International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Sex-Based Differences in the Efficacy of Immune Checkpoint Inhibitors (ICIs): A Protocol for Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - Not applicable.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025100019

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 October 2025 and was last updated on 7 October 2025.

INTRODUCTION

Review question / Objective To determine whether biological sex modifies the treatment benefit of ICIs across solid tumors in randomized controlled trials (RCTs). Specifically: Do males and females experience different overall survival (OS) and progression-free survival (PFS) benefits from ICIs compared with control therapies?

Rationale Patients with solid malignancies treated with ICIs; sex (female vs male, as reported) is evaluated as a potential effect modifier of ICI efficacy.

Condition being studied Patients with solid malignancies treated with ICIs; sex (female vs male, as reported) is evaluated as a potential effect modifier of ICI efficacy.

METHODS

Participant or population Patients with solid tumors enrolled in RCTs of ICIs. Studies must report, or allow derivation of, sex-stratified efficacy (female and male categories as defined by the trial). No restrictions by cancer type, line of therapy, ethnicity, or geography.

Intervention Any ICI-based regimen, including agents targeting CTLA-4 or PD-1/PD-L1, used as monotherapy or in combination.

Comparator Eligible comparators include placebo or standard of care regimens (e.g., chemotherapy, targeted therapy, best supportive care).

Study designs to be included Randomized controlled trials (RCTs).

Eligibility criteria Inclusion criteria:

RCTs of ICIs versus placebo/standard therapy;
Provide sex-stratified OS and/or PFS related results;
Participants with solid tumors.

Exclusion criteria:
Single-arm trials;
Trials where the control arm received ICIs;
Hematologic malignancy trials;
Missing sex-stratified data for primary outcomes.

Information sources We will search MEDLINE and EMBASE.

Main outcome(s) Overall survival (OS): time from randomization to death from any cause; extracted as hazard ratios (HRs) with 95% CIs.
Progression-free survival (PFS): time from randomization to progression or death; extracted as HRs with 95% CIs.

Quality assessment / Risk of bias analysis Risk of bias for RCTs will be assessed independently by two reviewers using the Cochrane Risk of Bias tool, with adjudication by a third reviewer as needed.

Strategy of data synthesis Primary synthesis will meta-analyze sex-specific HRs (female, male) using inverse-variance weighting. Heterogeneity will be quantified with I^2 and τ^2. A random-effects model will be used when between-study heterogeneity is non-trivial (e.g., $I^2 \geq 50\%$ or evident clinical/methodological diversity); otherwise, a fixed-effect model may be considered in sensitivity analyses.

Subgroup analysis Planned subgroups (as data allow): tumor type, ICI class (PD-1 vs PD-L1 vs CTLA-4), line of therapy, and combination vs monotherapy.

Sensitivity analysis Model choice (random-effects vs fixed-effect).
Outcome definition consistency across trials.
Publication bias will be explored using funnel plots and Begg/Egger tests when ≥10 studies contribute to the analysis.

Country(ies) involved United Kingdom.

Keywords Immune checkpoint inhibitors; sex; cancer treatment; efficacy.

Contributions of each author
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