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Review

Modified study designs to expand treatment options in personalised oncology: a multistakeholder view

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Abstract Personalised oncology, whereby patients are given therapies based on their molecular tumour profile, is rapidly becoming an essential part of optimal clinical care, at least partly facilitated by recent advances in next-generation sequencing-based technology using liquid- and tissue-based biopsies. Consequently, clinical trials have shifted in approach, from traditional studies evaluating cytotoxic chemotherapy in largely histology-based populations to modified, biomarker-driven studies (e.g. basket, umbrella, platform) of molecularly guided therapies and cancer immunotherapies in selected patient subsets. Such modified study designs may assess, within the same trial structure, multiple cancer types and treatments, and should

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incorporate a multistakeholder perspective. This is key to generating complementary, fit-for-purpose and timely evidence for molecularly guided therapies that can be used as proof-of-concept to inform further study designs, lead to approval by regulatory authorities and be used as confirmation of clinical benefit for health technology assessment bodies. In general, the future of cancer clinical trials requires a framework for the application of innovative technologies and dynamic design methodologies, in order to efficiently transform scientific discoveries into clinical utility. Next-generation, modified studies that involve the joint efforts of all key stakeholders will offer individualised strategies that ultimately contribute to globalised knowledge and collective learning. In this review, we outline the background and purpose of such modified study designs and detail key aspects from a multistakeholder perspective. We also provide methodological considerations for designing the studies and highlight how insights from already-ongoing studies may address current challenges and opportunities in the era of personalised oncology.

1. Introduction: the need for modified study designs in the era of personalised oncology

Personalised oncology, whereby patients are given therapies based on their molecular tumour profile, is critical in drug development and is rapidly becoming an essential part of optimal clinical care, with many molecularly guided therapies and corresponding markers approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [1]. Since 1992, there have been 42 FDA-accelerated approvals in personalised oncology, with 86% of these based on overall response rate (ORR) data [2]. None of the approvals have been withdrawn so far, and all that were granted before 26th November 2018 have been converted to a traditional approval [2]. Some molecularly guided therapies have even demonstrated clinical activity across multiple tumour types sharing the same molecular alteration (e.g. *RET* fusion, *NTRK* fusion, microsatellite instability, DNA mismatch repair deficiency, high tumour mutational burden [TMB]) [3,4], resulting in broad or tumour-agnostic approvals. This has been at least partly facilitated by recent advances in diagnostics, including next-generation sequencing (NGS)-based technology using liquid- and tissue-based biopsies [1,5,6]. Indeed, a number of liquid- and tissue-based NGS panels have been approved by the FDA for use in solid tumours as companion diagnostic assays [7], and the National Comprehensive Cancer Network® (NCCN®), American Society of Clinical Oncology, and European Society for Medical Oncology (ESMO) guidelines now recommend multigene panel testing, including via NGS, for a number of tumour types [8-10].

However, as such high-throughput technologies continue to evolve, the number of potential genomic markers is increasing and, subsequently, the size of each target population is reducing. Furthermore, a study of 5954 patient tumour biopsies found that 38% harboured an actionable alteration, although only 18% with an alteration could be assigned to an investigational or FDA-approved drug, after the application of clinical and molecular exclusion criteria [11]. This means that recruitment is becoming challenging for traditional phase III clinical trials investigating molecularly guided therapies, increasing the risk of these trials not taking too long to complete due to insufficient numbers or not beginning at all [12]. Indeed, the percentage of patients recruited onto a matched phase I–III trial following molecular prescreening was 11% in 2017 and 2018, a fall from 15% in 2016 [13]. In addition, to generate confirmatory clinical evidence for tumour-agnostic therapies, many parallel randomised phase III trials of the same drug in different cancer types would lead to a notable and unfeasible depletion of time and resources.

