Cancer Treatment Reviews 73 (2019) 20–30

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Hot Topic

New clinical trial designs in the era of precision medicine: An overview of definitions, strengths, weaknesses, and current use in oncology

Perrine Janiaud[a], Stylianos Serghiou[a,b], John P.A. Ioannidis[a,b,c,d,e,*]

[a] Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, CA 94305, USA
[b] Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA 94305, USA
[c] Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA
[d] Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, CA 94305, USA
[e] Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, CA 94305, USA

ARTICLE INFO

Keywords:
Precision medicine
Biomarker
Basket trial
Umbrella trial

ABSTRACT

With expanding knowledge in tumor biology and biomarkers, oncology therapies are increasingly moving away from the "one-size-fits-all" rationale onto biomarker-driven therapies tailored according to patient-specific characteristics, most commonly the tumor's molecular profile. The advent of precision medicine in oncology has been accompanied by the introduction of novel clinical trial designs that aim to identify biomarker-matched subgroups of patients that will benefit the most from targeted therapies. This innovation comes with the promise of answering more treatment questions, more efficiently and in less time. In this article, we give an overview of the different biomarker-based designs, comparing the features of enrichment, randomize-all, umbrella, and basket trials, and highlighting their advantages and disadvantages. We focus more on the novel designs known as master protocols, which include umbrella and basket trials. We have also conducted a search in ClinicalTrials.gov for registered oncology-related protocols of ongoing or completed trials labeled as umbrella or basket trials for solid tumors; we also included additional relevant trials retrieved from other reviews. We present and discuss the key features of the 30 eligible basket trials and 27 eligible umbrella trials. Only a minority of them are randomized (2 and 9, respectively), including three trials with adaptive randomization. Five of these trials have been completed as of July 2018. Precision medicine trial designs fuel new hopes for identifying best treatments, but there is also the potential for hype. The benefits and challenges associated with their use will need continued monitoring.

Introduction

The Food and Drug Administration (FDA), in 2017 and for the first time, approved a cancer treatment based on a common biomarker in lieu of the traditional tumor location in the body. The immune checkpoint inhibitor, pembrolizumab, is now labeled to treat any type of solid tumors expressing either microsatellite instability or mismatch repair biomarkers [1]. This milestone illustrates an evolving drastic alteration of the treatment landscape in oncology. The therapeutic paradigm is shifting from general purpose cytotoxic drugs towards precision medicine whereby drugs target specific tumors by inhibiting their peculiar growth and/or survival mechanisms [2]. The degree of individualization in precision medicine may still vary. Some molecular markers may define a set of tumors (and accompanying treatment options) that may still be pertinent to many thousands of patients. In other cases, tailoring of treatment is indeed highly individualized, as in the situation where treatment protocols aim to target and boost each specific patients' immune system against the specific cancer cells of his/her malignancy [3].

The common denominator in precision medicine approaches is that the therapeutic strategy is tailored using distinct patient characteristics, most commonly the biomarker-defined molecular profiles of tumors [4]. The aim is to optimize the outcome in biomarker-matched patients, while reducing, as much as possible, deleterious effects on healthy cells [4]. The expected benefits of using targeted therapies on biomarker-matched patients in oncology has been discussed in several reviews [5,6]. The number of predictive markers in clinical use in oncology is increasing [7] and there are over 40 assays approved as a companion diagnostic device by the FDA as of 2018 [8]. Genomic profiling is also being done routinely in many oncology centers [9].

* Corresponding author at: Departments of Medicine, Health Research and Policy, Biomedical Data Science, and Statistics, and Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, CA 94305, USA.
E-mail address: jioannid@stanford.edu (J.P.A. Ioannidis).

https://doi.org/10.1016/j.ctrv.2018.12.003
Received 14 September 2018; Received in revised form 7 December 2018; Accepted 10 December 2018

The accumulation of information in tumor biology and the development of efficient screening technologies [10,11] has propelled oncology clinical research to the forefront of precision medicine [12]. No other medical specialty to-date has had so many proposed and adopted precision medicine applications. However, this rapid growth challenges our ability to conduct appropriate and efficient clinical trials to keep up with this pipeline of new proposed treatments in precision settings. Proper testing in clinical trials is indispensable to validate claims of efficacy and safety.

The proportion of trials requiring the presence or absence of a genomic alteration increased over 5-fold between 2006 and 2013 [13] and the pace continues to accelerate. In 2017, trials using biomarkers to stratify patients most likely to respond to the treatment constituted 34% of the industry-sponsored oncology trials [14]. Such biomarker enrichment approaches are increasingly being implemented. However, the traditional 2-arms trial whereby one drug is compared to another in one biomarker-defined subgroup at a time, is tedious and may carry a very high financial burden when a large number of subgroups need to be tested separately one at a time [15].

The recruitment of sufficient patients with unique tumor subtypes is another prevailing limit in conducting such trials [16]. Precision medicine does remain in essence a population-based approach, albeit the population of interest is stratified into biomarker-defined subgroups which might increase the prevalence of rare cancer genetic subtypes [17]. The diversity in biomarkers combined with the unique evolution of malignant tumors (i.e. tumor growth and spread may be accompanied by changes in the biomarker profile) challenge the ability of traditional trials to test targeted therapies with enough statistical power due to high inter- and intra-patient heterogeneity [18]. These issues make it difficult to acquire evidence on the benefit of novel therapeutics, but also on the validity and clinical use of biomarkers, creating a large gap between biomarker discoveries and their clinical translation [19].

Several novel trial designs have been proposed over the last decade to answer more treatment-related questions, more efficiently and in less time. Such designs usually encompass several sub-studies under a unique master protocol and each sub-study may differ in design specifics and hypotheses. Here, we discuss the main features, strengths and weaknesses of these novel trial designs and we offer a systematic overview of their current applications in specific trials across the field of oncology.

Biomarker-driven approaches

Designs incorporating biomarker-matched subgroups of patients can be described according to the number of diseases included (i.e. different cancer histologies), number of molecular types (i.e. biomarkers) and number of targeted therapies [20], but also according to whether only biomarker-positive patients are randomized (excluding biomarker-negative patients) or both biomarker-positive and biomarker-negative patients are randomized [21] and according to biomarker credentials (i.e. biomarkers' analytic and clinical validation) [22]. Table 1 summarizes the main characteristics of the designs discussed here. The simplest design would be a single type of cancer histology expressing a specific biomarker targeted by a single therapy (Fig. 1).

The most common design in this category is the ***enrichment design***, whereby only biomarker-positive patients are randomly allocated to the targeted therapy or control arm [23]. They usually occur late in development and are very common in phase III as they require strong credentials for the biomarker's specificity and sensitivity [22]. Typically, one needs to be convinced that only biomarker-positive patients would benefit from the therapy and that excluding biomarker-negative patients has a protective effect by avoiding exposing them to unnecessary treatment risks. The strength of the enrichment design is its increased power to detect a treatment benefit, as it only includes patients who are most likely to respond to the treatment, which in turn minimizes the sample size required [22]. One well-known example would be the ToGA trial [24], a phase 3 enrichment randomized trial assessing trastuzumab in combination with chemotherapy versus chemotherapy alone. Only patients with gastric or gastro-oesophageal junction cancer whose tumors showed over-expression of the HER2 protein, were included. Even though they are straightforward to conduct, they are largely limited in the scope of research questions, as they only provide evidence on the treatment effect of biomarker-positive patients and by themselves they provide no information on the biomarker credentials [21].

