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Hot Topic

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

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## ARTICLE INFO

## 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].

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
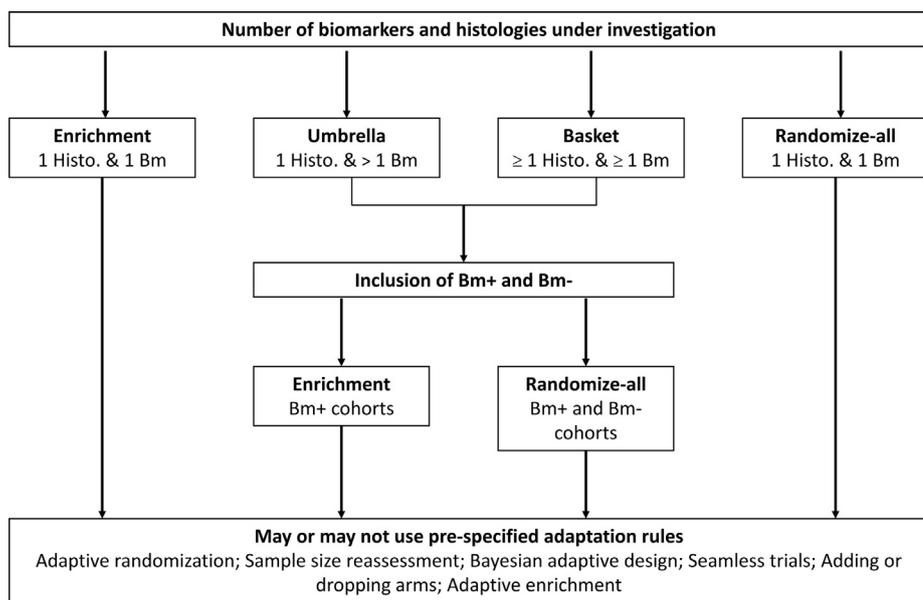


Fig. 1. Flowchart of study designs. Depending on the choice made on the number of histologies included and/or if all patients regardless of biomarker status are included, different designs will be implied. The decision of implementing adaptive rules is independent of these considerations but may be dependent 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 of 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** NCT03491345 | > 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) assessing two different drugs targeting different mutations. Plan to open new treatment arms. |
| NCT03017521 | > 1 | 2 | 1 | Overall response rate up to 12 m | 30 | Nov-17 | Recruiting | |
| **STARTRK-2** NCT02568267 | 3 | 3 | 1 | Objective Response Rate up to 24 m | 300 | Nov-15 | Recruiting | Phase 2; Non-randomized; Parallel assignment; 9 cohorts. One histology with one mutation represent a basket |
| **BASKET 1** NCT00928525 | 2 | 2 | 1 | Tumor response every 3 m | 35 | May-07 | Active, not recruiting | Phase 2; Single group assignment |
| **P10s Basket Trial** NCT03003195 | > 1 | N/A | 1 | Immune Response at 12 w | 80 | Jun-18 | Not yet recruiting | Phase 2; Single group assignment |
| **METADUR** NCT02811497 | 3 | N/A | 1 | Overall response rate at 4 w | 60 | Sep-16 | Recruiting | Phase 2; Single group assignment |
| **ORIOn-E** NCT03525795 | 4 | N/A | 1 | Phase 1: DLTs at 1 y Phase 2: ORR at 1 y | 134 | Dec-17 | Recruiting | Phase 1: Single group assignment; Open label Phase 2: Non-randomized; Parallel assignment; Open label |
| **MOVIE** NCT03518606 | 5 | N/A | 1 | Phase 1: MTD and RP2D at 9 m Phase 2: Clinical benefit rate at 24 w | 150 | Jun-18 | Not yet recruiting | Phase 1/2; Non-randomized; Parallel assignment; Open label 5 cohorts by cancer histology |
| **NCI CTRP** NCT02478320 | > 1 | 1 | 1 | Response rate at 56 d | 12 | Aug-16 | Active, not recruiting | Phase 2; Single group assignment; Open label |
| **MOBILITY-003** NCT02506517 | > 1 | 1 | 1 | Complete response and partial response at 2 y | 30 | Aug-15 | Recruiting | Phase 2; Single group assignment; Open label |
| **MOBILITY-002** NCT02428270 | 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 |
| **MOBILITY-001** NCT02399943 | 1 | 3 | 1 | Complete or partial response, or stable disease at 24 w | 26 | Jun-15 | Recruiting | Phase 2; Single group assignment; Open label |
| NCT03428802 | > 1 | 2 | 1 | Response rate at 2.5 y | 40 | Mar-18 | Recruiting | Phase 2; Single Group Assignment; Open Label |
| **NAVIGATE** NCT02576431 | 8 | 1 | 1 | ORR at 30 m | 151 | Oct-15 | Recruiting | Phase 2; Non-randomized; Parallel assignment; Open label 8 cohorts by cancer histology |
| **SUMMIT** NCT01953926 PMID:29420467 | > 1 | 4 | 4 | Overall response rate up to 30 m | 392 | Sep-13 | Recruiting | Phase 2; Non-randomized; Parallel assignment; Open label 4 cohorts depending on biomarker and intervention. All cohorts receive Neratinib with or without other drug |
| **Sym015-01** NCT02648724 | > 1 | 2 | 1 | Phase 1: Safety and tolerability at 12 m Phase 2: Antitumor activity at 24 m | 72 | Mar-16 | Recruiting | Phase1/2; Non-randomized; Parallel assignment; Open label 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 Phase 2: Objective response up to 2 y | 55 | Apr-15 | Recruiting | Phase 1/2; Single group assignment; Open label (pediatric population only) |
| NCT03266159 | 5 | 1 | 1 | Phase 1: Dose selection up to 12 m Phase 2: Overall response rate and clinical response up to 24 m | N/A | -Nov-17 | Withdrawn* | Phase 1/2; Non-randomized; Sequential assignment; Open label 5 cohorts by cancer histology |
| NCT03525392 | 2 | 1 | 1 | Phase 1: DLTs and organ exposure to radiation up to 6 weeks after second administration Phase 2: safety and efficacy | 300 | May-18 | Recruiting | Phase 1/2; Single group assignment; Open label Protocol might be extended to 3 other cancer histology. Uses the Simon's Two Stage design |
| **ESMART** NCT02813135 | > 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 (pediatric population only) 9 cohorts depending on the intervention given |
| **MiMe-A** NCT03339843 | 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 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)** PMID:28498256 | > 1 | 1 | 1 | Overall response to treatment | 333 | Aug-11 | Active, not recruiting | Phase 2; Single group assignment; Open label |

