PROTOCOL

Title of the study:	Multicenter Retrospective Observational Study for Real-World Data Collection on the Perioperative Use of Durvalumab in Combination with Neoadjuvant Chemotherapy in Patients with Operable Urothelial Carcinoma (DELTA)
Study ID:	
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APPROVAL OF THE PROTOCOL

The Experimenters:

- approve this Protocol;
- declare that the study will be conducted in accordance with what is reported in this Protocol.

Prof. Roberto Iacovelli *date:*

Dr.ssa Patrizia Giannatempo *date:*

Dr.ssa Mimma Rizzo *date:*

Prof. Giandomenico Roviello *date:*

Dr.ssa Rosa Tambaro *date:*

Dr. Marco Maruzzo *data:*

Dr. Carlo Messina *data:*

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Background and Rationale

Urothelial carcinoma of the bladder is one of the most common malignancies of the genitourinary tract worldwide. In patients with operable muscle-invasive or locally advanced disease, the current standard of care consists of platinum-based neoadjuvant chemotherapy followed by radical cystectomy. This strategy has demonstrated a survival benefit in terms of both overall survival and disease-free survival compared with surgery alone.

Despite these therapeutic advances, a substantial proportion of patients experience disease recurrence or progression following standard treatment, highlighting the need to optimize perioperative therapeutic strategies.

In recent years, the introduction of immune checkpoint inhibitors (ICIs) has significantly reshaped the treatment landscape of urothelial carcinoma. These agents have demonstrated meaningful clinical benefit in advanced disease and are currently being investigated in earlier stages.

In particular, the phase III NIAGARA trial evaluated the use of durvalumab, a monoclonal antibody targeting PD-L1, in combination with neoadjuvant chemotherapy followed by adjuvant durvalumab in patients with operable muscle-invasive urothelial carcinoma. The study demonstrated a significant improvement in event-free survival and overall survival compared with chemotherapy alone.

However, in real-world clinical practice, several aspects remain insufficiently explored, including the tolerability of perioperative immunotherapy in unselected populations, the feasibility of combining ICIs with standard chemotherapy outside clinical trials, and the identification of potential clinical or biological predictors of treatment response.

The present study aims to collect real-world evidence on the perioperative use of durvalumab in patients with operable urothelial carcinoma treated across multiple Italian oncology centers.

This study is observational and non-interventional. Treatment decisions, including the prescription of durvalumab and associated chemotherapy, are made by the treating physician in the context of routine clinical practice. The study does not provide treatment assignment by protocol and does not modify the standard diagnostic and therapeutic pathway of the patients.

Study Objectives

Primary Objective

To evaluate the pathological complete response (pCR) rate, defined as ypT0N0 at the time of radical surgery, in patients treated with durvalumab in combination with neoadjuvant chemotherapy in a real-world perioperative setting.

Secondary Objectives

The secondary objectives of the study include:

To evaluate Event-Free Survival (EFS)

To evaluate Overall Survival (OS)

To evaluate Disease-Free Survival (DFS)

To assess the safety and tolerability profile of perioperative durvalumab in real-world clinical practice

To evaluate the incidence and severity of immune-related adverse events

To assess treatment completion rates for both chemotherapy and immunotherapy

Study Design

This is a multicenter, retrospective, observational cohort study aimed at collecting real-world evidence on the perioperative use of durvalumab in patients with operable urothelial carcinoma.

Approximately 30 Italian oncology centers belonging to the MeetURO network will be involved in the study.

The study is non-interventional: treatment decisions, including the administration of durvalumab and associated chemotherapy regimens, are made independently by treating physicians according to routine clinical practice and approved therapeutic indications.

The protocol does not include any treatment assignment and does not require additional diagnostic or therapeutic procedures beyond standard clinical practice.

Clinical data will be retrospectively collected from medical records and institutional databases of the participating centers.

The expected duration of the study is 24 months, including data collection, statistical analysis, and dissemination of results.

Setting

The study will be conducted across approximately 30 Italian oncology centers belonging to the MeetURO network, including academic hospitals and referral cancer centers.

