

# INPLASY PROTOCOL

To cite: Raeber et al. A systematic review of interleukin-2-based immunotherapies in clinical trials for cancer and autoimmune diseases. Inplasy protocol 2022110086. doi: 10.37766/inplasy2022.11.0086

Received: 18 November 2022

Published: 18 November 2022

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**Support:** Public, no pharma funding.

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

## A systematic review of interleukin-2-based immunotherapies in clinical trials for cancer and autoimmune diseases

Raeber, ME<sup>1</sup>; Sahin, D<sup>2</sup>; Karakus, U<sup>3</sup>; Boyman, O<sup>4</sup>.

**Review question / Objective:** This study systematically reviews clinical results of improved IL-2-based compounds for the treatment of cancer or autoimmune diseases.

**Rationale:** The cytokine interleukin-2 (IL-2) can stimulate both effector immune cells and regulatory T (Treg) cells. The ability of selectively engaging either of these effects has spurred interest in using IL-2 for immunotherapy of cancer and autoimmune diseases. Thus, numerous IL-2-based biologic agents with improved bias or delivery toward effector immune cells or Treg cells have been developed. These improved IL-2-based compounds recently entered clinical trials. So far a systematic summary of these compounds including available clinical results is lacking.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 November 2022 and was last updated on 18 November 2022 (registration number INPLASY2022110086).

## INTRODUCTION

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Treg cells have been developed. These improved IL-2-based compounds recently entered clinical trials. So far a systematic summary of these compounds including available clinical results is lacking.

**Condition being studied:** Cancer and autoimmune diseases.

## METHODS

**Search strategy:** The ClinicalTrials.gov database was searched for registered clinical trials by applying in the field "Intervention/treatment" the search terms "interleukin-2" OR "interleukin 2" OR "IL-2" OR "IL2". The results were filtered for clinical trials with study start between 01.01.2010 and 31.10.2022.

**Participant or population:** Healthy participants in phase 1 clinical trials and patients with different autoimmune diseases and cancer in phase 1 to 3 studies.

**Intervention:** Improved interleukin-2 formulations.

**Comparator:** In controlled trials standard-of-care or placebo.

**Study designs to be included:** Phase 1 to 3 clinical trials.

**Eligibility criteria:** All clinical trials testing improved IL-2 formulations.

**Information sources:** ClinicalTrials.gov, MEDLINE Pubmed, authors knowledge, and grey literature.

**Main outcome(s):** Clinical efficacy of improved IL-2 formulations in cancer and autoimmune diseases. Available results will be reported, including overall survival, objective response, partial response, stable disease, progressive disease, and response according to validated clinical scores (e.g. Systemic Lupus erythematoses disease activity index).

**Quality assessment / Risk of bias analysis:** A Modified Downs and Black tool was

applied to assess bias of retrieved randomized controlled trials reporting clinical results. Scoring the studies according to the categories (a) reporting, (b) external validity, (c) internal validity and (d) power resulted in ranks of high (23–28 points), medium (15–22 points), and low (0–14 points) quality.

**Strategy of data synthesis:** Two authors will independently conducted the primary search and screened clinical trials testing improved IL-2-based compounds for inclusion. The resulting separate lists of clinical trials were compared, and improved IL-2-based compounds selected. In case of disagreement, a third author will be involved in the discussion to reach final consensus of whether to include or not a given trial. To find all registered clinical trials for identified improved IL-2 compounds, a second round of search will be performed for each of the identified compounds by using the ClinicalTrials.gov database, including alternative names of compounds. All identified clinical trials will be subsequently listed in Tables and amended with available information on the clinical development status. Clinical results will be retrieved from the described sources. Non-retrievable trials will be confirmed by an independent search by a second author.

**Subgroup analysis:** Subgroup analysis will be applied on patients with autoimmune diseases and cancer.

**Sensitivity analysis:** We will search the ClinicalTrials.gov database for all studies registered and conduct a secondary search for results available for these trials on MEDLINE, company websites, news sites, and other websites, reducing publication bias. We will include all retrieved clinical trials with improved IL-2 formulations independent of reported outcomes in order to avoid exclusion of specific compounds. We thus expect high sensitivity to meet the outcome of this study.

**Language restriction:** English.

**Country(ies) involved:** Switzerland.

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**Keywords:** Interleukin-2, IL-2, improved IL-2, IL-2 muteins, IL-2 complexes, IL-2 fusion proteins, cancer, autoimmune diseases, systematic review.

**Dissemination plans:** We aim to publish our results in peer-reviewed journals for public dissemination.

**Contributions of each author:**

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**Conflicts of interest:** MR, UK, and OB hold patents on improved IL-2-based compounds and OB is a shareholder of Anaveon. MR discloses paid consulting activities for Urogen. DS states no competing interests related to this work.