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**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** NCT03424005 | 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 |
| NCT03280563 | 1 | 1 | 5 | ORR up to 6 y | 111 | Sep-17 | | |
| NCT03555149 | 1 | N/A | 3 | ORR up to 3–5 y | 120 | Sep-18 | | |
| NCT03193190 | 1 | N/A | 4 | ORR up to 3–5 y | 185 | Jul-17 | | |
| NCT03281369 | 1 | N/A | 4 | ORR up to 3–5 y | 357 | Oct-17 | | |
| NCT03337698 | 1 | N/A | 10 | ORR up to 3–5 y | 292 | Dec-17 | | |
| **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 NCT00895128 NCT00895362 NCT00895687 | 1 | 1 | 3 | Part1: MTD and toxicity profiles Part 2: Response rate | Part 1: 16 Part 2: 154 | Apr-09 Apr-09 | Completed Completed | Phase 1; Single group assignment; Open label Part 1 correspond to 1 screening cohort. Part 2 has three treatment cohorts. All 4 have their own registered protocol |
| **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 |

**Table 3** (*continued*)

| Trial | N cancer histology | N targets | N therapies | Primary Outcomes | Sample size | Start date | Status as of July 2018 | Description |
|---|---|---|---|---|---|---|---|---|
| **ALCHEMIST***<br>NCT02194738<br>NCT02193282<br>NCT02201992<br>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<br>All are: randomized; parallel assignment; open label. One is versus placebo the others versus observation |
| **I-SPY-2***<br>NCT01042379 | 1 | 1 | 4 opened<br>11 closed | Pathologic complete response up to 24 w | 1920 | Mar-10 | Recruiting | Phase 2; Adaptive randomized; Parallel assignment; Open label; Bayesian adaptive trial<br>Currently 4 arms trial |
| **BATTLE-1***<br>NCT00411632<br>NCT00411671<br>NCT00410189<br>NCT00410059 | 1 | 4 | 4 | Progression-Free Survival Rate at 8 w | 255 | Nov-06 | Completed | Phase 2; Adaptive randomized; Parallel assignment; Open label<br>4 arms trial |
| **BATTLE-2***<br>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<br>Previously treated patients<br>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 pre-registration 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], ALC-HEMIST [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.

## 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.

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