INPLASY PROTOCOL

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Anti-tumor efficacy of anti-PD-1/PD-L1 antibodies in combination with other anticancer drugs in solid tumors: a systematic review and meta-analysis

Inoue, T[1]; Narukawa M[2].

Review question / Objective: **The aim of this systematic review is to compare the combination of PD-1/PD-L1 inhibitors plus other anticancer drugs and monotherapies of PD-1/PD-L1 inhibitors in terms of antitumor efficacy in the solid tumors to better inform clinical practice. To this end, the proposed systematic review will address the following question: Which is the best choice to enhance response rate in subjects with solid tumors, PD-1/PD-L1 inhibitors plus cytotoxic agents or PD-1/PD-L1 inhibitors plus other targeted anticancer drugs?**
Condition being studied: **Cancer is the leading cause of death worldwide, accounting to approximately 9.6 million deaths worldwide in 2018. The clinical efficacy of immune checkpoint inhibitors (CPIs) including PD-1/PD-L1 inhibitors has been proven; however, it is also known that their efficacy as monotherapy is limited, with a response rate of 20% or less in solid tumors. The combination of CPIs and anticancer agents has been actively attempted in solid tumors area.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 October 2022 and was last updated on 02 October 2022 (registration number INPLASY2022100004).

INTRODUCTION

Review question / Objective: **The aim of this systematic review is to compare the combination of PD-1/PD-L1 inhibitors plus other anticancer drugs and monotherapies of PD-1/PD-L1 inhibitors in terms of antitumor efficacy in the solid tumors to better inform clinical practice. To this end, the proposed systematic review will address the following question: Which is the best choice to enhance response rate in subjects with solid tumors, PD-1/PD-L1 inhibitors plus cytotoxic agents or PD-1/PD-L1 inhibitors plus other targeted anticancer drugs?**

Rationale: The clinical efficacy of PD-1/PD-L1 inhibitors has been proven in clinical settings; however, it is also known that their efficacy as monotherapy is limited to a subset of patients with most tumor types studied to date. In this study, we conduct a meta-analysis to evaluate the contribution of combinations of anticancer drugs and PD-1/PD-L1 inhibitors to the improved clinical tumor response and antitumor efficacy, particularly the anticancer drugs that may induce immunogenic cell deaths and other molecular targeted agents.

Condition being studied: Cancer is the leading cause of death worldwide, accounting to approximately 9.6 million deaths worldwide in 2018. The clinical efficacy of immune checkpoint inhibitors (CPIs) including PD-1/PD-L1 inhibitors has been proven; however, it is also known that their efficacy as monotherapy is limited, with a response rate of 20% or less in solid tumors. The combination of CPIs and anticancer agents has been actively attempted in solid tumors area.

METHODS

Search strategy: We utilize ClinicalTrials.gov using each of the drug names (nivolumab including [nivolumab or BMS-936558 or MDX-1106 or MDX-1106-04 or nivolumab BMS or ONO-4538 or Opdivo], pembrolizumab including [pembrolizumab or Keytruda or ambrolizumab or lambrolizumab or mDX-400 or MK-3475 or SCH-900475], atezolizumab including [atezolizumab or MPDL-3280A or PRO-304397 or RG-7446 or RO-5541267 or Tecentriq], avelumab including [avelumab or MSB-0010682 or MSB-0010718C or PF-06834635 or Bavencio], and durvalumab in [durvalumab or MEDI-4736 or Imfinzi]) as the key words. We also use PubMed as a secondary data source and searched for clinical trials on solid tumors in which article type was registered as "Clinical Trial" using (pembrolizumab or nivolumab or atezolizumab or avelumab or durvalumab) and (clinical or trial) and (combination or plus or with) as the search terms. As a third data source, the ASCO Meeting Library and the ESMO are referenced using the search terms, including (nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) and (clinical or trial) and (combination or plus or with) in the abstract of the Annual Meetings.

Participant or population: This meta-analysis is based on patient population in randomized controlled trials (RCTs) and Non-randomized trials designed to compare FDA-approved combination therapies of anti PD-1/PD-L1 inhibitors as of December 2020 (i.e., nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) in addition to anticancer drug therapies with a comparator arm of either PD-1/PD-L1 inhibitor or other anticancer drug monotherapy.

Intervention: Combination therapies of anti PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) plus other anticancer drug therapies.

Comparator: Monotherapies of either PD-1/PD-L1 inhibitor (nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) or other anticancer drugs.

Study designs to be included: This meta-analysis includes randomized controlled trials (RCTs) designed to compare FDA-approved combination therapies of anti PD-1/PD-L1 inhibitors as of December 2020 (i.e., nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) in addition to anticancer drug therapies with a comparator arm of either PD-1/PD-L1 inhibitor or other anticancer drug monotherapy. Non-randomized trials are included if multiple treatment arms or cohorts of combination of either of the PD-1/PD-L1 inhibitors plus other anticancer drug-containing therapies and either of the PD-1/PD-L1 inhibitors or other anticancer drug monotherapy were within the same study.