Overall, with the increasing numbers of targeted treatments and smaller molecular-based patient subgroups, it is impossible to solely use fully statistically powered clinical trials to assess the clinical benefit of molecularly guided therapies [14]. Therefore, modified study designs are becoming increasingly important in this setting. These studies assess, within the same trial structure, more than one treatment in the same cancer type, more than one cancer type with the same/different treatments, or both, potentially allowing for borrowing of information between parallel subcohorts and a shared control arm [14]. They may also incorporate interim decision points and adaptive elements [14]. This is key to increasing operational efficiency and generating complementary, fit-for-purpose, and timely evidence for molecularly guided therapies that can be used as a proof-of-concept to inform further study designs, lead to approval by regulatory authorities, and be used as confirmation of clinical benefit for health technology assessment (HTA) bodies (which typically require randomised data to assess comparative effectiveness). This is particularly important for rare tumour-agnostic biomarkers that are increasingly being recognised in guidelines [3,8,10]. For example, *NTRK* fusions occur at a low prevalence across solid tumours (0.30%) [15], and a feasibility analysis of an *NTRK*

trial programme of entrectinib in 12 tumour types found the time to study results (progression-free survival) to range from 17 to 105 years [12]. Thus, it was deemed that traditional clinical trials are not always feasible for this approach. One example of a modified study design that may be used to circumvent this challenge is the phase II, global, open-label, multicohort TAPISTRY trial (NCT04589845), which provides a platform for evaluating the safety and efficacy of targeted therapies or immunotherapy in patients with metastatic solid tumours harbouring specific oncogenic targetable genomic alterations or a high TMB, as identified by a validated NGS assay [16].

Modified study designs might also be important for tumour types for which histological classifications are challenging, such as cancer-of-unknown-primary-origin (CUP), a heterogeneous group of metastatic cancers without an identifiable primary tumour, despite thorough clinical workup [17]. In this malignancy, median overall survival remains particularly low at ≤1 year amongst patients in the unfavourable cohort (80–85% of cases, defined per ESMO guidelines) [18,19]. For these patients, previous clinical guidelines still recommended empirical platinum- or taxane-based chemotherapy [20,21]. However, the ESMO guidelines now recommend the application of NGS to identify potentially actionable genomic alterations in patients with CUP [19], and previous retrospective NGS-based analyses of CUP specimens have shown that patients can be matched to tailored treatment arms based on their molecular profile [22–24]. Moreover, retrospective data also suggest that patients with CUP benefit from molecularly informed treatments [25]. Therefore, molecularly guided therapies are becoming a consideration and are being tested in clinical trials of CUP [26]. Other pertinent examples exist, such as in HER2-negative metastatic breast cancer, where the SAFIR02-Breast trial (NCT02299999), a prospective, randomised trial, showed that targeted therapies matched to genomic alterations classified as level I/II, based on the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT, which provides a robust, precise definition of actionability despite several less-robust definitions existing) [27], improved progression-free survival in these patients, compared with maintenance chemotherapy [28].

In this review, we outline the background and purpose of modified study designs and detail important aspects of these studies from a multistakeholder perspective (patient representatives, treating physicians, principal investigators, industry, regulatory bodies, HTA bodies) [29]. We also provide methodological considerations when designing modified studies to support decision-making (e.g. regulatory approval, HTA body reimbursement decisions and/or clinical treatment decisions) and highlight how insights from certain trials may address current challenges and opportunities in the era of personalised oncology.

2. Modified study designs: background, purpose and key aspects

In 2006, imatinib was approved for five new indications based on a single-arm, non-randomised phase II clinical trial, in which patients were only eligible if they had a life-threatening malignancy known to be associated with one or more imatinib-sensitive tyrosine kinases that had proven refractory to standard therapy, or for whom no proven conventional therapy existed [30]. The approval was granted due to the responses seen, the rarity of the diseases and the fact that there were no proven therapies with a good outcome; this was despite the single-arm study design (which is still accepted for drug approvals in certain circumstances; the question then is around the required confirmatory data). Since then, many other studies with modified designs have been performed, with a rapid increase over the years [31]. Such studies may be used alone or in combination with randomised trials, depending on the rarity of the malignancies investigated. Table 1 presents a summary of key, currently ongoing studies with modified designs [16,32–45].

Modified study designs may be exploratory or confirmatory. Exploratory trials (e.g. SHIVA01 [NCT01771458] [46], MOSCATO 01 [NCT01566019] [47], I-SPY 2 [NCT01042379] [48]) typically do not require type I error protection, and adding/removing treatment arms does not generate statistical challenges. Confirmatory trials (e.g. ALKA-372-001 [EudraCT 2012-000148-88], STARTRK-1/2 [NCT02097810/NCT02568267], the randomised Lung-MAP trial [NCT02154490]), on the other hand, ideally include a control and are randomised (control could also be non-randomised, internal or external, concurrent or non-concurrent), have type I error protection and the addition/removal of arms must happen within statistically rigorous, adaptive design methodology [49]. Exploratory trials may be used to facilitate regulatory approvals of molecularly guided therapies and as proof-of-concept studies to inform the design of postapproval confirmatory trials, which can generate clinically meaningful data for HTA reimbursement decisions.