To circumvent this limitation, several options have been proposed allowing to gather evidence on the treatment effect but also on whether the biomarker indeed modifies the treatment effect [21,25]. Understanding effect modification requires the inclusion of and comparison with biomarker-negative patients. One strategy is to ***randomize-all*** patients regardless of their biomarker status. This strategy is still deemed appropriate if it is unclear that the treatment benefit is higher in biomarker-positive patients versus the overall population [26]. In essence, they are the design of choice when a clinically meaningful effect in biomarker-negative patients cannot be ruled out. Most importantly and conversely to enrichment trials, they allow for testing whether the biomarker is differentially associated with the outcome in the experimental and control group [21].

Two main sub-designs in the randomize-all designs emerge: biomarker-stratified and biomarker-based strategy. Distinguishably, patients in a biomarker-based strategy trial are randomized to a thorough therapeutic strategy based on identifying a biomarker and not solely to a treatment like it is the case for biomarker-stratified trials [21,26]. For example, the EORTC10994 trial in breast cancer used a biomarker-stratified design whereby all patients were randomized to taxane versus non-taxane neoadjuvant chemotherapy regardless of their biomarker status and the endpoint, progression-free survival, was assessed with stratification according to p53 biomarker status [27]. Conversely, the MINDACT trial, also in breast cancer, used a biomarker-based strategy approach within its design [28]. Before allocation, the patients' risk was determined according to their clinical profile and according to their genomic profile (a 70-gene signature). In case of discordant results between the two, patients were randomized to clinical risk versus genomic risk assessment to determine the use, or not, of chemotherapy [28]. Biomarker-based strategy trials may be preferred in more confirmatory phases when clinical validation of the biomarker use in the treatment decision-making process is needed [26]. Randomize-all design may not always be feasible in cases where the biomarker is rare as it will require to screen a very large number of patients. However, they can be considered a sound choice as the allocation is independent of the biomarker status and there is the possibility of extending the treatment to a broader population.

Many sub-designs of those two main approaches exist in the literature under a variety of labels and they have already been extensively described elsewhere [17,20–23,25,26,29]. Of note, there are 2 main sources of variation explaining this multitude of labels: the randomization and the statistical analysis [21].

Randomization can either be parallel (i.e. biomarker-positive and biomarker-negative patients are assessed at the same time) or sequential (i.e. biomarker-negative patients are only included if a benefit is shown in biomarker-positives patients).

The statistical analysis plan can vary substantially depending on the research question and on the design chosen, especially in the context of adaptive designs [4,30,31]. Adaptive designs let us analyze accumulating data through pre-specified interim analyses. Depending on the results, the design and conduct of the trial can be modified following pre-specified rules such as: stopping early with a conclusion of either superiority or futility; adaptively assigning doses (to assess dose-outcome relationships); dropping or adding arms or doses; combining two phases in one trial, known as seamless trials; changing the proportion of patients randomized to each arm; and reassessing the required sample

Table 1
Typical characteristics of the different biomarker-driven approaches.

	Enrichment	Randomize-all	Adaptive design	Umbrella	Basket
Histology	Dependent	Dependent	Dependent	Dependent	Independent
Number of targeted therapies	1	1	≥1	> 1	1
Number of biomarkers	1	1	≥1	> 1	≥1
Type of biomarkers	Bm+	Bm+ and Bm−	Bm+ and Bm−	Bm+ if exploratory Bm+ and Bm− if confirmatory	Usually Bm+
Biomarker credentials (a priori knowledge)	Very strong	+/−	+/−	Strong	Very strong
Biomarker assay	Single, locally	Single, locally	Single, locally	Multiplex, centralized	Single, locally
Provides information on the Biomarker-treatment benefit association (is the biomarker predictive?)	−	+/−	+/−	+	−
Number of patients required to screen	Prevalence-dependent	Prevalence-dependent	Prevalence-dependent	Prevalence-dependent	Prevalence-dependent
Sufficiently large sample size (depends on the rarity of the mutation)*	+	+ +	+/−	+ + +	+ +
Overlap of patients	−	+/−	+/−	+	−
Statistical complexity	+	+	+ + +	+ +	+ +
Tradeoff between power versus sample size	−	+	+ +	+ + +	+ + +
Subgroup analyses – multiplicity	−	−	+ + +	++	+ + +
Type 1 error problems	+	+	+ +	+ +	+ + +
Flexibility†	−	−	+ + +	+	+
Time efficiency and cost savings	− −	− −	+	+ +	+ +

− −: very low; −: no; +: yes; + +: above average; + + +: very high. The evaluation is based on authors' appreciation and is prone to subjectivity.
+/−: depends on the study sub-design.
* Umbrella designs usually require larger sample size compared with basket trials as they can be confirmatory.
† For all designs, flexibility can be increased if adaptive decisions are applied to the design.

size; [4,32]. The key feature that different adaptive designs have in common is maximizing flexibility without undermining the validity and integrity of the trial [4,25,30]. Consequently, a Bayesian framework is often preferred to the frequentist one as it is more flexible [33], but this choice may render the statistical analysis more complex [34]. Another strong premise for adaptive trials is to increase efficiency by reducing costs and the required time it takes to run a trial. However, a recent review suggests that adaptive designs are not necessarily faster than traditional designs, although the comparisons are limited [35]. Modeling also suggests [36] that the gains in cost and efficiency may not always be as clear as commonly speculated.

While focusing only on one histology, one biomarker and one targeted therapy at a time, large populations of patients may remain non-eligible for enrollment. To answer those unmet needs, novel biomarker-based designs have expanded on the previously described designs with the aim to answer more than one treatment question concurrently. Such designs are sometimes referred to as master protocols [37] and include umbrella and basket trials [16].

Master protocols

The guiding tenet of master protocols is to regroup, under the same protocol, sub-studies sharing key designs and operational aspects [16] but differing in tumor types and/or biomarkers assessed. Master protocols can be seen as a collection of enrichment sub-studies or even randomize-all sub-studies if a biomarker-negative patient subgroup is added (Fig. 1). The first and foremost reason for choosing such designs is to facilitate screening and patient accrual [16].

