INPLASY

Long-term survival outcomes of first-line immune checkpoint inhibitor in PD-L1 negative metastatic non-small cell lung cancer

INPLASY202480120
doi: 10.37766/inplasy2024.8.0120
Received: 26 August 2024
Published: 26 August 2024

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - Janakiraman Subramanian is in the Speaker Bureau of Astra-Zeneca, G1 therapeutics, Jazz, Janssen & Merck; and Advisory board of Astra-Zeneca, Cardinal, DSI, GLG, Guidepoint, OncoHost, Regeneron, and Sanofi. Dhruv Bansal is on the advisory board for Tempus.

INPLASY registration number: INPLASY202480120

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 August 2024 and was last updated on 26 August 2024.

INTRODUCTION

Review question / Objective To determine the long-term survival benefit of immune checkpoint inhibitor (ICI) in patients with PD-L1 negative metastatic non-small cell lung cancer (NSCLC) and evaluate the differential outcomes based on the number of ICI utilized in the first-line setting.

Rationale First-line ICI has been established as the standard of care for patients with metastatic NSCLC. However, the optimal treatment regimen for PD-L1-negative patients is still unclear.

Condition being studied First-line treatment of PD-L1 negative metastatic NSCLC.

METHODS

Search strategy EMBASE

1.'non small cell lung cancer'/exp OR 'non small cell lung cancer'
2.nsclc
3.'squamous cell lung carcinoma'/exp OR 'squamous cell lung carcinoma'
4.'lung adenocarcinoma'/exp OR 'lung adenocarcinoma'
5.'large cell lung carcinoma'/exp OR 'large cell lung carcinoma'
6.'lung adenosquamous carcinoma'/exp OR 'lung adenosquamous carcinoma'
7.#1 OR #2 OR #3 OR #4 OR #5 OR #6
8.'immune checkpoint inhibitor'/exp OR 'immune checkpoint inhibitor'
9.'pd1 antibody'/exp OR 'pd1 antibody'
10.'pd l1 antibody'/exp OR 'pd l1 antibody'
11.'cytotoxic t lymphocyte antigen 4 antibody'/exp OR 'cytotoxic t lymphocyte antigen 4 antibody'
12.'pembrolizumab'/exp OR 'pembrolizumab' OR 'nivolumab'/exp OR 'nivolumab' OR 'cemiplimab'/exp OR 'cemiplimab' OR 'atezolizumab'/exp OR