The major types of modified study designs include umbrella, basket, and platform trials (Fig. 1). In basket trials, patients with multiple cancer types are enrolled, with eligibility based on a particular predictive biomarker that is targeted by the same compound (Fig. 1a). Key basket trials include ALKA-372-001, STARTRK-1 and STARTRK-2, which investigated entrectinib in patients with metastatic or locally advanced *NTRK* fusion-positive solid tumours [50]. Other examples include LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687) and NAVIGATE (NCT02576431; larotrectinib for metastatic

Table 1
Summary of key, ongoing trials with modified study designs.

Trial	Recruitment start date	Design	Target population	Treatment arms	Primary endpoints	Inclusion of national MTB?
STAMPEDE (UK and Switzerland) [32,33]	October 2005	Phase II–III, platform, multiarm, multistage, randomised, open-label trial	Men with hormone-sensitive, high-risk localised or metastatic prostate cancer	One control arm (standard of care) and multiple parallel cohorts defined by study drug and genomic alteration	Three stages: 1) Pilot (early-phase): safety 2) Three intermediate: failure-free survival 3) Final efficacy: overall survival	No
PARAGON (Australia and Belgium) [34]	February 2012	Phase II, basket, single-arm, open-label	Postmenopausal patients with a wide range of oestrogen receptor-positive and/or progesterone receptor-positive, recurrent or metastatic gynaecological tumours	Anastrozole monotherapy	Clinical benefit rate	No
KEYNOTE-158 (global) [35]	January 2016	Phase II, basket, non-randomised, open-label, multicohort study	Patients with advanced solid tumour types that have progressed with standard-of-care systemic therapy	Pembrolizumab monotherapy	Objective response rate	No
TAPUR (United States) [36]	March 2016	Phase II, prospective, non-randomised, multibasket, signal-seeking, pragmatic, open-label trial, based on a Simon two-stage model of expanding cohorts	Patients with advanced, measurable, or evaluable solid tumours, multiple myeloma, or B-cell non-Hodgkin lymphoma	One of multiple parallel cohorts defined by study drug, genomic alteration and tumour type	Objective response rate or stable disease of at least 16 weeks duration	Yes
DRUP (Netherlands) [37]	September 2016	Phase II, prospective, non-randomised, signal-seeking, open-label trial, based on a Simon two-stage model of expanding cohorts	Patients with progression of an advanced or metastatic solid tumour, multiple myeloma, or B-cell non-Hodgkin lymphoma and no suitable standard treatment options	One of multiple parallel cohorts defined by study drug, genomic alteration, and tumour type	Clinical benefit	Yes
MoST (Australia) [38]	October 2016	Multiple, parallel, phase Ib–IIa clinical substudies of novel treatments or indications	Patients with pathologically confirmed advanced or metastatic solid cancers of any histological type, either during or after their last line of effective therapy	Each substudy consists of one or more modules of 16 patients in an open-label, single-arm, signal-seeking platform design assessing a particular molecularly guided therapy	1) Clinical activity (objective tumour response rate, PFS rate at 6 months, and ratio of time to progression on prior therapy to therapy on trial)	Yes
SHIVA02 (France) [39,40]	May 2017	Multicentre, prospective, open-label, non-randomised study taking each patient as their own control	Patients with advanced solid tumours after disease progression on standard treatment	One of multiple parallel cohorts defined by study drug, genomic alteration, and tumour type	PFS ratio, defined as the PFS on matched therapy to the PFS on treatment initiated following the on-purpose biopsy of a metastatic site performed in the frame of the trial	No

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Table 1 (*continued*)