The ***umbrella design*** tests multiple targeted therapies in different biomarker-matched subgroups of patients, all of whom present the same tumor type or cancer histology [29]. Because of their multi-therapy multi-biomarker design, they require rigorous planning with

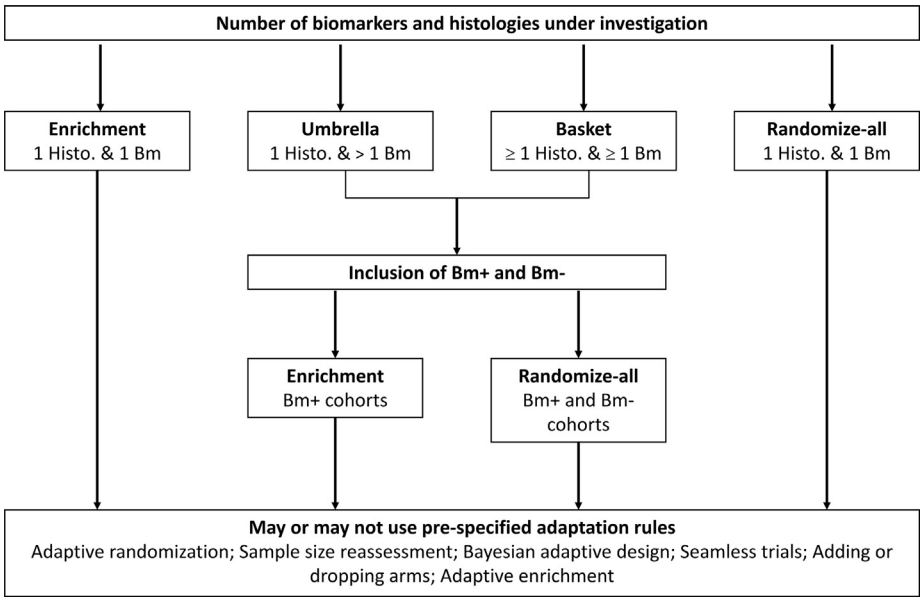

Fig. 1. Flowchart of study designs. Depending on the choice made on the number of histologies included and/or if all patients regardless of biomarker status are included, different designs will be implied. The decision of implementing adaptive rules is independent of these considerations but may be dependent on how much we know on the biomarker credentials, the prevalence of the biomarker and the efficiency needed. Histo.: Histology; Bm: Biomarker.

the development of a multiplex assay and a centralized screening infrastructure [16]. However, the array of biomarkers tested significantly improves screening rates and patients are more likely to meet eligibility criteria and thus be able to take part in the trial compared with a single biomarker enrichment study. The downside is when one patient presents with more than one biomarker. That patient might end up being included in more than one arm; such overlap then has to be accounted for in the statistical analysis plan [17]. Umbrella trials can span the spectrum from exploratory proof-of-concept to confirmatory applications. Proof-of-concept trials are often single arm cohorts of sub-studies; in confirmatory umbrella trials, patients are typically randomized to targeted versus non-targeted or standard of care therapy [17].

The distinguishable feature of ***basket trials*** is their inclusion of multiple tumor types and cancer histologies, and the term "histology-independent" is often used to characterize this feature [29]. The different tumor types can express the same mutation or different ones and are targeted by either one unique therapy or biomarker-specific therapies. As a consequence of their broad eligibility criteria at the tumor-type level, basket trials enable the inclusion of highly rare cancer types within the biomarker-defined basket [38]. Moreover, when the treatment is already approved for one indication (i.e. one tumor type) its efficacy assessment can be quickly extrapolated to another indication. The biggest challenge with basket trials is that different tumor types, whilst expressing the same biomarker, may respond differently to the targeted therapy [25]. They are, therefore, mostly discovery-based trials and generally occur early in development [39].

With the multiplicity of questions asked and of subgroups to analyze, the analysis plan of these trials requires careful thinking in advance and appropriate statistical tools. The critical issue is to control for type I error, especially for basket trials for which the heterogeneity of indication puts them at higher risk of having false positive results (i.e. a result falsely indicating that a therapy is effective, whereas in fact it is not) [40,41]. As the key aim is to identify patients that will benefit most from the targeted therapy, subgroup analysis is a cornerstone of precision medicine but also a major drawback, as it increases the statistical complexity of basket and umbrella trials. Another consideration to keep in mind is the tradeoff between power versus sample size [17]. For feasibility considerations, the lower the prevalence of the biomarker, the larger the effect size needs to be for the trial to be meaningful [17]. If this is not the case, assuming unrealistically large effect sizes, results in small planned sample sizes, limited power to detect the real effects and thus high rates of both false negatives and false positives.

Current use of precision medicine trial designs in oncology

A search on ClinicalTrials.gov and PubMed to identify all planned, ongoing and completed umbrella and basket trials in oncology was conducted in July 2018. The search strategy was restricted to trials that were clearly labeled as basket or umbrella trials (Supplement information). A total of 75 trials were found (i.e. registered protocols). After screening for interventional studies in solid tumors, 48 trials were eligible, of which 27 were basket trials (Table 2 and Supplement information) and 21 umbrella trials (Table 3 and Supplement information). An additional nine trials were found while going through the literature, but were not found when conducting our searches, as they were not coded as such in ClinicalTrials.gov. Among the nine, three were basket trials and the rest were umbrella trials (Tables 2 and 3, and Supplement information), bringing the total to 30 basket trials and 27 umbrella trials.

The majority of these trials are exploratory or proof-of-concept (i.e. Phase 1 or/and 2) except for four umbrella trials: ALCHEMIST (NCT02194738), Lung-MAP (NCT02154490), FOCUS-4 (2012-005111-12) and ADAPT (NCT01781338). For example, the ADAPT trial is an ongoing umbrella trial in breast cancer, regrouping four randomized sub-studies comparing different therapies based on the patients' hormone receptor and HER2 status and which plans to include 4936 patients in a Phase 2 and 3 evaluation [42].

While 9 umbrella trials use randomization, only two basket studies are randomized (NCT03022409 and SHIVA (NCT01771458)). Out of the 9 umbrella trials, 3 use an adaptive randomization: I-SPY-2 (NCT01042379), BATTLE-1 (NCT00411632) and BATTLE-2 (NCT01248247). In the literature they are often tagged as Bayesian-biomarker adaptive designs [20,43,44] meaning that their adaptive randomization assigns more patients to the most promising therapies based on an appraisal of the accumulated data. The aim is to accelerate the identification of targeted therapies performing better within a biomarker-matched subgroup while avoiding unnecessary exposure of patients to therapies that are not beneficial to them [31].

The observation that the majority of these trials are non-randomized or even single-group assignment studies is consistent with the fact that they are mostly exploratory, early-phase trials. However, our sample does reflect the relative dearth of randomized clinical trials in precision oncology for solid tumors [45]. The FDA regularly approves oncologic therapies based on uncontrolled trials especially when it comes to accelerated approvals [46] and such accelerated approvals are very common in this field both for solid tumors and for hematologic malignancies. For example, the dabrafenib-trametinib combination in metastatic non-small cell lung cancer (NSCLC) expressing the BRAF V600E mutation [47] was approved based on an uncontrolled enrichment trial. However, randomization remains the only way to deal with unknown confounders and plays a major role in validating the predictive role of biomarkers [45].

The most frequent endpoint used in these trials is the response rate (i.e. complete or partial response). Only one trial uses a biomarker as a surrogate endpoint. The basket trial NCT03022409 is testing the immune activation due to DNA damage repair inhibition by monitoring the induction of TH1/IFNγ responses. Relatively low correlation has been found between surrogate endpoints and overall survival in oncology [48] and surrogate endpoints are known to be misleading across many medical fields [49,50]. The use of surrogate endpoints for survival is nevertheless extremely common in oncology [45,51] as it is in our sample of trials.

