Supplement Material 1

1. Data sources and searches

Systematic searches were conducted on March 30, 2023, in EMBASE and PubMed. The search strategy mirrored the approach of Park et al. [1] and Meyer et al. [2], with minor modifications, such as modifying search terms to focus only on biomarker-driven, adaptive design phase II oncology trials, and we supplemented the search with a review of bibliographies from included publications and trial registries (ClinicalTrials.gov) for registered precision oncology trial protocols. Further details on the number of hits from each database are presented in S5-S7 Tables.

2. EQUATOR Checklist

The EQUATOR checklist for the systematic review of precision oncology clinical trials is provided (S1 Table).

3. Systematic review protocol

Precision oncology clinical trials: A systematic review of phase II clinical trials with biomarker-driven, adaptive design

1) Introduction

Better understanding and expanded knowledge in tumor biology and biomarkers together with the advancement of diagnostic technology, including NGS, have been driving the "one-size-fits-all" rationale of cancer treatments toward more personalized or tailored therapies according to the unique tumor molecular profile. The rise of novel clinical trial designs that aim to identify biomarker-matched subgroups of patients that would benefit the most from targeted agents accompanied the introduction of precision medicine in oncology [3].

Wider implementation of biomarker(s) in clinical trials has fueled the evolvement of an *adaptive* design, which allows prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial [4]. The term *master protocol* is frequently used to describe such trials implementing an adaptive design, with a variety of terms, such as *umbrella*, *basket*, or *platform*, describing specific designs [5].

The innovative clinical trials were designed to assess the efficacy and safety of anticancer agent(s) in more efficient and faster ways [6]. They helped the investigators evaluate a single investigational drug and/or their combination in different populations defined by different cancers, disease stages for specific cancers, histology, number of previous therapies, genetic or other biomarkers, or demographic characteristics (i.e., *basket trial*) or evaluate multiple investigational drugs administered as single drugs or as their combination in single disease population (i.e., *umbrella trial*). The *Platform* trial is a clinical study that is designed to evaluate multiple investigational drugs and/or drug

combination regimens across multiple tumor types [5].

Regulatory authorities, such as the United States Food and Drug Administration (U.S. FDA) have published guidelines regarding precision oncology clinical trials (POCTs) alongside this advancement [4,5]. Investigator-initiated precision oncology clinical trials have been quickly translated into sponsor-initiated precision oncology clinical trials (SIPOCTs), which were conducted to gain regulatory approval for a new anticancer agent in less time with a smaller number of patients.

Early POCTs reported rather disappointing results and thus did not result in any regulatory approval, but trials have been conducted more recently yielded positive results and become the basis of regulatory approvals, frequently through accelerated pathways. Thus, we aimed to systematically review and analyze the efficacy and safety profile of POCTs as well as their infrastructure with funding sources, other operational statuses, and requirements.

2) Methods and analysis

(1) Search strategy

Our search strategy mirrored the search strategy of preceding systematic reviews by Park et al. [1] and Meyer et al with minor modifications. Search terms were modified to focus on biomarker-driven, adaptive design, phase II trials (S5-S7 Tables). We will search EMBASE and PubMed/MEDLINE to identify eligible studies and trials. The search will be supplemented with a review of bibliographies from included publications and trial registries (ClinicalTrials.gov) for registered POCTs.

(2) Study inclusion and exclusion criteria

Peer-reviewed publications, conference abstracts, and clinical registry records reporting on precision oncology trials that are ongoing or have already been conducted will be included in the review. The eligible papers, protocols, and abstract are restricted to English language only.

We as two teams in pair will independently review all abstracts and proceedings identified in the literature searches. The full-text publications of potentially relevant abstracts will then be retrieved and assessed for eligibility. We will also screen the bibliographies of published literature reviews on precision oncology trial protocols and trial registries. Discrepancies in study selection will be resolved by discussion or, when necessary, by a third investigator. Broader eligibility criteria according to PICOS are presented in S4 Table.