Trial	Recruitment start date	Design	Target population	Treatment arms	Primary endpoints	Inclusion of national MTB?
CAPTUR (Canada) [41]	November 2017	Multicentre, open-label, phase II basket trial, based on a Simon two-stage model of expanding cohorts	Patients with incurable metastatic solid tumours, multiple myeloma, or B-cell non-Hodgkin lymphoma	One of multiple parallel cohorts defined by study drug, genomic alteration, and tumour type	Objective response rate	Yes
MAGMA (Australia) [42]	September 2020	Phase III, multiarm, multistage platform, randomised, open-label trial	Glioblastoma	1) Neoadjuvant temozolomide prior to chemoradiotherapy versus neoadjuvant temozolomide at the same time as chemoradiotherapy 2) Extended adjuvant temozolomide versus standard six cycles of adjuvant temozolomide	Overall survival	No
PEVOsq (Europe) [43]	October 2020	Phase II, prospective, basket, single-arm, open-label trial	Patients with late-stage squamous cell carcinoma of different locations, including head and neck, lung, anus, cervix, vulva, and penis	Pembrolizumab and vorinostat	Objective response rate	No
TAPISTRY (Global) [16]	January 2021	Phase II, platform, open-label, multicohort study	Patients with unresectable, locally advanced, or metastatic solid tumours determined to harbour specific oncogenic genomic alterations or who are TMB-high, as identified by a validated next-generation sequencing assay	One of multiple parallel cohorts defined by study drug, genomic alteration, and tumour type	Objective response rate	No
IMPRESS-Norway [44,45]	April 2021	Phase II, prospective, open-label, non-randomised, combined basket and umbrella trial, based on a Simon two-stage model of expanding cohorts	Patients with advanced malignancies after disease progression on standard treatment	One of multiple parallel cohorts defined by study drug, genomic alteration, and tumour type (commercially available licenced drugs provided by Roche, Novartis, Eli Lilly, Incyte and AstraZeneca)	1) Clinical benefit (objective complete response, partial response, or stable disease after 16 weeks); a response rate of 30% or more will be considered of sufficient interest to warrant further study in a confirmatory trial 2) Safety 3) Patient access to commercially available molecularly guided therapies	Yes

MTB, molecular tumour board; PFS, progression-free survival; TMB, tumour mutational burden; UK, United Kingdom.