As of July 2018, only 5 trials in our sample have been completed. BRAF V600 (NCT01524978) a basket trial testing vemurafenib in 6 cancer histologies expressing the BRAF V600 mutation, only showed a modest antitumor activity but no strong inference could be made from the study results [52]. Another completed basket trial is the SHIVA trial (NCT01771458), for which no improvement was shown on progression-free survival with targeted therapy based on molecular profiling compared with standard chemotherapy [53]. The SIGNATURE basket trial has also been completed. Preliminary results report 30 partial or complete responses with 6 out of the 8 evaluated compounds in 16 different tumor types [54]. Finally, two umbrella studies have also been completed: NCT00903734 which does not have study results posted in ClinicalTrials.gov and has not been published as of the writing of this review; and BATTLE-1 (NCT00411632). The latter is an adaptive randomized umbrella trial in advanced non-small cell lung cancer. Patients were assigned to 4 biomarker-positive and one biomarker-negative subgroups and then within each subgroup patients were randomized to 4 different targeted therapies [55]. Each biomarker-positive subgroup was comprised of several biomarkers, for example the EGFR biomarker group included EGFR mutation, EGFR overexpression, and EGFR increased copy number. The grouping of biomarkers diluted the effect whereby some groups were less predictive than the individual biomarkers comprising them, thus weakening the potential inferences [43].

Overlapping and mislabeled trials

In this complex setting of precision medicine trial designs, confusion in the definition and appropriate use of each of the different labels can occur [17,21,26,30]. For example, NCI-MATCH (NCT02465060) has

Table 2
Basket trials in oncology.

Trial	N cancer histology	N targets	N therapies	Primary Outcomes	Sample size	Start date	Status as of July 2018	Description
K-BASKET	> 1	3	1	Overall response rate up to 6 w	60	Aug-17	Recruiting	Phase 2; Single group assignment; 2 basket trials (1 cohort each)
NCT03491345	> 1	2	1	Overall response rate up to 12 m	30	Nov-17		assessing two different drugs targeting different mutations. Plan to open
NCT03017521								new treatment arms.
STARTRK-2	3	3	1	Objective Response Rate up to 24 m	300	Nov-15	Recruiting	Phase 2; Non-randomized; Parallel assignment;
NCT02568267								9 cohorts. One histology with one mutation represent a basket
BASKET 1	2	2	1	Tumor response every 3 m	35	May-07	Active, not recruiting	Phase 2; Single group assignment
NCT00928525								
P10s Basket Trial	> 1	N/A	1	Immune Response at 12 w	80	Jun-18	Not yet recruiting	Phase 2; Single group assignment
NCT03003195								
METADUR	3	N/A	1	Overall response rate at 4 w	60	Sep-16	Recruiting	Phase 2; Single group assignment
NCT02811497								
ORIOn-E	4	N/A	1	Phase 1: DLTs at 1 y	134	Dec-17	Recruiting	Phase 1: Single group assignment; Open label
NCT03525795				Phase 2: ORR at 1 y				Phase 2: Non-randomized; Parallel assignment; Open label
MOVIE	5	N/A	1	Phase 1: MTD and RP2D at 9 m	150	Jun-18	Not yet recruiting	Phase 1/2; Non-randomized; Parallel assignment; Open label
NCT03518606				Phase 2: Clinical benefit rate at 24 w				5 cohorts by cancer histology
NCI CTRP	> 1	1	1	Response rate at 56 d	12	Aug-16	Active, not recruiting	Phase 2; Single group assignment; Open label
NCT02478320								
MOBILITY-003	> 1	1	1	Complete response and partial response at 2 y	30	Aug-15	Recruiting	Phase 2; Single group assignment; Open label
NCT02506517								
MOBILITY-002	1	N/A	1	Complete or partial response, or stable disease at 24 w	16	Apr-16	Active, not recruiting	Phase 2; Single group assignment; Open label
NCT02428270								
MOBILITY-001	1	3	1	Complete or partial response, or stable disease at 24 w	26	Jun-15	Recruiting	Phase 2; Single group assignment; Open label
NCT02399943								
NCT03428802	> 1	2	1	Response rate at 2.5 y	40	Mar-18	Recruiting	Phase 2; Single Group Assignment; Open Label
NAVIGATE	8	1	1	ORR at 30 m	151	Oct-15	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label
NCT02576431								8 cohorts by cancer histology
SUMMIT	> 1	4	4	Overall response rate up to 30 m	392	Sep-13	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label
NCT01953926								4 cohorts depending on biomarker and intervention. All cohorts receive
PMID:29420467								Neratinib with or without other drug
Sym015-01	> 1	2	1	Phase 1: Safety and tolerability at 12 m	72	Mar-16	Recruiting	Phase1/2; Non-randomized; Parallel assignment; Open label
NCT02648724				Phase 2: Antitumor activity at 24 m				2 cohorts, one with > 1 cancer histology and 1 biomarker (basket cohort). The other one is the NSCLC cohort
NCT02372006	2	1	1	Phase 1: Dose finding up to 1 y	55	Apr-15	Recruiting	Phase 1/2; Single group assignment; Open label
				Phase 2: Objective response up to 2 y				(pediatric population only)
NCT03266159	5	1	1	Phase 1: Dose selection up to 12 m	N/A	-Nov-17	Withdrawn*	Phase 1/2; Non-randomized; Sequential assignment; Open label
				Phase 2: Overall response rate and clinical response up to 24 m				5 cohorts by cancer histology
NCT03525392	2	1	1	Phase 1: DLTs and organ exposure to radiation up to 6 weeks after second administration	300	May-18	Recruiting	Phase 1/2; Single group assignment; Open label
				Phase 2: safety and efficacy				Protocol might be extended to 3 other cancer histology. Uses the Simon's Two Stage design
ESMART	> 1	N/A	9	Objective tumor response and Time to progression after 56 d	397	Aug-16	Recruiting	Phase 1/2; Non-randomized; Parallel assignment; Open label
NCT02813135								(pediatric population only) 9 cohorts depending on the intervention given
MiMe-A	5	N/A	1	Anti-tumor activity assessed using FDG-PET/CT at 2 m	85	Feb-18	Not yet recruiting	Phase 2; Sequential assignment (depending on patient outcomes might include more patients); Open label
NCT03339843								Only one cohort planned
NCT03022409	1	1	2	Proportion of patients who had modulation of selected at 31 d	44	Oct-17	Recruiting	Phase 1; Randomized; Parallel assignment; Open label
								2 treatment arms
NCT02587650	1	4	4	Overall response rate at 24 w	44	Mar-15	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label
								4 cohorts Each cohort is considered as a basket
Paragon (ANZGOG-0903)	> 1	1	1	Overall response to treatment	333	Aug-11	Active, not recruiting	Phase 2; Single group assignment; Open label
PMID:28498256								

(*continued on next page*)

Table 2 (*continued*)