Patients will be identified through clinical databases and medical records of the participating centers.

Eligible patients will include those treated with durvalumab in the perioperative setting within routine clinical practice or within compassionate use programs.

Available follow-up data will be collected.

Study Population

The study population will consist of adult patients with operable urothelial carcinoma treated with durvalumab in the perioperative setting, either in combination with neoadjuvant chemotherapy or as adjuvant monotherapy in routine clinical practice.

Patients will be identified through the clinical databases of the participating centers.

Inclusion Criteria

Patients meeting all of the following criteria will be eligible for the study:

- Age ≥ 18 years
- Histologically confirmed diagnosis of muscle-invasive or locally advanced operable urothelial carcinoma (clinical stage ≥ T2 and M0)
- Perioperative treatment with durvalumab, in combination with neoadjuvant chemotherapy or as adjuvant monotherapy
- Radical surgery (cystectomy or nephroureterectomy) planned or already performed
- Availability of clinical and radiological data related to the neoadjuvant and/or adjuvant phases
- ECOG performance status 0–2

Exclusion Criteria

Patients meeting any of the following criteria will be excluded:

- Patients not eligible for surgery with curative intent
- Presence of metastatic disease at diagnosis
- Concomitant treatment with other investigational immunotherapies
- History of uncontrolled active autoimmune disease or need for chronic systemic immunosuppression
- Known contraindications to durvalumab
- Pregnancy or breastfeeding

Study Outcomes

Study outcomes are defined to evaluate the effectiveness and safety of perioperative durvalumab in real-world clinical practice in patients with operable urothelial carcinoma.

Primary Endpoint

The primary endpoint is:

- Pathological complete response (pCR) rate, defined as the absence of residual urothelial carcinoma in the surgical specimen (ypT0) and absence of lymph node involvement (ypN0) at the time of radical surgery

Pathological response will be assessed based on the histopathological report of the surgical specimen obtained at the time of cystectomy or nephroureterectomy.

Secondary Endpoints

Secondary endpoints include:

- Event-Free Survival (EFS)
- Disease-Free Survival (DFS)
- Overall Survival (OS)
- Completion rate of neoadjuvant and adjuvant treatment
- Safety profile of treatment, including the incidence and severity of immune-related adverse events

Adverse events will be recorded based on the information available in patients' clinical documentation.

Variables

The main variables collected in the study include demographic, clinical, pathological, and treatment-related characteristics.

Demographic and Clinical Variables

- Age at diagnosis
- Sex
- ECOG Performance Status
- Relevant comorbidities
- Clinical stage at diagnosis

Tumor Variables

- Histological subtype
- Clinical and pathological TNM stage
- Presence of lymph node involvement
- Presence of histological variants

Treatment Variables

- Type of neoadjuvant chemotherapy regimen
- Number of chemotherapy cycles administered
- Durvalumab administration (dose and number of cycles)

- Adjuvant treatment with durvalumab (if applicable)
- Date of surgery

Outcome Variables

- Pathological response (pCR, pathological partial response, no response)
- Date of disease recurrence
- Date of disease progression
- Date of death or last follow-up
- Treatment-related adverse events

Data Sources

All variables will be collected from medical records and institutional databases of the participating centers.

Clinical, radiological, and pathological assessments will be those routinely performed in standard clinical practice at each center.

Bias

Given the observational nature of the study, potential sources of bias may include selection bias and information bias.

To minimize these biases, the following measures will be adopted:

- Consecutive inclusion of eligible patients at each participating center
- Use of standardized definitions for clinical endpoints
- Data collection through a standardized Case Report Form (CRF) shared across participating centers
- Data review and quality control procedures prior to statistical analysis

Sample Size

As this is a descriptive observational study, no formal sample size calculation based on statistical hypotheses is planned.

Based on the number of participating centers (approximately 30 Italian oncology centers) and the real-world use of perioperative durvalumab, it is estimated that approximately 150–200 patients may be included.

All patients meeting the eligibility criteria will be included in the analysis.