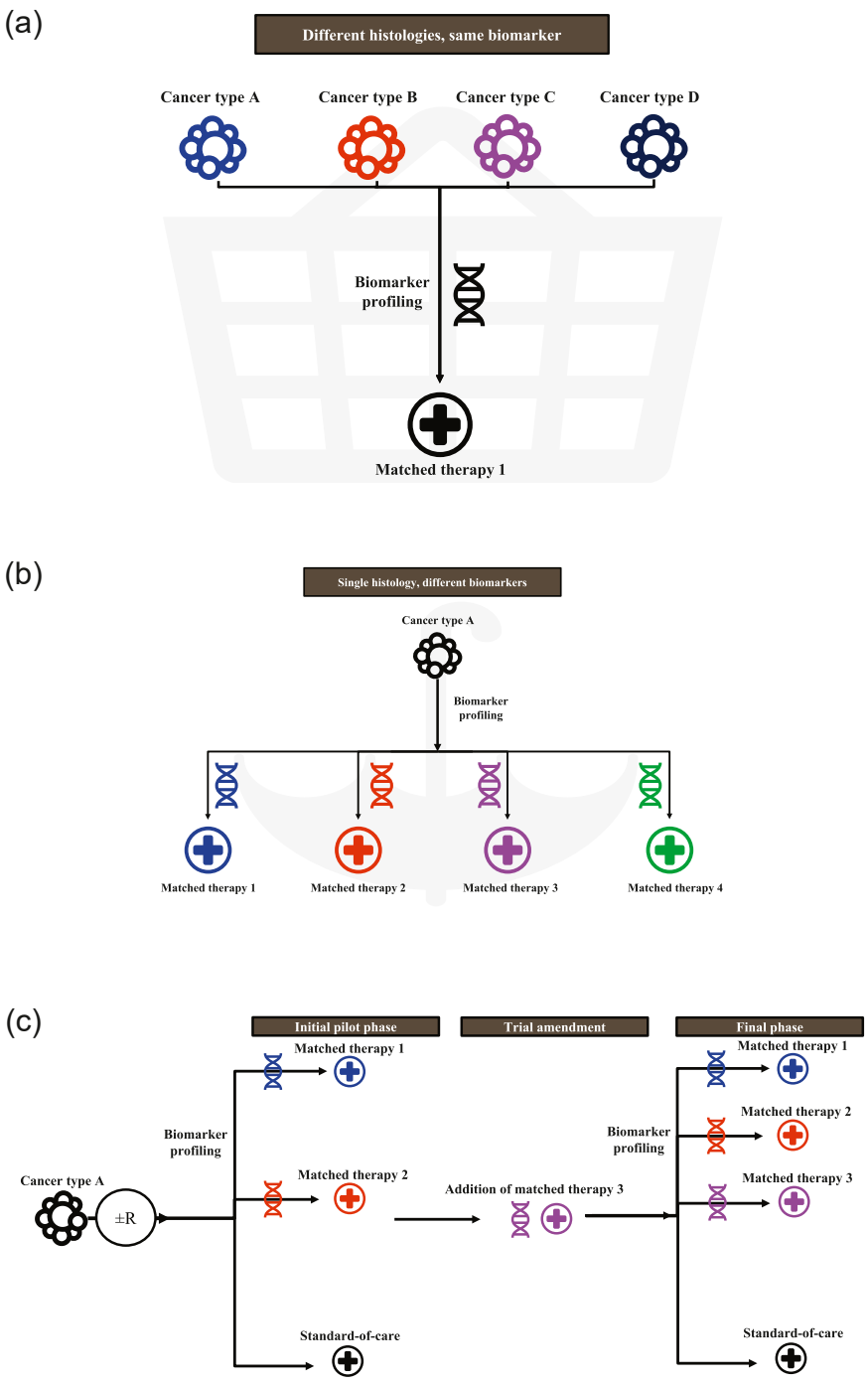

Fig. 1. Summary of (a) basket, (b) umbrella and (c) platform trial methodology. R, randomisation.

NTRK fusion-positive solid tumours) [51], ARROW (NCT03037385; pralsetinib for metastatic *RET* fusion-positive medullary thyroid cancer, non-small cell lung cancer, and other solid tumour types) [52], and LIBRETTO-001 (NCT03157128; selpercatinib for metastatic solid tumours and *RET* fusion-positive solid tumours) [4,53]. Such a homogeneous approach assumes extrapolation of the clinical effect of a compound across multiple tumour types based on a single marker; however, as seen historically, different tumour types with the same molecular alteration may not respond equally to the same targeted therapy [54]. Basket trials may be particularly useful for tumour-agnostic biomarkers, and ESMO has deemed such study designs appropriate when assessing the suitability of a particular biomarker for routine clinical use [27].

In an umbrella trial, a particular cancer type is stratified into smaller biomarker-driven subgroups, with a different therapy given to each; this is often applied to cancer types in which multiple biomarkers of predictive efficacy exist (Fig. 1b). Under the design of umbrella studies, each parallel substudy includes distinct assumptions about the underlying

effect size. Key examples of umbrella studies include UPSTREAM (NCT03088059) for squamous cell carcinoma of the head and neck, VIKTORY (NCT02299648) for gastric cancer, ALCHEMIST (NCT02194738) and Lung-MAP (NCT02154490) for lung cancer, and ADAPT (NCT01781338) and plasmaMATCH (NCT03182634) for breast cancer.

In contrast with umbrella and basket studies, platform trials, or multiarm, multistage trials assess multiple targeted therapies in multiple biomarker-selected populations of particular or multiple cancer types (Fig. 1c). Platform trials are conducted in a perpetual and open-ended manner, with treatment arms being removed from the trial and additional treatment arms being added, as appropriate. An example of a platform trial is the TAPISTRY study, as discussed above. The primary endpoint of TAPISTRY, as is the case for many platform trials (see Table 1), is ORR using the Response Evaluation Criteria in Solid Tumours. ORR is generally assessed earlier in the trial, requires a smaller sample size compared with time-to-event endpoints such as overall survival, and has already been used for targeted therapy regulatory approvals in oncology [55]. ORR may be more robust than the short-term time-to-progression ratio, which has also been used in modified studies [38], but has a greater potential to be adversely affected by disease characteristics unique to each patient's tumour [56]. However, while a good measure of antitumour activity, ORR does not capture patients with stable disease (or differentiate between those with a complete or partial response), may vary in definition between studies, requires frequent radiological or other assessments and does not always correlate with other endpoints such as progression-free or overall survival (particularly for immune checkpoint inhibitors) [55–57]. A detailed review of oncology clinical trial endpoints is not in the scope of this article but can be found in Delgado et al. 2021 [56].

Umbrella, basket and platform trials may all include an 'adaptive' element, enabling new substudies to be introduced or existing substudies to be removed, or existing arms to be expanded to include more patients, as evidence is generated [14,58]. A major example of such a study design is the STAMPEDE trial (NCT00268476), which was initially structured in 2005 as a six-arm (control arm and five experimental therapy arms), five-stage platform trial of different therapies for men with locally advanced or metastatic prostate cancer starting hormone therapy [32,33]. Since then, the trial has been modified multiple times [33], with the STAMPEDE protocol currently being on its 23rd version [59]. STAMPEDE has been successful thus far with non-targeted approaches that can apply across the entire population (e.g. radiotherapy, chemotherapy).