Trial	N cancer histology	N targets	N therapies	Primary Outcomes	Sample size	Start date	Status as of July 2018	Description
KEYNOTE-012 *NCT01848834* *PMID:28081914*	4	1	1	Adverse events; discontinuation; overall Response up to 34 months	297	May-13	Active, not recruiting	Phase 1; Non-randomized; Parallel assignment; Open label 5 cohorts by cancer histology. Two cohorts were added after the study start (one expansion and one new cancer histology)
BRAF V600 *NCT01524978* *PMID:26287849*	6	1	1	Overall Response Rate up to 3 years	208	Apr-12	Completed (28-Oct-16)	Phase 2; Non-randomized; Parallel assignment; Open label 6 cohorts by cancer histology A subset of patients with colorectal cancer receive the trial intervention combined with another drug (vemurafenib + cetuximab)
NCT01306045 *PMID:25667274*	3	11	6	Response rate of molecular-profile directed treatments	600	Feb-11	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label 6 cohorts
NCI-MATCH† *NCT02465060*	> 1	30	30	ORR up to 3 y	6452	Aug-15	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label 30 cohorts
SHIVA† *NCT01771458*	> 1	> 1	> 1	Patient's progression free survival every 2 m	742	Oct-12	Completed	Phase 2; Randomized; Crossover assignment; Open label Two arm trial comparing standard chemotherapy versus targeted therapy based on molecular profiling
SIGNATURE† *NCT01831726* *NCT01885195* *NCT01981187* *NCT02002689* *NCT02160041* *NCT02186821* *NCT02187783* *NCT01833169*	> 1	8	8	Clinical Benefit Rate (complete or partial response, or stable disease) at 16 w	596	Aug-13	Completed (one was terminated for low recruitment	Phase 2; Single group assignment; 8 cohorts which have their own registered protocol

mCRC: metastatic Colorectal Cancer; NSCLC: Non-Small Cell Lung Cancer; RCC: Renal Cell Carcinoma.

* According to the sponsor, the study was withdrawn due to changing practice in the target population (https://www.gsk-clinicalstudyregister.com/study/204673?search=compound&compound=gsk525762#ps).

† The three trials added manually.

Table 3
Umbrella trials in oncology.

Trial	N cancer histology	N targets	N therapies	Primary Outcomes	Sample size	Start date	Status as of July 2018	Description
TRIUMPH *NCT03292250* *NCT03356587*	1	5	5	Disease control rate and Response rate at 24 m	259	Sep-17	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label 5 cohorts. The CDK4/6 inhibitor cohort has its own protocol registered (NCT03356587)
HUDSON *NCT03334617*	1	4	7	ORR at 12 w	200	Dec-17	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label; 5 cohorts among which one is for biomarker non-matched patients with the choice between three treatments. New cohorts will be added as new data emerge
ENGOT-OV30/NSGO *NCT03267589*	1	1	3	Disease control rate up to 16 weeks	75	Mar-18	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label; 3 cohorts but only one is biomarker matched. A part 2 is planned with a randomization and comparison to standard of care
MORPHEUS	1	1	7	ORR up to 4 y	260	Mar-18	All are recruiting except one	Phase 1/2; Randomized; Parallel assignment; Open label. Each cancer histology as its own registered protocol
NCT03424005	1	1	5	ORR up to 6 y	111	Sep-17		
NCT03280563	1	N/A	3	ORR up to 3–5 y	120	Sep-18		
NCT03555149	1	N/A	4	ORR up to 3–5 y	185	Jul-17		
NCT03193190	1	N/A	4	ORR up to 3–5 y	357	Oct-17		
NCT03281369	1	N/A	10	ORR up to 3–5 y	292	Dec-17		
NCT03337698								
plasmaMATCH *NCT03182634*	1	6	4	ORR up to 24 w	1000	Dec-16	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label. 4 cohorts, one of which is a basket study with > 1 biomarker
MLN1117 *NCT02551055*	2	N/A	4	Part 1: DLT Part 2: Overall Response	32	Sep-15	Terminated (Business decision)	Phase 1; Randomized; Parallel assignment; Open label
TRUMP *NCT03574402*	1	4	4	Response rate up to 24 m	400	Jul-18	Not yet recruiting	Phase 2; Non-randomized; Parallel assignment; Open label 4 cohorts
N2M2 *NCT03158389*	1	N/A	7	Progression-free survival at 6 m	350	May-18	Recruiting	Phase 1/2; Non-randomized; Parallel assignment; Open label 7 cohorts
NCT00903734	1	1	3	Part1: MTD and toxicity profiles	Part 1: 16	Apr-09	Completed	Phase 1; Single group assignment; Open label
NCT00895128				Part 2: Response rate	Part 2: 154	Apr-09	Completed	Part 1 correspond to 1 screening cohort. Part 2 has three treatment cohorts. All 4 have their own registered protocol
NCT00895362								
NCT00895687								
National Lung Matrix Trial *NCT02664935* *PMID:26410619*	1	6	7	Best ORR and Progression-free survival time up to 18 m	630	Mar-15	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label 6 biomarker matched cohorts and 1 no biomarker-matched
Pediatric MATCH *NCT03155620* *PMID:28376230*	> 1	15	8	ORR up to 3 y	1500	Jul-17	Recruiting	Phase 2; Non-randomized; Parallel assignment; Open label 8 cohorts
WSG ADAPT *NCT01781338* *PMID:23958221*	1	4	8	Responders with intermediate and high risk up to 8 y	4936	May-12	Recruiting	Phase 2/3; Randomized; Single group assignment; Open label 4 sub-trials with 2 arms in each
FOCUS-4[*] *2012-005111-12*	1	4	5	Progression-free survival (PFS)	4200	N/A	Ongoing	Phase 2/3 Part 1: Single group assignment Part 2: Randomization (multi-arm, multi-stage). 5 sub-trials: 4 biomarker matched and 1 non-matched. 3 use a placebo as comparator
Lung-MAP[*] *NCT02154490* *NCT02766335* *NCT02785913* *NCT02785939* *NCT02965378* *NCT02926638* *NCT03373760* *NCT03377556* *NCT02785952*	1	6	8	ORR up to 3 y	1099 (screening 10,000)	Jun-14	Active recruiting (N = 5) Recruiting (N = 3)	Phase 2/3; The master protocol is registered (NCT02154490) then each sub-trial has its own protocol registered. There are 8 sub-trials: 6 are Randomized, parallel assignment, and open label while 2 are single group assignment. Two sub-trials are for all biomarker negatives

(*continued on next page*)

Table 3 (*continued*)

Trial	N cancer histology	N targets	N therapies	Primary Outcomes	Sample size	Start date	Status as of July 2018	Description
ALCHEMIST* *NCT02194738* *NCT02193282* *NCT02201992* *NCT02595944*	1	1	3	Overall survival up to 10 y	1542 (screening 8300)	Aug-14	Recruiting	Phase 3. Have the screening trial then each sub-trial has its own registered protocol All are: randomized; parallel assignment; open label. One is versus placebo the others versus observation
I-SPY-2* *NCT01042379*	1	1	4 opened 11 closed	Pathologic complete response up to 24 w	1920	Mar-10	Recruiting	Phase 2; Adaptive randomized; Parallel assignment; Open label; Bayesian adaptive trial Currently 4 arms trial
BATTLE-1* *NCT00411632* *NCT00411671* *NCT00410189* *NCT00410059*	1	4	4	Progression-Free Survival Rate at 8 w	255	Nov-06	Completed	Phase 2; Adaptive randomized; Parallel assignment; Open label 4 arms trial
BATTLE-2* *NCT01248247*	1	4	4	Progression-Free Survival Rate at 8 weeks	334	Jun-11	Active, not recruiting	Phase 2; Adaptive randomized; Parallel assignment; Open label Previously treated patients 4 arms trial

MTD: Maximum Tolerated Dose; ORR: Objective Response Rate.

