SIOG-IO Reporting of Older Subgroups Enrolled to Pivotal Immunotherapy Trials 2018-2022 V.1

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VERSION 1

OCT 10, 2023

OPEN ACCESS

DOI:
dx.doi.org/10.17504/protocols.io.3byl4q5d2vo5/v1

Protocol Citation: Mac Eochagain Colm 2023. SIOG-IO Reporting of Older Subgroups Enrolled to Pivotal Immunotherapy Trials 2018-2022. **protocols.io** https://dx.doi.org/10.17504/protocols.io.3byl4q5d2vo5/v1

Protocol status: Working

Created: Oct 09, 2023

ABSTRACT

Reporting of older subgroups enrolled to drug trials in solid oncology immunotherapy leading to FDA approvals between 2018-2022

Last Modified: Oct 10, 2023

PROTOCOL integer ID:
89041

Review Title

1 Reporting of Older Subgroups in Immunotherapy Registration Trials, 2018-2022

Language

2 English

Anticipated or Actual Start Date

3 15/10/23

Anticipated Completion Date

4 28/02/2024

Stage of Review at the time of Submission

5 Preliminary searches commenced 28 September 2023

Review Stage

6 Preliminary Searches: Yes
Piloting of the study selection process: Yes
Formal Screening: No
Data Extraction: No
Risk of Bias: No
Data Analysis: No

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Funding Sources

11 None

Grant Sources

12 None

Conflicts of Interest

13 NB: Pfizer, Sanofi, Astellas, ExactSciences, Lilly, Novartis, AbbVie, Roche, Servier, Gilead, Astrazeneca.

Other Authors: No conflicts of interest

Review Question

14 **Population**
Older patients enrolled to FDA registration clinical trials of immunotherapy in solid-tumor malignancies, where FDA registration was granted between 2018-2022.

Intervention
Studies assessing immunotherapy for solid-tumor malignancies, and leading to FDA registration between 2018-2022 will be included. Trials defined as paediatric trials or trials with a mean participant age of under 18 years will be excluded. Registration trials assessing immunotherapy in haematological malignancies, including lymphoma, will be excluded. Approvals relating exclusively to biosimilar or alternative formulation indications will be excluded.

Comparator
Studies including any comparator; including no comparator, or placebo comparators, will be included.

Outcome
Reporting completeness for older subgroups enrolled to FDA registration studies of immunotherapy, where such registration was granted between 2018-2022. The following domains will be systematically and hierarchically assessed according to criteria established by Chan & Altman (10.1001/jama.291.20.2457), and developed by MacEochagain & Battisti (10.1007/s10549-023-07081-0):

- (Protocol-defined) Clinical Efficacy Endpoints among the older subgroup
- Baseline characteristics among the older subgroup
- Health-related quality of life among the older subgroup
- Toxicity among the older subgroup
- The following domains will be assessed using descriptive statistics, as appropriate:
- % of patients within the older subgroup
- % of total enrolment stratified by ECOG score
- Conduct and reporting of Baseline Geriatric Assessment
- Conduct and reporting of Geriatric-Specific Geriatric PRO Outcome Metrics
- Textual analysis of trial inclusion and exclusion criteria
- Textual analysis of efficacy outcomes
- Trial characteristics (including but not limited to: trial phase, enrolment size, treatment setting)

Searches

15 MEDLINE/PubMed will be searched on 22/09/23 in accordance with the search strategy outlined in section in the following document: https://docs.google.com/spreadsheets/d/1TJN-s0i6U8ueN67ldYe4zj_GLUZ1Q-kG/edit?usp=sharing&ouid=111700888844224692585&rtpof=true&sd=true

The search strategy was devised in collaboration with Mr Paul Howell, librarian at David Adams Library, Royal Marsden Hospital, London. Publications between 01/01/2000 and 22/09/2023 will be included.

Condition or domain being studied

16 Reporting of older subgroups enrolled to FDA registration trials of cancer immunotherapy (2018-2022).

Participants/Population

17 Subgroup reporting of 'older subgroups' enrolled to registration trials (2018-2022) in immunotherapy for solid-tumor malignancies will be assessed. In accordance with established precedent within medical literature, 'older subgroups' will generally be defined as subgroups of patients aged 65 and older. An absolute minimum of 60 years will be used to define an 'older subgroup' where a stratification threshold of 65 years is not provided by individual studies.

