Official Title: A Randomized Prospective Trial Comparing Bacillus Calmette-Guerin (BCG) RIVM and Russian Strains in Non-Muscle Invasive Bladder Cancer: Efficacy and Side Effects

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Study Protocol and Statistical Analysis Plan

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Background and Rationale

Bladder cancer remains a significant health burden globally, with non-muscle invasive bladder cancer (NMIBC) representing a majority of cases. Intravesical Bacillus Calmette-Guerin (BCG) therapy is widely accepted as a standard adjuvant treatment for intermediate- and high-risk NMIBC. However, the comparative efficacy and safety profiles of different BCG substrains remain unclear. This study aims to address this gap by comparing the RIVM and Russian BCG substrains.

Objectives

- **Primary Objective:** To evaluate the efficacy of BCG RIVM versus BCG Russian substrains in terms of recurrence-free survival (RFS) and progression-free survival (PFS).
- **Secondary Objective:** To compare the safety and adverse event profiles between the two substrains.

Study Design

This is a randomized prospective clinical trial conducted at Ankara University Ibni Sina Hospital from January 2019 to December 2022.

Inclusion Criteria

1. Age ≥18 years.
2. Histopathologically confirmed NMIBC (Ta, T1, or CIS).
3. Intermediate-, high-, or very high-risk classification based on EAU guidelines.
4. No prior BCG therapy within the last year.
5. No evidence of upper urinary tract carcinoma or distant metastases.
6. Minimum follow-up period of 12 months.

Exclusion Criteria

1. Inadequate BCG therapy (fewer than 5 induction doses or fewer than 2 maintenance doses).
2. Follow-up period less than 12 months.
3. Use of multiple BCG strains.
4. Previous history of BCG therapy.

Methods

Randomization

Patients were randomly assigned to receive either BCG RIVM (n=61) or BCG Russian (n=64).

Intervention

Both groups received an induction course of six weekly intravesical BCG instillations, followed by maintenance therapy as per risk stratification protocols.

Outcome Measures

- **Primary Outcomes:**
    - Recurrence-free survival (RFS): Time from randomization to tumor recurrence.
    - Progression-free survival (PFS): Time from randomization to disease progression.
- **Secondary Outcomes:**
    - Adverse events: Assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

Statistical Analysis

- Kaplan-Meier survival analysis for RFS and PFS.
- Chi-square tests for categorical variables.
- Cox proportional hazards model for multivariate analysis.
- P-value <0.05 considered statistically significant.

Results Summary

- A total of 125 patients were analyzed: 61 in the BCG RIVM group and 64 in the BCG Russian group.
- No significant difference in RFS or PFS between the groups.
- Adverse event rates were comparable.

Conclusion

This trial demonstrates that BCG RIVM and Russian substrains offer similar efficacy and safety for the treatment of NMIBC. These findings provide flexibility in substrain selection based on availability and institutional preference.