* The six trials added manually,

been labeled as an umbrella trial as a result of the multiple drugs tested (19 different drugs) [16,56] but also as a basket trial due to the histology-independent design of the trial (including solid tumors or lymphoma) [23,57]. Those trials are sometimes referred to as hybrid designs, a mix of basket and umbrella trials [58]. However, it seems that the only distinguishing feature between umbrella and basket trials is the number of histologies assessed. Following this definition hybrid designs are often mislabeled, for example, the Pediatric MATCH trial (NCT03155620). Like NCI-MATCH, it assesses multiple drugs, but it has no tumor type or cancer histology prerequisites, therefore it should be labeled as a basket trial.

One additional factor making it difficult to appropriately label and track trials is the multiple registrations for one trial. For example, MORPHEUS has 6 different protocols registered and labeled as umbrella trials. Each protocol is histology-dependent with multiple treatment arms, but apparently, they share the same infrastructure and key design aspects. If a master protocol existed and presented all those histologies under the same unique protocol, the appropriate label would be a basket trial. The frontier between basket and umbrella trials can become unclear.

Recently another label has emerged: platform trial. Much like an umbrella trial, it studies multiple therapies in the context of one histology but in an ongoing perpetual manner with arms being added or dropped as new knowledge and data appear [16]. One example would be I-SPY-2 (NCT01042379) in breast cancer. As of now, 11 treatment arms have been tested and closed and 4 are still opened and ongoing.

Limitations of our sample of trials

Our sample of ongoing and completed registered trials gives a bird-eye-view of what is currently being pursued in precision medicine trials in oncology and how the novel designs are being implemented. However, it has limitations. Firstly, our search was not exhaustive as we only identified umbrella and basket trials that were clearly labeled as such. The fact that we could identify some additional relevant trials from other sources suggests that some more trials may have been missed and, as discussed above, trial design nomenclature is not standardized and used properly. Secondly, our yield of trials was dependent of the amount and quality of information registered. The completeness of registration for precision medicine trials in the current era is unknown. It is possible that some studies remain unregistered. Other trials may be registered in registries other than ClinicalTrials.gov. Lastly, many of the trials that we retrieved are ongoing trials without any registered full protocol or publication and this renders a detailed appraisal of the methodology of implementation, conduct and statistical analysis impossible. This is unfortunate, because these are the biggest challenges for those novel designs. The complexity of precision medicine trials adds an extra reason why full, detailed protocols should become routinely available in public before these trials are launched. Protocol amendments should also be transparent. The degrees of freedom in modifying design and analytical choices are far more in these trials compared with traditional two parallel arm trials. Thus preregistration and full protocol transparency are essential to avoid selective analysis and outcome reporting [59–61].

Concluding remarks

The speculated advantages of novel trial designs in precision oncology offer some exciting opportunities. Large consortia and infrastructures have been created such as the Paediatric Oncology Platform [62] or the NCI and the Precision Medicine Initiative, which launched in partnership with the industry NCI-MATCH, NCI-MPACT [63], ALCHEMIST [64] and Lung-MAP [65]. The involvement and collaboration of multiple stakeholders such as academia, industry, patient associations and regulatory agencies may favor the accrual of high-quality evidence in precision medicine. Patients may have more opportunities to enroll in a clinical trial where they may be allocated to the targeted therapy that is in principle the best fit for them. However, it should be remembered that clinical trials are not a way to allow participants to be assigned earlier to the best treatment before that treatment is approved and licensed. All trials, including precision medicine trials, have been and should continue to be governed by the principle of equipoise. Benefits are expected to accrue for future patients, not for the study participants themselves and trials should not be seen as a way to bypass rigorous clinical testing for expedited access to unproven treatment options. With increased efficiency in conducting trials, the hope is to make innovative therapies more rapidly available to the broader oncology population.

Nevertheless, as in any new field, cautious steps should be taken allowing for the standardization of these precision medicine approaches and the evaluation of their impact. For example, several evaluations have suggested that accelerated approvals have not necessarily delivered the expected benefits in hard core outcomes, such as improved survival [48,49,51]. Appropriate post-licensing trials on effectiveness are often lacking and new treatments approved on limited evidence are often expanded to other unproven indications or become backbone routine treatments without having enough evidence to support these choices [66]. The wider use of some convoluted precision designs may increase these challenges. Other potential disadvantages need to be counted as well, e.g. early stopping may increase trial efficiency but has the tendency to generate inflated estimates of treatment effect [67]. Furthermore, with increasing complexity of decision-making, training of practicing oncologists and improvements in the oncology care are needed to ensure that knowledge is accurately translated and implemented in real-life. Incorporation of biomarkers in clinical care pipelines may not be straightforward [68] and clinical trials may be needed to test different implementation strategies. Precision medicine carries tremendous hope but also much hype [15,69,70]. Careful continuous assessment of its new trial design tools and their performance is needed.

Acknowledgements

METRICS is supported by a grant from the Laura and John Arnold Foundation. The work of JPA Ioannidis is supported by an unrestricted gift from Sue and Bob O'Donnell. The authors assume full responsibility for the accuracy and completeness of the ideas presented.

Conflict of interest

All authors declare that they have no potential conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2018.12.003.

References

[1] Heymach J, Krilov L, Alberg A, Baxter N, Chang SM, Corcoran R, et al. Clinical cancer advances 2018: annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol 2018;36:1020–44. https://doi.org/10.1200/JCO.2017.77.0446.
[2] McDermott U, Settleman J. Personalized cancer therapy with selective kinase inhibitors: an emerging paradigm in medical oncology. J Clin Oncol 2009;27:5650–9. https://doi.org/10.1200/JCO.2009.22.9054.
[3] Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480:480–9. https://doi.org/10.1038/nature10673.
[4] Heckman-Stoddard BM, Smith JJ. Precision medicine clinical trials: defining new treatment strategies. Semin Oncol Nurs 2014;30:109–16.
[5] Schwaederle M, Zhao M, Lee JJ, Eggermont AM, Schilsky RL, Mendelsohn J, et al. Impact of precision medicine in diverse cancers: a meta-analysis of phase II clinical trials. J Clin Oncol 2015;33:3817–25. https://doi.org/10.1200/JCO.2015.61.5997.
[6] Jardim DL, Fontes Jardim DL, Schwaederle M, Wei C, Lee JJ, Hong DS, et al. Impact of a biomarker-based strategy on oncology drug development: a meta-analysis of

