INPLASY

Impact of Age on the Efficacy of Immune Checkpoint Inhibitors (ICIs) in Cancer Treatment: A Protocol for a 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.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 August 2025 and was last updated on 28 August 2025.

INTRODUCTION

Review question / Objective The aim of this systematic review is to compare the efficacy of ICIs in patients aged 65 years and older versus those under 65 years with various cancers, to better inform clinical practice. To this end, the proposed systematic review will address the following question: Which age group responds better to ICIs in terms of efficacy?

Rationale Despite the increasing number of clinical trials related to ICIs, there is a lack of comprehensive analyses highlighting age as a factor affecting their efficacy. The latest meta-analysis by Kasherman et al. (2022) [1], which focuses on similar themes, only includes literature up to 2018, highlighting a recent gap in knowledge. Our review aims to address this gap by systematically analyzing relevant studies.

Condition being studied This systematic review focuses on the use of ICIs in the treatment of various tumors, with a specific emphasis on the role of patient age as a determining factor in treatment outcomes.

METHODS

Participant or population Participants will include patients diagnosed with solid tumors who are enrolled in randomized controlled trials of ICIs. Eligibility criteria include patients aged 65 years and older and those under 65, with no exclusions based on gender, ethnicity, or cancer type.

Intervention The primary intervention includes ICIs, specifically targeting CTLA-4 and PD-1 pathways. Trials assessing the effectiveness of these therapies used alone or in combination with other treatments will be included.

Comparator Comparators will be standard treatment protocols or placebos. We will compare the efficacy of ICIs between older and younger populations.

Study designs to be included The review will include phase II/III randomized controlled trials (RCTs). Non-randomized studies and observational studies will be excluded to maintain rigor.

Eligibility criteria
Inclusion criteria:
Randomized controlled phase II/III clinical trials of ICIs.
Trials reporting age-related clinical outcomes with a cutoff age of 65 years.

Exclusion criteria:
Single-arm trials.
Phase I trials.
Trials where the control group received ICIs.
Trials involving hematologic malignancies.

Information sources We will search for studies in the following databases:
MEDLINE
EMBASE.

Main outcome(s) The main outcomes of this systematic review will focus on patient-relevant outcomes, specifically overall survival (OS) and progression-free survival (PFS). These outcomes will be measured as follows:

Overall Survival (OS): Defined as the time from randomization until death from any cause, reported as hazard ratios (HRs) with 95% confidence intervals (CIs).
Progression-Free Survival (PFS): Defined as the time from randomization until disease progression or death from any cause, also reported as HRs with 95% CIs.
Surrogate outcomes will be avoided; only outcomes directly related to patient survival will be considered.

Quality assessment / Risk of bias analysis The methodological quality of the included studies will be assessed using the Cochrane Risk of Bias Tool. This assessment will include evaluating potential biases, inconsistencies, and imprecision in the studies included in the review.

Strategy of data synthesis Data synthesis will involve the use of an inverse variance weighted model to combine effect sizes for both age groups. The outcomes will be expressed as risk ratios for dichotomous data and mean differences for continuous data. The following statistical methods will be employed based on heterogeneity assessment:
If the I^2 statistic is greater than 50% and the p-value is greater than 0.05, a fixed-effects model will be utilized to interpret the results, suggesting that observed heterogeneity is due to chance.
Conversely, if the I^2 statistic is less than or equal to 50%, a random-effects model will be used, indicating that there may be true variation in effects across studies.
Additionally, the Q_between test will be utilized to compare differences between age subgroups. Missing data and heterogeneity will be addressed using appropriate statistical methods to ensure robustness in our findings.

Subgroup analysis Subgroup analyses will focus on age stratification (participants aged <65 years versus ≥65 years) and the type of cancer.

Sensitivity analysis Sensitivity analyses will be pre-specified to explore the impact of methodological quality on the results. These analyses will include the following components:
Begg and Egger Tests: We will perform the Begg test for funnel plot asymmetry and the Egger regression test to assess potential publication bias in the included studies.
Funnel Plot: A funnel plot will be generated to visually inspect for publication bias and to evaluate the symmetry of effect sizes across studies. Any asymmetry observed will be thoroughly investigated.
Methodological Quality Sensitivity: We will assess the robustness of findings by including or excluding studies based on their methodological quality assessments.
Consistency across various sensitivity analyses will enhance the credibility of the results. By addressing potential biases through these tests, we aim to provide a more nuanced understanding of the data.

Country(ies) involved United Kingdom.

Other relevant information [1] Kim CM, Lee JB, Shin SJ, Ahn JB, Lee M, Kim HS. The efficacy of immune checkpoint inhibitors in elderly patients: a meta-analysis and meta-regression. ESMO Open. 2022;7(5):100577. doi:10.1016/j.esmoop.2022.100577.

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

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