Eligibility criteria: To evaluate the benefit of contribution of PD-1/PD-L1 inhibitors and non-immunomodulatory intent anticancer drugs for the clinical tumor response in

solid organ cancers, the following criteria are applied to select clinical studies to be evaluated in this study: (i) RCT or multi-arm/cohort studies that compared the efficacy of PD-1/PD-L1 inhibitor (nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) and anticancer drug combination therapy with a control group; (ii) studies with PD-1/PD-L1 inhibitor monotherapy or non PD-1/PD-L1 inhibitor treatment group as a control group; and (iii) studies in which efficacy data of ORR were published. Clinical trials that met the following criteria are excluded: (i) trials in patients with hematological cancers; (ii) trials in which immunotherapy (vaccines, CPIs other than the above PD-1/PD-L1 inhibitors, cytokines, and treatments with immunostimulatory effects such as Bacillus Calmette-Guérin (BCG)s and indoleamine 2,3-dioxygenase (IDO) inhibitors) are included; (iii) trials in which anticancer procedures (radiotherapy, tumorectomy, etc.) were included, and (iv) trials evaluating adjuvant or neo-adjuvant therapy.

Information sources: As a primary data source, we utilize ClinicalTrials.gov (https://ClinicalTrials.gov). We also use PubMed (https://pubmed.ncbi.nlm.nih.gov/) as a secondary data source and searched for clinical trials on solid tumors. Furthermore, as a third data source, the ASCO Meeting Library (https://meetinglibrary.asco.org/) and the European Society for Medical Oncology (ESMO (https://oncologypro.esmo.org/meeting-resources) are referenced to find clinical trials with solid tumor subjects in the abstract of the Annual Meetings.

Main outcome(s): The primary endpoint is tumor response rate (i.e., objective response rate; ORR). The tumor response rate is defined as the proportion of subjects whose objective response is confirmed complete response or partial response. For response rate, we collect the exact number of events and the total number of subjects included in the analysis. We also identify all the trials by ClinicalTrials.gov identification number (i.e., NCT number), identification number in other local study registration, or first author and the year of publication, and extract the following information from the reports: NCT number or other local study identification number, first author, publication year, intervention of experimental treatment and control groups, number of subjects enrolled in each group, study phase, subject allocation (i.e., randomized or non-randomized), and tumor type/disease condition. Analyses are conducted for the following groups: PD-1/PD-L1 inhibitor plus other anticancer drugs vs. control therapies, and PD-1/PD-L1 inhibitor plus other anticancer drugs vs. PD-1/PD-L1 inhibitor monotherapies.

Data management: Two independent reviewers (TI and MN) screen the names and designs of the clinical trials for the records derived from ClinicalTrials.gov or the titles and abstracts derived from the other data sources, followed by assessment of eligibility based on the full texts. Disagreements about eligibility are resolved through discussion. A single reviewer (TI) performs the initial data extraction using a standardized data collection form and second reviewer (MN) carefully checks them. Discrepancies are resolved through a discussion between them. The meta-analysis is performed using the RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Quality assessment / Risk of bias analysis: The quality and risk of bias of randomized controlled trials (RCTs) are assessed with the revised Cochrane Collaboration's risk of bias tool (Rob 2.0). Nonrandomized cohort studies are assessed using the Newcastle-Ottawa Scale, ranging between zero up to nine stars. We follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for the purpose of this analysis.

Strategy of data synthesis: The meta-analysis is performed using the RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). All analyses are performed using a random effects model because study

cohorts are expected to be different (e.g., multiple cancer types) and treatment regimens are not identical among studies. Analyses are conducted for the following groups: PD-1/PD-L1 inhibitor plus other anticancer drugs vs. control therapies, and PD-1/PD-L1 inhibitor plus other anticancer drugs vs. PD-1/PD-L1 inhibitor monotherapies. For all analyses, pooled risk ratios for ORR with 95% CI in the intention-to-treat (ITT) population are calculated, and P<0.05, using a two-sided test, is considered statistically significant. Heterogeneity among studies is assessed using the Q test and I2 index, and statistically significant heterogeneity is considered at P50%. Lastly, publication bias is evaluated by drawing a funnel plot of the effect size for each trial against the reciprocal of SE.

Subgroup analysis: Subgroup analyses by mechanism of action of the concomitant anticancer drugs, PD-1 or PD-L1 inhibitors, and tumor types are performed.

Sensitivity analysis: If heterogeneity exists, continue with sensitivity analysis after excluding heterogeneity.

Language restriction: Only randomized clinical trials/non-randomized clinical trials published in English are considered for inclusion.

Country(ies) involved: Japan.

Keywords: Solid tumors; Objective response rate; Immune checkpoint inhibitor; PD-1 inhibitor; PD-L1 inhibitor; Systematic review; Meta-analysis

Dissemination plans: Publication in a peer-review journal.

Contributions of each author:
Author 1 - Takashi Inoue - conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing-original draft, writing-editing.
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Conflicts of interest: Takashi Inoue is an employee of Astellas Pharma Inc.; however, employment in the company has not influenced the results and discussion presented in this paper. The other authors declare no competing interests.