Based on the type of modified study, various methodological aspects should be considered during development. Examples of such considerations are detailed in the next section.

3. Modified study designs: key methodological considerations, challenges and opportunities

Emerging modified studies must generate fit-for-purpose evidence (i.e. for proof-of-concept, regulatory approval or confirmatory clinical evidence) that is aligned with the perspectives/requirements of multiple stakeholders (Table 2). With the continually rising number of new molecular entities and diagnostic tests, there is an increased need for biopharma and multistakeholder, private–public collaboration to enable the optimal treatment strategy for each patient based on their molecular profile.

Modified study designs can expedite drug development by enhancing operational efficiency. This is because the same infrastructure is developed and implemented for multiple substudies, including site selection, centralised patient screening and molecular testing, data management and analysis, and investigational review board/ethics/trial monitoring committees [60]. In addition, basket studies offer the opportunity for borrowing of information between parallel substudies, which (under some assumptions) makes for more efficient use of the available data compared with a per-substudy analysis. This can reduce patient burden, expedite drug development, reduce cost, increase multistakeholder engagement, and, in turn, improve patient care. Borrowing will require a careful review of the assumptions depending on the scientific purpose and needs of the trial (e.g. exploratory or confirmatory) [60–62]. The key assumption for borrowing when using Bayesian hierarchical models is the full parameter (e.g. response proportion) exchangeability (e.g. as shown in Neuenschwander et al. [62]). The main challenges in a basket trial are (1) whether the exchangeability assumption is realistic, and (2) assessing the operating characteristics of the design. For the former, extensions such as the exchangeability–non-exchangeability design exist, which allows each stratum-specific parameter to be exchangeable with other similar strata parameters or non-exchangeable with any of them. Operating characteristics are typically assessed via simulations. To increase trial efficiency further, confirmatory umbrella and platform trials may utilise a common, typically randomised control for all treatment arms, which would normally be the accepted standard of care for the particular tumour type being studied [63]. This can save time and resources and make a trial more appealing/accessible to patients as they have a greater chance of being randomised to an experimental treatment arm [60]. However, having a shared control arm increases the risk of false positives, as tests against the shared control are all correlated [61]. In addition, it should be noted that the standard of care in a particular indication may vary over time, introducing a risk of bias for non-aligned controls; this may require analytical adjustments or setup of new, aligned controls [61]. The subsequent impact on the

Table 2
Multistakeholder perspectives of modified study designs.

Stakeholder	Key aspects of modified study design
Patient representatives	• Involves quick, affordable and easy access to the most promising treatment under one trial and is aligned with current standard of care • Enables simultaneous testing at the earliest possible disease stage, with minimal movement between centres to ensure low burden • Ensures patients have access to both diagnostic and treatment centres, as appropriate • Allows patients who have already received treatment to participate • Demonstrates a global footprint, with patients able to enter regardless of their geographical location • Ideally been set up in collaboration with patients and patient advocates, who are able to raise awareness of pan-tumour and agnostic trials as well as details of the approvals process • Uses learnings from trials conducted during the COVID-19 pandemic (e.g. decentralised, digital-based options) to reduce patient burden • Provides insights into possible new tumour markers or information on prevalence of certain tumour markers that have been able to be tested on more people using CGP in modified study designs • Has the potential to identify the most efficacious treatment options with the fewest possible side-effects quicker • Addresses unmet need in disease area • Generates best possible evidence to assist patients and their physicians to assess potential therapies, particularly if several treatment options exist
Treating physician	• Increases the chance for identifying the best possible treatment for the patients (most efficacious with the fewest possible side-effects) • Generates the most appropriate evidence to aid treatment decision-making with their patient, particularly if several treatment options exist • Facilitates equity of access for all patients with different tumour types that may benefit from molecularly guided therapies, with appropriate referral networks if needed • Involves minimal financial burden for patients
Principal investigator	• Is well designed to provide clear clinical answers and enable effective therapeutic decisions and appropriate safety measures for the patients in the trial • Increases data harmonisation • Provides guidance on protocol development and answers to any outstanding questions (e.g. for regulatory decision-making to inform clinical practice) • Enables patients to access promising molecular therapies • Facilitates support for investigator-initiated studies and translational studies • Harnesses communication between investigators
Industry	• Demonstrates incentive to develop targeted drugs and market treatment algorithms • Uses shared learnings to result in efficient clinical trials/drug development that provide answers quicker, without compromising on patient safety and data integrity • Provides a platform to incorporate treatments from different companies under one trial, enabling risk sharing
Regulatory body[a]	• Informs benefit–risk decisions (particularly in late-phase drug development) • Incorporates type I error protection (which many academic platform trials, e.g. STAMPEDE and those run for COVID-19, do not offer) in a confirmatory setting • Considers that acceptability of RWE may differ between regulatory bodies
HTA body	• Establishes evidence for clinical and cost-effectiveness • Has a high internal validity • Provides support for the required external validity in order to enable reimbursement decisions • Reduces decision uncertainty