We will further apply the exclusion conditions described below in order: (1) noncancer disease and non-human studies; (2) nonintervention clinical studies, including music therapy, psychological treatment, behavioral therapy, cognitive therapy, etc., survey or online-based opinion gathering of patients with cancer, and clinical study design; (3) intervention trials but noncancer drug studies, including diagnostics (positron emission tomography–CT scan, CT scan, and magnetic resonance

imaging, etc.), screening, surgery, radiation therapy, photodynamic therapy, digital therapeutics, chemoprevention, etc.; (4) preclinical studies, including in vitro cell line and/or in vivo animal studies; (5) editorials, letters to the editor, news in brief, and comments; (6) case reports, case series, cross-sectional studies, review articles, systematic reviews, meta-analysis, cost-effectiveness analysis, pooled analysis, secondary analysis, and post-hoc analysis; (7) biomarker study, including retrospective biomarker analysis, correlative biomarker analysis and imaging biomarker study, genetic analysis, quality of life assessment, management of adverse events (AEs) by oncologic drugs, and pharmacokinetics/pharmacodynamics study, mode of action or proof-of-concept study; (8) proposal of clinical study protocol alone with no clinical outcomes; (9) clinical study, excluding an adaptive design or master protocol; (10) phase I or III clinical study with adaptive, biomarker-driven master protocol design.

(3) Data extraction

The studies retrieved during the search will be screened for eligibility, and those identified as being potentially eligible will be fully assessed against the inclusion/exclusion criteria. Data from the eligible studies will be extracted using a standardized form to be developed by the team prior to the beginning of the literature search. Study design elements, patient characteristics, and outcomes will be extracted independently by investigators using the standardized data extraction template. Information on trial registry, trial recruitment status, phase, number of clinical centers, sample size, trial duration, interventions and control, disease area, age of population, number of conventional diseases recruited, key eligibility for stratification, number of subgroups defined, and geographic location of the trials will be recorded.

(4) Risk of bias

The systematic literature review will be designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

We will conduct the assessment, to ensure consistency and to minimize individual bias, using the Cochrane risk of bias tools [7]. Every sub-trial/arm will be assessed separately by reading all relevant literature. Disagreements will be resolved by discussion, as necessary.

(5) Data synthesis and analysis

A narrative synthesis will be used to present the current landscape of precision oncology clinical trials based on key features including trial sponsor and coordinating center, number of study sites and locations, funding source, cancer indications, type of treatment, number of patients, phase of trial,

type of study (basket, umbrella, platform, etc.) biomarker screening methods and type of specimen, type of endpoints (objective response rate or others), presence of independent central review committee, and stage of study (whether it proceeds to expansion cohort or phase III study, or whether it was given an FDA approval). The narrative synthesis will be done under four broad categories: (1) infrastructure for trial operations, (2) biomarker screening, (3) efficacy results, (4) and safety results.

References

1. Park JJ, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials. 2019;20:572.
2. Meyer EL, Mesenbrink P, Dunger-Baldauf C, Fulle HJ, Glimm E, Li Y, et al. The evolution of master protocol clinical trial designs: a systematic literature review. Clin Ther. 2020;42:1330-60.
3. Janiaud P, Serghiou S, Ioannidis JP. New clinical trial designs in the era of precision medicine: an overview of definitions, strengths, weaknesses, and current use in oncology. Cancer Treat Rev. 2019:73:20-30.
4. Adaptive design clinical trials for drugs and biologics guidance for industry [Internet]. U.S. Food and Drug Administration; 2019 [cited 2023 Dec 29]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry.
5. Master protocols: efficient clinical trial design strategies to expedite development of oncology drugs and biologics guidance for industry [Internet]. U.S. Food and Drug Administration; 2019 [cited 2023 Dec 29]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and.
6. Kim ES, Herbst RS, Wistuba II, Lee JJ, Blumenschein GR Jr, Tsao A, et al. The BATTLE trial: personalizing therapy for lung cancer. Cancer Discov. 2011;1:44-53
7. Higgins JPT, Green S. The Cochrane handbook for systematic reviews of interventions, version 5.1.0. London: The Cochrane Collaboration, 2011 [cited 2023 Dec 29]. Available from: http://handbook.cochrane.org