Enrollment Procedure

Eligible patients will be identified at each participating center through:

- Institutional clinical databases

- Internal oncology treatment registries
- Review of electronic medical records

All patients meeting the inclusion criteria as defined in the protocol will be included.

Follow-up Procedure

Follow-up data will be collected from available clinical records according to routine clinical practice at each participating center.

Collected follow-up data will include:

- Disease recurrence
- Disease progression
- Overall survival
- Treatment-related adverse events

For patients who discontinue treatment or deviate from the initial therapeutic plan, all available clinical data relevant to study outcomes will still be collected.

Definition of Study Completion

For each individual patient, the study will be considered complete at the time of the last available clinical follow-up information.

At the global level, the study will be considered complete after:

- Completion of data collection across all participating centers
- Database lock
- Completion of the final statistical analysis

Data Management

Data Collection

Clinical data will be retrospectively collected from medical records and entered into the REDCap platform.

Collected information will include demographic data, disease characteristics, treatments received, pathological findings, and follow-up data.

Data Handling

Data will be entered into the study database by authorized personnel at each participating center.

Appropriate security measures will be implemented to ensure:

- Data confidentiality

- Protection of sensitive information
- Traceability of database modifications

Data Storage

Data will be pseudonymized and processed in accordance with the European General Data Protection Regulation (GDPR 2016/679).

The study sponsor will be responsible for data management and storage.

Data will be retained for the time necessary to conduct the study and to comply with any applicable regulatory requirements.

Statistical Analysis Plan

Statistical analyses will be performed on all patients who meet the eligibility criteria and for whom the required clinical data are available.

Demographic, clinical, and pathological characteristics will be summarized using descriptive statistics. Continuous variables will be reported as mean and standard deviation or median and interquartile range, depending on data distribution. Categorical variables will be presented as absolute frequencies and percentages.

The pathological complete response (pCR) rate will be calculated as the proportion of patients achieving pCR among those undergoing radical surgery.

Survival curves for Event-Free Survival (EFS), Disease-Free Survival (DFS), and Overall Survival (OS) will be estimated using the Kaplan–Meier method and compared using the log-rank test.

Univariate and multivariate analyses will be performed using Cox proportional hazards regression models to identify potential prognostic factors associated with clinical outcomes, with estimation of hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs).

The multivariable analysis will include clinically relevant variables such as:

- Age
- Sex
- Performance status
- Clinical stage
- Pathological characteristics
- Chemotherapy regimen
- Number of treatment cycles received

Statistical significance will be set at $p < 0.05$.

Missing Data Management

Missing data will be handled using a complete-case analysis approach. If the proportion of missing data is substantial for specific variables, sensitivity analyses may be conducted to assess their impact on the results.

Subgroup Analyses

Exploratory subgroup analyses will be performed according to clinically relevant variables, including:

- Disease stage
- Primary tumor site
- Type of neoadjuvant treatment
- Completion of perioperative treatment

Loss to Follow-up

Given the observational non-interventional nature of the study, loss to follow-up will be handled by censoring data at the date of the last available clinical information.

Sensitivity Analyses

Sensitivity analyses will be performed to assess the robustness of the results under different analytical assumptions or in the presence of missing data.

Statistical analyses will be conducted using dedicated statistical software (e.g., STATA, R, or equivalent).

Safety Management

Given the observational non-interventional nature of the study, no therapeutic intervention is assigned by the protocol.

Treatment with durvalumab and associated chemotherapy has been administered as part of routine clinical practice.

Adverse events will be recorded exclusively based on information available in patients' medical records and institutional databases.

No prospective adverse event reporting system or centralized pharmacovigilance is предусмотрено, as the study does not involve any modification of treatments or additional procedures beyond standard clinical practice.

Administrative Aspects

Study Funding

This study is conducted as an independent academic research project promoted by the Department of Experimental and Clinical Medicine of the University of Florence in collaboration with the participating centers of the MeetURO network.

The study may receive non-conditioning financial support from external sources intended to support organizational and operational activities related to the conduct of the study, including study coordination, database management, data collection, and statistical analysis. Any external support will not influence the scientific design of the study, data collection, data analysis, interpretation of results, or publication policy.