clinical trials leading to FDA approval. J Natl Cancer Inst 2015;107. https://doi.org/10.1093/jnci/djv253.
[7] Goossens N, Nakagawa S, Sun X, Hoshida Y. Cancer biomarker discovery and validation. Transl Cancer Res 2015;4:256–69. https://doi.org/10.3978/j.issn.2218-676X.2015.06.04.
[8] FDA Center for Devices and Radiological. In vitro diagnostics – list of cleared or approved companion diagnostic devices (in vitro and imaging tools); n.d. <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm> [accessed August 21, 2018].
[9] Jürgensmeier JM, Eder JP, Herbst RS. New strategies in personalized medicine for solid tumors: molecular markers and clinical trial designs. Clin Cancer Res: Off J Am Assoc Cancer Res 2014;20:4425–35. https://doi.org/10.1158/1078-0432.CCR-13-0753.
[10] Abrams J, Conley B, Mooney M, Zwiebel J, Chen A, Welch JJ, et al. National Cancer Institute's precision medicine initiatives for the new national clinical trials network. Am Soc Clin Oncol Educ Book Am Soc Clin Oncol Meet 2014;34:71–6. https://doi.org/10.14694/EdBook_AM.2014.34.71.
[11] Johansen Taber KA, Dickinson BD, Wilson M. The promise and challenges of next-generation genome sequencing for clinical care. JAMA Intern Med 2014;174:275–80. https://doi.org/10.1001/jamainternmed.2013.12048.
[12] Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med 2015;372:793–5. https://doi.org/10.1056/NEJMp1500523.
[13] Roper N, Stensland KD, Hendricks R, Galsky MD. The landscape of precision cancer medicine clinical trials in the United States. Cancer Treat Rev 2015;41:385–90. https://doi.org/10.1016/j.ctrv.2015.02.009.
[14] IQVIA Institute. Global oncology trends 2018; 2018. <https://www.iqvia.com/institute/reports/global-oncology-trends-2018> [accessed August 22, 2018].
[15] Lawler M, Sullivan R. Personalised and precision medicine in cancer clinical trials: panacea for progress or Pandora's box? Publ Health Genom 2015;18:329–37. https://doi.org/10.1159/000441555.
[16] Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med 2017;377:62–70. https://doi.org/10.1056/NEJMra1510062.
[17] Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. Ann Oncol 2017;28:34–43. https://doi.org/10.1093/annonc/mdw413.
[18] Catenacci DVT. Next-generation clinical trials: novel strategies to address the challenge of tumor molecular heterogeneity. Mol Oncol 2015;9:967–96. https://doi.org/10.1016/j.molonc.2014.09.011.
[19] Bossuyt PMM. The thin line between hope and hype in biomarker research. JAMA 2011;305:2229–30. https://doi.org/10.1001/jama.2011.729.
[20] Renfro LA, An M-W, Mandrekar SJ. Precision oncology: a new era of cancer clinical trials. Cancer Lett 2017;387:121–6. https://doi.org/10.1016/j.canlet.2016.03.015.
[21] Tajik P, Zwinderman AH, Mol BW, Bossuyt PM. Trial designs for personalizing cancer care: a systematic review and classification. Clin Cancer Res 2013;19:4578–88. https://doi.org/10.1158/1078-0432.CCR-12-3722.
[22] Freidlin B, Korn EL. Biomarker enrichment strategies: matching trial design to biomarker credentials. Nat Rev Clin Oncol 2014;11:81–90. https://doi.org/10.1038/nrclinonc.2013.218.
[23] Renfro LA, Mallick H, An M-W, Sargent DJ, Mandrekar SJ. Clinical trial designs incorporating predictive biomarkers. Cancer Treat Rev 2016;43:74–82. https://doi.org/10.1016/j.ctrv.2015.12.008.
[24] Bang Y-J, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687–97. https://doi.org/10.1016/S0140-6736(10)61121-X.
[25] Shah SJ. Innovative clinical trial designs for precision medicine in heart failure with preserved ejection fraction. J Cardiovasc Transl Res 2017;10:322–36. https://doi.org/10.1007/s12265-017-9759-8.
[26] Antoniou M, Kolamunnage-Dona R, Jorgensen AL. Biomarker-guided non-adaptive trial designs in phase II and phase III: a methodological review. J Pers Med 2017;7. https://doi.org/10.3390/jpm7010001.
[27] Bonnefoi H, Piccart M, Bogaerts J, Mauriac L, Fumoleau P, Brain E, et al. TP53 status for prediction of sensitivity to taxane versus non-taxane neoadjuvant chemotherapy in breast cancer (EORTC 10994/BIG 1–00): a randomised phase 3 trial. Lancet Oncol 2011;12:527–39. https://doi.org/10.1016/S1470-2045(11)70094-8.
[28] Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 2016;375:717–29. https://doi.org/10.1056/NEJMoa1602253.
[29] Menis J, Hasan B, Besse B. New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new end-points and new evaluations of response. Eur Respir Rev 2014;23:367–78. https://doi.org/10.1183/09059180.00004214.
[30] Antoniou M, Jorgensen AL, Kolamunnage-Dona R. Biomarker-guided adaptive trial designs in phase II and phase III: a methodological review. PLoS ONE 2016;11:e0149803https://doi.org/10.1371/journal.pone.0149803.
[31] Berry DA. The Brave New World of clinical cancer research: adaptive biomarker-driven trials integrating clinical practice with clinical research. Mol Oncol 2015;9:951–9. https://doi.org/10.1016/j.molonc.2015.02.011.
[32] Park JJ, Thorlund K, Mills EJ. Critical concepts in adaptive clinical trials. Clin Epidemiol 2018;10:343–51. https://doi.org/10.2147/CLEP.S156708.
[33] Lee JJ, Chu CT. Bayesian clinical trials in action. Stat Med 2012;31:2955–72. https://doi.org/10.1002/sim.5404.
[34] Berry DA. Bayesian clinical trials. Nat Rev Drug Discov 2006;5:27–36. https://doi.org/10.1038/nrd1927.
[35] Bothwell LE, Avorn J, Khan NF, Kesselheim AS. Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov. BMJ Open 2018;8:e018320https://doi.org/10.1136/bmjopen-2017-018320.
[36] Emerson SC, Rudser KD, Emerson SS. Exploring the benefits of adaptive sequential designs in time-to-event endpoint settings. Stat Med 2011;30:1199–217. https://doi.org/10.1002/sim.4156.
[37] Redman MW, Allegra CJ. The master protocol concept. Semin Oncol 2015;42:724–30. https://doi.org/10.1053/j.seminoncol.2015.07.009.
[38] Clinical Trial Designs for Studying Targeted Therapies. In: ASCO annual meeting; 2015. <https://am.asco.org/clinical-trial-designs-studying-targeted-therapies> [accessed August 28, 2018].
[39] Mandrekar SJ, Dahlberg SE, Simon R. Improving clinical trial efficiency: thinking outside the box. Am Soc Clin Oncol Educ Book 2015:e141–7. https://doi.org/10.14694/EdBook_AM.2015.35.e141.
[40] Chen C, Li (Nicole) X, Yuan S, Antonijevic Z, Kalamegham R, Beckman RA. Statistical design and considerations of a phase 3 basket trial for simultaneous investigation of multiple tumor types in one study. Stat Biopharm Res 2016;8:248–57. https://doi.org/10.1080/19466315.2016.1193044.
[41] Cunanan KM, Gonen M, Shen R, Hyman DM, Riely GJ, Begg CB, et al. Basket trials in oncology: a trade-off between complexity and efficiency. J Clin Oncol 2017;35:271–3. https://doi.org/10.1200/JCO.2016.69.9751.
[42] Hofmann D, Nitz U, Gluz O, Kates RE, Schinkoethe T, Staib P, et al. WSG ADAPT – adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early breast cancer: study protocol for a prospective, multi-center, controlled, non-blinded, randomized, investigator initiated phase II/III trial. Trials 2013;14:261. https://doi.org/10.1186/1745-6215-14-261.
[43] Liu S, Lee JJ. An overview of the design and conduct of the BATTLE trials. Chin Clin Oncol 2015;4. https://doi.org/10.21037/cco.v4i3.6846.
[44] Rugo HS, Olopade OI, DeMichele A, Yau C, van 't Veer LJ, Buxton MB, et al. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. N Engl J Med 2016;375:23–34. https://doi.org/10.1056/NEJMoa1513749.
[45] Saad ED, Paoletti X, Burzykowski T, Buyse M. Precision medicine needs randomized clinical trials. Nat Publ Group 2017;14:317–23. https://doi.org/10.1038/nrclinonc.2017.8.
[46] DeLoughery EP, Prasad V. The US Food and Drug Administration's use of regular approval for cancer drugs based on single-arm studies: implications for subsequent evidence generation. Ann Oncol 2018;29:527–9. https://doi.org/10.1093/annonc/mdy008.
[47] Odogwu L, Mathieu L, Blumenthal G, Larkins E, Goldberg KB, Griffin N, et al. FDA approval summary: dabrafenib and trametinib for the treatment of metastatic non-small cell lung cancers harboring BRAF V600E mutations. Oncologist 2018;23:740–5. https://doi.org/10.1634/theoncologist.2017-0642.
[48] Prasad V, Kim C, Burotto M, Vandross A. The strength of association between surrogate end points and survival in oncology: a systematic review of trial-level meta-analyses. JAMA Intern Med 2015;175:1389–98. https://doi.org/10.1001/jamainternmed.2015.2829.
[49] Ciani O, Buyse M, Garside R, Pavey T, Stein K, Sterne JAC, et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. BMJ 2013;346:f457.
[50] Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605–13.
[51] Kim C, Prasad V. Strength of validation for surrogate end points used in the US Food and Drug Administration's approval of oncology drugs. Mayo Clin Proc 2016. https://doi.org/10.1016/j.mayocp.2016.02.012.
[52] Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay J-Y, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 2015;373:726–36. https://doi.org/10.1056/NEJMoa1502309.
[53] Le Tourneau C, Delord J-P, Gonçalves A, Gavoille C, Dubot C, Isambert N, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol 2015;16:1324–34. https://doi.org/10.1016/S1470-2045(15)00188-6.
[54] Slosberg ED, Kang BP, Peguero J, Taylor M, Bauer TM, Berry DA, et al. Signature program: a platform of basket trials. Oncotarget 2018;9:21383–95. https://doi.org/10.18632/oncotarget.25109.
[55] Kim ES, Herbst RS, Wistuba II, Lee JJ, Blumenschein GR, Tsao A, et al. The BATTLE trial: personalizing therapy for lung cancer. Cancer Discov 2011;1:44–53. https://doi.org/10.1158/2159-8274.CD-10-0010.
[56] Conley BA, Doroshow JH. Molecular analysis for therapy choice: NCI MATCH. Semin Oncol 2014;41:297–9. https://doi.org/10.1053/j.seminoncol.2014.05.002.
[57] Redig AJ, Jänne PA. Basket trials and the evolution of clinical trial design in an era of genomic medicine. J Clin Oncol 2015;33:975–7. https://doi.org/10.1200/JCO.2014.59.8433.
[58] Siu LL, Conley BA, Boerner S, LoRusso PM. Next-generation sequencing to guide clinical trials. Clin Cancer Res 2015;21:4536–44. https://doi.org/10.1158/1078-0432.CCR-14-3215.
[59] Ioannidis JP, Caplan AL, Dal-Ré R. Outcome reporting bias in clinical trials: why monitoring matters. BMJ 2017;356:j408.
[60] Zhang S, Liang F, Li W. Comparison between publicly accessible publications, registries, and protocols of phase III trials indicated persistence of selective outcome reporting. J Clin Epidemiol 2017;91:87–94. https://doi.org/10.1016/j.jclinepi.2017.07.010.
[61] Raghav KPS, Mahajan S, Yao JC, Hobbs BP, Berry DA, Pentz RD, et al. From protocols to publications: a study in selective reporting of outcomes in randomized trials in oncology. J Clin Oncol 2015;33:3583–90. https://doi.org/10.1200/JCO.

