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Efficacy and Safety of FGFR Inhibitor Monotherapy versus Combination with Immune Checkpoint Inhibitors in FGFR-Altered Advanced or Metastatic Urothelial Carcinoma: AMeta-Analysis

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 March 2026 and was last updated on 16 March 2026.

INTRODUCTION

Review question / Objective P (Population / Patients): Adult patients (typically > 18 years) diagnosed with advanced or metastatic urothelial carcinoma (UC) whose tumors harbor susceptible FGFR alterations .
I (Intervention): Combination therapy comprising an FGFRi and an immune checkpoint inhibitors (ICIs).
C (Comparison): FGFRi administered as a monotherapy.
O (Outcomes): Reported at least one extractable efficacy outcome or safety outcome.
S (Study Design): Prospective clinical trials (single-arm or multi-arm) and observational studies.

Condition being studied Urothelial carcinoma (UC) is the most common malignancy of the urinary tract, and patients with metastatic disease face a dismal prognosis. Approximately 15% to 20% of metastatic UC cases harbor activating alterations in the fibroblast growth factor receptor (FGFR) genes (predominantly FGFR2 or FGFR3 mutations/fusions). These FGFR-altered tumors are frequently characterized by an immunosuppressive, "non-T-cell-inflamed" tumor microenvironment, which limits the efficacy of standard immune checkpoint blockade. This review focuses on advanced or metastatic UC harboring these specific FGFR alterations and evaluates strategies to overcome immune resistance.

METHODS

Participant or population Adult patients (>18 years old) diagnosed with locally advanced, unresectable, or metastatic urothelial carcinoma (mUC). The tumors must harbor susceptible FGFR alterations (including FGFR2 or FGFR3 mutations or fusions) or FGFR mRNA overexpression, as confirmed by molecular profiling (e.g., next-generation sequencing or PCR). Patients may be in any line of systemic therapy (treatment-naïve or previously treated), provided they have no prior history of resistance to FGFR inhibitors.

Intervention Combination therapy consisting of a targeted pan-FGFR tyrosine kinase inhibitor (FGFRi; e.g., erdafitinib, rogaratinib, pemigatinib, or others) concurrently administered with an immune checkpoint inhibitor (ICI; targeting PD-1 or PD-L1, such as pembrolizumab, atezolizumab, cetrelimab, or avelumab).

Comparator FGFR inhibitor (FGFRi) administered as a single-agent targeted monotherapy.

Study designs to be included We will include prospective clinical trials (Phase I, II, and III; encompassing both single-arm cohorts and randomized/multi-arm trials) as well as observational cohort studies (both prospective and retrospective real-world data).

Eligibility criteria Inclusion criteria
Studies that enrolled adult patients with advanced or metastatic urothelial carcinoma harboring confirmed FGFR alterations and evaluated FGFR inhibitor (FGFRi) monotherapy or FGFRi combined with immune checkpoint inhibitors (ICIs) were eligible for inclusion. Eligible records must report at least one extractable efficacy or safety outcome. Peer-reviewed publications and major conference abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) with sufficient unique data were both accepted.
Exclusion criteria
We excluded case reports, narrative reviews, systematic reviews, meta-analyses, editorials, letters, comments, expert opinions, or other publications without original extractable data. Studies enrolling mixed tumor populations will be excluded unless data for urothelial carcinoma can be extracted separately. In addition, studies focusing on patients with prior resistance or progression on FGFRi therapy before enrollment will be excluded.

Information sources Comprehensive literature searches will be conducted across the following major electronic databases: PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). Furthermore, grey literature and recent conference proceedings from major international oncology meetings (e.g., ASCO, ESMO, ASCO GU) will be manually searched to identify unpublished or recently updated trial data.

Main outcome(s) Primary Outcome: Objective Response Rate (ORR), defined as the proportion of patients achieving a confirmed complete response (CR) or partial response (PR) according to RECIST criteria.

Secondary Outcomes (Safety): The incidence of severe (Grade 3–4 and Grade 5) treatment-emergent and treatment-related adverse events (TEAEs/TRAEs). Additionally, tolerability will be evaluated by measuring the rates of adverse events leading to dose reduction, dose interruption, and definitive treatment discontinuation.

Effect Measures: Pooled proportions with 95% confidence intervals (CIs) for single-arm aggregate data; Risk Ratios (RRs) or Odds Ratios (ORs) with 95% CIs for direct comparative (multi-arm) data.

Quality assessment / Risk of bias analysis Two independent investigators will critically appraise the methodological quality and risk of bias for all included studies. Any discrepancies or disagreements during the assessment process will be resolved through discussion and consensus, or by consulting a third senior reviewer.

Strategy of data synthesis Statistical analyses will be performed using R software . For single-arm cohorts, pooled incidence rates (ORR and adverse event rates) will be calculated utilizing a generalized linear mixed model (GLMM) with a logit transformation to appropriately weight studies with varying sample sizes. For direct head-to-head comparisons, pooled Risk Ratios (RRs) will be computed using the Mantel-Haenszel method. Statistical heterogeneity among studies will be evaluated using the Cochran's Q test and quantified by the I2 statistic. Given the anticipated clinical and methodological heterogeneity across the included diverse trials and observational studies, a random-effects model will be strictly adopted for all pooled syntheses.

Subgroup analysis Pre-specified subgroup analyses will be conducted to explore potential sources of heterogeneity and clinical variances:
Treatment Modality: Comparing the outcomes of FGFRi monotherapy versus FGFRi combined with ICIs (to assess the synergistic efficacy and cumulative toxicity).
Study Design: Comparing outcomes between rigorously controlled clinical trials versus observational/real-world studies (to evaluate real-world consistency).

Sensitivity analysis A "leave-one-out" sensitivity analysis will be systematically performed by iteratively omitting one study at a time and recalculating the pooled estimates. This approach

will evaluate the robustness of our primary findings and determine whether any single study or outlier disproportionately influences the overall pooled effect size or heterogeneity.

Country(ies) involved China.

Keywords FGFR; targeted therapy; immunotherapy.

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