Intervention/Exposure

18 All studies leading to Food and Drug Administration of immunotherapy indications in solid-tumor malignancy for adult populations, where registration was granted between 2018-2022 inclusive, will be included, with exclusion criteria as previously described herein. Immunotherapy is defined here as including: (anti-) PD1, PDL1, CTLA-4, and Lag-3 therapies only, whether given as monotherapy, or combination therapy (including in combination, before, or following any of, or any combination of, chemotherapy, radiotherapy, hormonotherapy, surgery, or targeted therapy, including but not exclusively: tyrosine kinase inhibitors, monoclonal antibodies, antibody-drug conjugates, PARP inhibitors, CDK4/6 inhibitors), regardless of whether this treatment was given in the curative (neo-adjuvant / adjuvant), palliative (metastatic), or any other setting.

Comparator/Control

19 Studies including any comparator; including no comparator, or placebo comparators, and multi-arm studies, will be included.

Types of study to be included

20 Inclusion Criteria: All studies leading to Food and Drug Administration of immunotherapy indications in solid-tumor malignancy, where registration was granted between 2018-2022 inclusive, will be included.

Identified trials will be assessed for the presence of both primary and secondary peer-reviewed publications containing or potentially containing information regarding older subgroups enrolled to the study, as outlined in the search strategy. Data and publication references archived at the trial's clinicaltrials.org repository will also be assessed for older-population subgroup data. Review and compilation of data sources will be carried out by two reviewers working independently. Scoring of individual trials will be conducted by two (different) reviewers, working independently, with conflicts resolved by consensus.

Exclusion Criteria:
Review papers
Pharmacokinetic/Preclinical focus
Wrong Study
Economic Analyses
Non peer-reviewed data, including abstract / conference proceedings data
Publications not in English, or without an English translation
Meta-analyses / combined analyses
Real world data / Real world comparison
Commentaries

Correspondence
Guidelines
Errata
Data not in the public domain

Context

21 Individual PubMed/MEDLINE searches will be conducted for each included clinical trial, as outlined in the search strategy.

Search results will be screened using Covidence (Title/Abstract) by two reviewers for relevant, or potentially relevant primary or secondary publications, which may contain information relating to older subgroups enrolled to the study. Relevant data sources relating to individual trials will be compiled in datasets according to the underlying clinical trial.

Each trial-level dataset will comprise all of the available published data for that individual study (i.e. relevant or potentially relevant publications, including such publications' supplementary information, as well as results reported in the trial's ClinicalTrials.gov repository). Review, extraction, and compilation of geriatric subgroup information for individual trials from individual trial datasets will be carried out by two reviewers working independently, using the Covidence tool for systematic reviews. Scoring of individual trials will be conducted by two (different) reviewers, working independently, with conflicts resolved by consensus.

Main Outcome(s)

22 Efficacy endpoints will be determined with reference to the most recent available study protocol or statistical analysis plan. In instances where no protocol or statistical analysis plan is available in the public domain, reference will be made to licensing authority documentation.

Where studies assess efficacy across multiple timepoints, or according to multiple definitions, (for instance: Overall Survival (OS) assessed at year 1, 2, 3, or Progression-Free Survival (PFS) assessed both centrally and by local investigators), these will be considered as a single endpoint; provided data is available for at least one of the defined components within such compound endpoints, these data will be considered to be assessable.

Where endpoints are defined hierarchically and differentially in the protocol as distinct primary and secondary endpoints (i.e. primary endpoint: PFS in the intention to treat population; secondary endpoint: PFS in the population with brain metastases), these will be considered to be separate endpoints.

Immature efficacy endpoints for which no interim data are available in the full study cohort will be excluded from relevant analyses.

Measures of effect

23 Reporting completeness for efficacy endpoints will be assessed and categorised as being either complete, partial, qualitative, or unreported, according to hierarchical criteria assessing the availability of data relating to sample size, effect size, and measures of precision, as well as requirements to satisfy criteria for inclusion metaanalysis,to which vary according to the statistical characteristics of the data examined (i.e. paired or unpaired, continuous or binary, or survival data as follows:

Level of Reporting: Complete
Reported Data: Number of participants per group, Effect size, Precision or precise P value for continuous data
Sufficient for Inclusion in Metaanalysis: Yes

Level of Reporting: Partial
Reported Data: Effect size or precision (± p value ± sample size)
Sufficient for Inclusion in Metaanalysis: No