The sponsor and investigators maintain full scientific independence in the conduct of the study and in the dissemination of study results. Any supporting organization will not be involved in treatment decisions, patient management, or interpretation of study findings.

All funding relationships and potential conflicts of interest will be managed in accordance with applicable institutional policies and regulatory requirements.

Ethical Considerations

This study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and applicable national and European regulations governing clinical research and data protection.

As this is a non-interventional observational study, no treatment assignment is предусмотрено by the protocol, and no additional diagnostic or therapeutic procedures beyond routine clinical practice are required.

Treatment with durvalumab and associated chemotherapy regimens has been administered exclusively within routine clinical practice, at the discretion of the treating physician.

The study protocol, together with all required documentation, will be submitted for review and approval to the competent Ethics Committee prior to study initiation.

The study will comply with applicable data protection regulations, including Regulation (EU) 2016/679 (GDPR) and Legislative Decree No. 196/2003, as amended by Legislative Decree No. 101/2018 and Law No. 56 of April 29, 2024.

Informed Consent and Data Processing

Given the non-interventional observational nature of the study, clinical data will be collected from information already available in medical records and institutional databases of the participating centers.

The processing of personal data will be carried out in compliance with Regulation (EU) 2016/679 (GDPR) and applicable national data protection legislation.

In accordance with Article 110 of Legislative Decree No. 196/2003, as amended by Law No. 56 of April 29, 2024, in cases where patients cannot be contacted (e.g., deceased, untraceable, or where obtaining consent is not feasible for justified ethical or organizational reasons), data processing may be carried out subject to approval by the competent Ethics Committee and authorization by the General Directorate of the sponsoring institution, without the need for prior consultation of the Data Protection Authority.

To ensure compliance with fundamental data protection principles (data minimization, relevance, security, and integrity), a simplified Data Protection Impact Assessment (DPIA) will be prepared and submitted as part of the documentation to the Ethics Committee.

Collected data will be pseudonymized prior to entry into the study database and processed exclusively for scientific research purposes.

Data collection will be performed באמצעות an electronic Case Report Form (eCRF) developed using the REDCap (Research Electronic Data Capture) platform, accessible to participating centers through personal credentials.

Conflict of Interest

All investigators involved in the study will be required to disclose any financial or professional conflicts of interest related to the study or to the investigational treatments.

Any financial relationships, consultancies, scientific collaborations, or other relevant interests will be declared transparently in accordance with institutional policies and applicable regulations.

The presence or absence of potential conflicts of interest will be documented for each participating center.

Responsibilities and Publication Policy

Role of the Sponsor and Investigators

The study is conducted as an independent, academic, multicenter study.

The sponsor is responsible for the scientific and organizational coordination of the project, including:

- Study design
- Development of the protocol and study documentation
- Coordination of participating centers
- Oversight of data collection and management
- Statistical analysis and interpretation of results

Investigators at participating centers are responsible for:

- Identifying eligible patients at their respective centers
- Collecting and entering clinical data into the study electronic platform
- Ensuring the accuracy and completeness of entered data
- Contributing to data interpretation and dissemination of study results

All research activities will be conducted in compliance with applicable regulations and principles of scientific integrity.

Data Ownership

Ownership of the data collected within the study is attributed to the study sponsor.

Participating centers will have access to data related to patients enrolled at their respective centers and may contribute to data analysis and interpretation in agreement with the sponsor.

Data will be managed and stored in pseudonymized form within the study database and used exclusively for scientific research purposes in compliance with applicable regulations.

Publication Policy

Study results will be disseminated through presentations at national and international scientific conferences and through publication in peer-reviewed journals.

Publication will adhere to principles of transparency and scientific integrity.

Authorship of publications arising from the study will be determined in accordance with the criteria established by the International Committee of Medical Journal Editors (ICMJE).

All participating centers that have made a significant contribution to data collection and study conduct may be involved in publication activities, according to agreements established by the study steering committee.

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