'atezolizumab' OR 'durvalumab'/exp OR 'durvalumab' OR 'ipilimumab'/exp OR 'ipilimumab' OR 'ticilimumab'/exp OR 'ticilimumab' OR 'ipilimumab plus nivolumab'/exp OR 'ipilimumab plus nivolumab' OR 'mk 3475'/exp OR 'mk 3475' OR 'keytruda'/exp OR Keytruda OR 'opdivo'/exp OR opdivo OR 'ono 4538'/exp OR 'ono 4538' OR 'bms 936558'/exp OR 'bms 936558' OR 'mdx1106'/exp OR mdx1106 OR 'regn 2810'/exp OR 'regn 2810' OR 'libtayo'/exp OR libtayo OR 'rg7446'/exp OR rg7446 OR 'mpdl3280a'/exp OR mpdl3280a OR 'tecentriq'/exp OR tecentriq OR 'medi4736'/exp OR medi4736 OR 'imfinzi'/exp OR Imfinzi OR 'bms 734016'/exp OR 'bms 734016' OR 'mdx 010'/exp OR 'mdx 010' OR 'mdx 101'/exp OR 'mdx 101' OR 'yervoy'/exp OR yervoy OR 'cp 675206'/exp OR 'cp 675206' OR imjudo OR ‘camrelizumab’/exp OR ‘camrelizumab’ OR ‘shr 1210’/exp OR ‘shr 1210’OR ‘airuika’/exp OR ‘airuika’ OR ‘toripalimab’/exp OR ‘toripalimab’OR ‘bgb a 317’/exp OR ‘bgb a 317’ OR ‘sintilimab’/exp OR ‘sintilimab’ OR ‘tyvyt’/exp OR tyvyt OR ‘ibi308’/exp OR ibi308
13.#8 OR #9 OR #10 OR #11 OR #12
14.'randomized controlled trial'/de OR 'controlled clinical trial'/de OR random*:ti,ab,tt OR 'randomization'/de OR 'intermethod comparison'/de OR placebo:ti,ab,tt OR compare:ti,tt OR compared:ti,tt OR comparison:ti,tt OR (open NEXT/1 label):ti,ab,tt OR 'double blind procedure'/de OR (parallel NEXT/1 group*):ti,ab,tt OR crossover:ti,ab,tt OR 'cross over':ti,ab,tt OR ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt OR ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt OR assigned:ti,ab,tt OR allocated:ti,ab,tt OR (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt OR volunteer:ti,ab,tt OR volunteers:ti,ab,tt OR 'human experiment'/de OR trial:ti,tt OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
15.((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt) OR ('cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt)) OR ('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt) OR 'update review':ab OR (databases NEAR/5 searched):ab) OR ('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt)) OR (nonrandom*:ti,ab,tt NOT random*:ti,ab,tt) OR 'random field*':ti,ab,tt OR ('random cluster' NEAR/4 sampl*):ti,ab,tt OR (review:ab AND review:it NOT trial:ti,tt) OR ('we searched':ab AND (review:ti,tt OR review:it)) OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
16.#14 NOT #15
17.‘metastasis’/exp OR ‘metastasis’
18.‘advanced cancer’/exp OR ‘advanced cancer’
19.‘cancer recurrence’/exp OR ‘cancer recurrence’
20.#17 OR #18 OR #19
21.#7 AND #13 AND #16 AND #20
Ovid Medline
1.non small cell lung cancer.mp. or exp Carcinoma, Non-Small-Cell Lung/
2.lung adenocarcinoma.mp. or exp "Adenocarcinoma of Lung"/
3.exp Carcinoma, Squamous Cell/ or squamous cell carcinoma lung.mp.
4.large cell carcinoma lung.mp. or exp Carcinoma, Large Cell/
5.exp Carcinoma, Adenosquamous/ or adenosquamous carcinoma lung.mp.
6.nsclc.mp.
7.immune checkpoint inhibitor.mp. or exp Immune Checkpoint Inhibitors/
8.exp Programmed Cell Death 1 Receptor/ or pd1 antibody.mp.
9.exp B7-H1 Antigen/ or pdl1 antibody.mp.
10.exp CTLA-4 Antigen/ or ctla4 antibody.mp.
11.nivolumab.mp. or exp Nivolumab/
12.ipilimumab.mp. or exp Ipilimumab/
13.pembrolizumab.mp. or cemiplimab.mp. or atezolizumab.mp. or durvalumab.mp. or tremelimumab.mp. or ticilimumab.mp. or mk-3475.mp. or keytruda.mp. or opdivo.mp. or ono-4538.mp. or bms-936558.mp. or mdx1106.mp. or regn2810.mp. or libtayo.mp. or rg7446.mp. or mpdl3280a.mp. or tecentriq.mp. or medi4736.mp. or imfinzi.mp. or bms-734016.mp. or mdx-010.mp. or mdx-101.mp. or yervoy.mp. or cp-675206.mp. or imjudo.mp. or camrelizumab.mp. or SHR-1210.mp. or airuika.mp. or toripalimab.mp. or tuoyi.mp. or js001.mp. or