Level of Reporting: Qualitative
Reported Data: P value ± sample size
Sufficient for Inclusion in Metaanalysis: No

Level of Reporting: Unreported
Reported Data: Not available
Sufficient for Inclusion in Metaanalysis: No

Additional Outcomes

24 Baseline characteristics
Health Related Quality of Life
Toxicity

Trial characteristics including:

- % of patients within the older subgroup
- % of total enrolment stratified by ECOG score
- Conduct and reporting of Baseline Geriatric Assessment
- Conduct and reporting of Geriatric-Specific Geriatric PRO Outcome Metrics
- Textual analysis of trial inclusion and exclusion criteria
- Textual analysis of efficacy outcomes
- Other trial characteristics (including but not limited to: trial phase, enrolment size, treatment

setting)

Measures of Effect

25 Scoring of Baseline characteristics, Health related Quality of Life, and Toxicity Domains:

Domain Minimum Threshold

Baseline characteristics

Performance status OR comorbidities
AND
>=1 Key prognostic OR predictive factor(s)

Toxicity
>=3 Key toxicity Domain(s) by organ site
OR
Overall G3 toxicity AND >=1 toxicity domain

HRQOL
>=1 Validated HRQOL instrument(s)

Level of reporting Reported Data
Complete: Meets minimum threshold; including numerical data sufficient for inclusion in meta-analysis

Partial: Meets minimum threshold; including numerical data insufficient for inclusion in meta-analysis

Qualitative: Meets minimum threshold; without numerical data

Unreported: Does not meet minimum threshold

Reporting of other domains will be by descriptive statistical methods +/- exploratory analyses only.

Data Extraction (Selection & Coding)

26 Food and Drug Administration oncology approvals in immunotherapy granted between 01/01/2018 and 31/12/2022 will be retrieved from publicly available FDA sources (Center for Drug Evaluation, Research. Drug Approvals and Databases. U.S. Food and Drug Administration. https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases). Studies relating to approval of biosimilar, alternative formulation, paediatric (as

defined by the study authors, or where mean/median participant age is 18), and haematology indications, including lymphoma, will be excluded.

Individual PubMed/MEDLINE searches will be conducted for each included clinical trial, as outlined in the search strategy (s17). Search results will be screened using Covidence (Title/Abstract) by two reviewers for relevant, or potentially relevant primary or secondary publications, which may contain information relating to older subgroups enrolled to the study. Included studies will be assessed in full, including publication supplements and data archived at the study's ClinicalTrials.gov repository, by two reviewers. Data relating to the following domains (as they relate to older subgroups) will be collected:
Clinical Efficacy Endpoints (as defined by the study protocol / statistical analysis plan)
Baseline characteristics
Health-related quality of life
Toxicity
% of patients within the older subgroup
% of total enrolment stratified by ECOG score
Conduct and reporting of Baseline Geriatric Assessment
Conduct and reporting of Geriatric-Specific Geriatric PRO Outcome Metrics
Textual analysis of trial inclusion and exclusion criteria
Following screening and compiling of data from relevant publications, the completeness of reporting for individual trials will be scored by two reviewers according to hierarchical criteria established by Chan & Altman (10.1001/jama.291.20.2457), and further developed by MacEochagain & Battisti (10.1007/s10549-023-07081-0).

Risk of Bias

27 Risk of bias will not be formally assessed. This study will assess outcome reporting, rather than treatment effect.

Strategy for data synthesis

28 This study aims to assess the completeness and adequacy of reporting among older subgroups, without intending to undertake cross-trial comparisons, meta-analysis, or synthesis of data across or between trials. All data results presented will be descriptive in nature. No meta-analysis of collected data is planned.

Analysis of subgroups or subsets

29 Not applicable. The intention of the review is to assess reporting of older subgroups, as previously defined. Analysis of further subgroups within this (older) subgroup (i.e. according to

gender, ECOG, clinical stage, etc) population are not planned.

Type and Method of Review

30 Systematic review

Health area of the review

31 Solid tumor oncology
Geriatric oncology

Language

32 English

Country

33 Ireland

Other Registration Details

34 Not applicable

Dissemination Plans

35 This review will be published in an international peer reviewed journal focussing on cancer, immunotherapy, or geriatric oncology.

Keywords

36 Geriatric oncology, subgroup, reporting, older, cancer, immunotherapy

Details of any existing review of the same topic by the same ...

37 Not applicable

Current review status

38 Screening commenced 23.09.23