2015.62.4148.
[62] Vassal G, Rousseau R, Blanc P, Moreno L, Bode G, Schwoch S, et al. Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. Eur J Cancer 2015;51:218–24. https://doi.org/10.1016/j.ejca.2014.10.029.
[63] Do K, O'Sullivan Coyne G, Chen AP. An overview of the NCI precision medicine trials-NCI MATCH and MPACT. Chin Clin Oncol 2015;4:31. https://doi.org/10.3978/j.issn.2304-3865.2015.08.01.
[64] Alden RS, Mandrekar SJ, Oxnard GR. Designing a definitive trial for adjuvant targeted therapy in genotype defined lung cancer: the ALCHEMIST trials. Chin Clin Oncol 2015;4:37. https://doi.org/10.3978/j.issn.2304-3865.2015.09.03.
[65] Ferrarotto R, Redman MW, Gandara DR, Herbst RS, Papadimitrakopoulou VA. Lung-MAP–framework, overview, and design principles. Chin Clin Oncol 2015;4:36. https://doi.org/10.3978/j.issn.2304-3865.2015.09.02.
[66] Naci H, Wouters OJ, Gupta R, Ioannidis JPA. Timing and characteristics of cumulative evidence available on novel therapeutic agents receiving food and drug administration accelerated approval. Milbank Q 2017;95:261–90. https://doi.org/10.1111/1468-0009.12261.
[67] Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA 2010;303:1180–7. https://doi.org/10.1001/jama.2010.310.
[68] Ioannidis JPA, Bossuyt PMM. Waste, leaks, and failures in the biomarker pipeline. Clin Chem 2017;63:963–72. https://doi.org/10.1373/clinchem.2016.254649.
[69] Joyner MJ, Paneth N, Ioannidis JPA. What happens when underperforming big ideas in research become entrenched? JAMA 2016;316:1355–6. https://doi.org/10.1001/jama.2016.11076.
[70] Adams SA, Petersen C. Precision medicine: opportunities, possibilities, and challenges for patients and providers. J Am Med Inform Assoc 2016;23:787–90. https://doi.org/10.1093/jamia/ocv215.