tislelizumab.mp. or BGB-A317.mp. or sintilimab.mp. or tyvyt.mp. or ibi308.mp.
14.randomized controlled trial.pt. or controlled clinical trial.pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.
15.exp animals/ not humans.sh.
16.14 not 15
17.metastasis.mp. or exp Neoplasm Metastasis/
18.advanced cancer.mp. or cancer recurrence.mp.
19.1 or 2 or 3 or 4 or 5 or 6
20.11 or 12 or 13
21.17 or 18
22.16 and 19 and 20 and 21
CENTRAL
1.MeSH descriptor:[Carcinoma, Non-Small-Cell Lung] explode all trees
2.MeSH descriptor:[Adenocarcinoma of Lung] explode all trees
3.MeSH descriptor:[Carcinoma, Large Cell] explode all trees
4.MeSH descriptor:[Carcinoma, Adenosquamous] explode all trees
5.MeSH descriptor:[Carcinoma, Squamous Cell] explode all trees
6.MeSH descriptor:[Immune Checkpoint Inhibitors] explode all trees
7.MeSH descriptor:[Programmed Cell Death 1 Receptor] explode all trees
8.MeSH descriptor:[B7-H1 Antigen] explode all trees
9.MeSH descriptor:[CTLA-4 Antigen] explode all trees
10.MeSH descriptor:[Nivolumab] explode all trees
11.MeSH descriptor:[Ipilimumab] explode all trees
12.'pembrolizumab'or'cemiplimab'or'atezolizumab' or'durvalumab'or' tremelimumab'or 'ticilimumab'or'camrelizumab'or'toripalimab'or'tislelizumab'or'sintilimab'or'mk-3475'or'keytruda'or'opdivo'or'ono-4538'or'bms-936558'or'mdx1106'or'regn2810'or'libtayo'or'rg7446'or'mpdl3280a'or'tecentriq'or'medi4736'or'imfinzi'or'bms-734016'or'mdx-010'or'mdx-101'or'yervoy'or'cp-675206'or'imjudo' or'SHR-1210'or'airuika'or'tuoyi'or'js001'or'BGB-A317'or'tyvyt'or'ibi308'
13.MeSH descriptor: [Neoplasm Metastasis] explode all trees
14.'advanced cancer' or 'cancer recurrence'
15.MeSH descriptor:[Randomized Controlled Trial] explode all trees
16.MeSH descriptor:[Clinical Trials, Phase III as Topic] explode all trees
17.MeSH descriptor:[Randomized Controlled Trials as Topic] explode all trees
18.#1 or #2 or #3 or #4 or #5 or #6
19.#7 or #8 or #9 or #10 or #11 or #12
20.#13 or #14
21.#15 or #16 or #17
22.#18 and #19 and #20 and #21.

Participant or population PD-L1 negative metastatic or recurrent NSCLC patients who did not receive prior systemic therapy; for nonsquamous histological subtype, they must not have EGFR mutation or ALK rearrangement.

Intervention ICI-based therapy.

Comparator Chemotherapy only.

Study designs to be included Phase III randomized controlled trials.

Eligibility criteria Patients must not receive any previous systemic therapy. At least one group from the study must receive ICI with or without chemotherapy as their first-line treatment, while one group received chemotherapy alone with or without placebo. Patients with nonsquamous histological subtype must not have EGFR mutations or ALK rearrangements. Eligible studies must report the hazard ratio and 95% confidence intervals for the overall survival (OS) or progression-free survival (PFS).

Information sources Electronic databases.

Main outcome(s) Overall survival (OS) and progression-free survival (PFS). OS and PFS were defined as the time from randomization to death, and the time from randomization to disease progression or death, respectively.

Additional outcome(s) None.

Data management A standardized data collection form.

Quality assessment / Risk of bias analysis Quality assessment: the Jadad quality assessment scoring system for randomized controlled studies.

Strategy of data synthesis Program: R version 4.3.2 software (Vienna, Austria) and “meta” version 7.0-0. Calculation method: the generic inverse variance method and random effects model due to the high likelihood of interstudy heterogeneity. Statistical heterogeneity: via Cochran’s Q test and I2 statistic.

Subgroup analysis Based on histological subtype (nonsquamous vs squamous).

Sensitivity analysis None.

Language restriction No.

Country(ies) involved Unites States.

Keywords NSCLC; immunotherapy; immune checkpoint inhibitor; survival outcome; overall survival; progression-free survival; lung cancer.

Dissemination plans Publication as a full manuscript.

Contributions of each author

Author 1 - Ben Ponvilawan - Author 1 designed the study, screened studies, performed statistical analysis, and drafted the manuscript.
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