of the PURE-01 cohort. *Journal of Clinical Oncology* 41, no. 6_suppl (February 20, 2023) 552-552.

- Andrea Necchi, Giuseppe Basile, Ewan Gibb, Giuseppina Calareso, Tiago Padua, Damiano Patanè, Emanuele Crupi, Chiara Mercinelli, Andrea Del Prete, Patrizia Giannatempo, Marco Moschini, Jeffrey Ross, Alberto Briganti, Francesco Montorsi, Antonella Messina, Francesco De Cobelli, and Giorgio Brambilla. BIOLOGY AND PERFORMANCE OF PRE- AND POST-PEMBROLIZUMAB (PEMBRO) VESICAL IMAGING-REPORTING AND DATA SYSTEM (VI-RADS) TO PREDICT THE PATHOLOGICAL RESPONSE IN MUSCLE-INVASIVE UROTHELIAL BLADDER CANCER (MIBC): FULL DATA ANALYSIS FROM A CLINICAL TRIALS PIPELINE. *The Journal of Urology*, Vol. 209, No. 4S, Supplement, Sunday, April 30, 2023

- Giuseppe Basile, Giorgio Brambilla, Marco Bandini, Daniele Raggi, Laura Marandino, Tiago Costa De Padua, Emanuele Crupi, Renzo Colombo, Maurizio Colecchia, Roberta Lucianò, Marco Moschini, Jeffrey S Ross, Alberto Briganti, Francesco Montorsi, Francesco De Cobelli, and Andrea Necchi. UTILITY OF PRE- AND POST-PEMBROLIZUMAB VESICAL IMAGING - REPORTING AND DATA SYSTEM (VIRADS) TO PREDICT THE PATHOLOGICAL RESPONSE IN MUSCLE-INVASIVE UROTHELIAL BLADDER CANCER (MIBC): AN ANALYSIS OF THE PURE-01 COHORT. *The Journal of Urology*, Vol. 209, No. 4S, Supplement, Sunday, April 30, 2023

- Crupi E, de Padua TC, Marandino L, Raggi D, Dyrskjøt L, Spiess PE, Sonpavde GP, Kamat AM, Necchi A. Circulating tumor DNA as a Predictive and Prognostic Biomarker in the Perioperative Treatment of Muscle-invasive Bladder Cancer: A Systematic Review. *Eur Urol Oncol*. 2023 Jun 15:S2588-9311(23)00111-6. doi: 10.1016/j.euo.2023.05.012. Epub ahead of print. PMID: 37330413.

**Selection of Courses and Workshops
Attended During the Fellowship**

Methods in Clinical Cancer Research Workshop 2022

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Personal Statement (not mandatory)

The fellowship was a very enriching experience, with important development, both personally and professionally. I am very grateful for this opportunity.

References

1. Necchi A, et al. J Clin Oncol. 2018 Dec 1;36(34):3353-3360.
 2. Bandini M, et al. J Natl Cancer Inst. 2020 Jun 9;djaa076.doi: 10.1093/jnci/djaa076.
 3. Necchi A, et al. Ann Oncol. 2020 Dec;31(12):1755-1763.
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Signature - Award Recipient



Signature - Mentor



Photo 1

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Photo 2

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