CGP, comprehensive genomic profiling; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HTA, health technology assessment; RWE, real-world evidence.

[a] Accelerated or conditional pathways for FDA and EMA may allow for smaller, more efficient studies to be used for initial acceptance, but may limit the chances of acceptance by other regulators.

patient population and study timelines must also be considered. For example, the control arm of STAMPEDE was amended to include docetaxel, as well as androgen deprivation therapy, to reflect the change in the standard of care for prostate cancer.

A second option for the control arm is using the patient as their own control, by comparing the efficacy of a particular drug to that of prior treatments received, as is being performed in the SHIVA02 trial (NCT03084757) [39,40]. This requires assumptions related to the growth of the tumour over time, a likely reasonable task over a short period in the recurrent/metastatic setting and avoids challenges associated with interpatient heterogeneity (particularly for tumour-agnostic therapies) [40]. However, this is not applicable to all tumour types; for example, central nervous system-based tumours. Such a control is only valid if the efficacy of the treatments at the two time points has been assessed using the same response evaluation criteria and with the same timing (e.g. in SHIVA02) [39,40].

Lastly, high-quality real-world data (RWD) from patient registries or electronic health records may also be used as an external control arm, by comparing the outcomes of treated and non-treated patients and using the appropriate methodology to account for potential sources of bias [64]. Wearables are another source. Examples of such methodology may include the use of control groups with highly detailed data regarding baseline demographics, and selection of a control prior to performing comparative analyses [65]. Multiple initiatives to collect RWD are ongoing, including the American Association for Cancer Research Project GENIE [66], WAYFIND-R [67], MoST [38], cancer registries of Norway, Finland and Denmark [68–70], the Netherlands Cancer Registry [71], DIGital Institute for Cancer Outcomes Research [72], and the European Health Data Space by the European Commission [73]. The US FDA and the EMA have recently recognised the importance of RWD as a source of complementary evidence for regulatory decisions [74,75]. However, data in registries and other sources of RWD, while plentiful, are frequently non-standardised, incomplete, non-accessible and siloed, which limits linkage and pooling between data sets and their consequent usefulness in answering particular scientific questions [76]. Measures and processes to ensure data quality or relevancy are often missing [76]. Therefore, to enable the use of RWD as an external control in modified study designs, standardised, global and longitudinal data-collection platforms are needed to obtain high-quality RWD from patients with solid tumours who have undergone NGS profiling. Overall, the choice of control arm depends on previous clinical evidence and the purpose of the trial [65]. For the use of RWD external controls, there are different considerations; for example, having the right data source, ensuring that the patient population in the RWD source is not too different from the trial population to avoid bias, context of use and good rationale of why a concurrent control in the trial is not possible (e.g. small patient population) and standard of care that has not changed much between the RWD source and the trial [77].

A key consideration in modified study designs is the use of centralised or investigator-assessed molecular profiling. Large-scale centralised profiling can be utilised in umbrella studies, allowing the testing of multiple biomarkers at once, reducing dependency on the resources of individual sites, and, critically, increasing patient convenience/accessibility. However, it traditionally relies on a large amount of high-quality tissue, which may not always be available in the context of multiple trials and diverse diagnostic tests [14]. In contrast with centralised screening, investigator-assessed profiling can speed up enrolment and identification of eligible subjects and is more suitable for basket trials in which only one biomarker is being assessed; however, such profiling may lead to a lack of harmonisation of screening and challenges with the generalisability of the results [14]. In the European Union (EU), regardless of the test to be used, all *in vitro* diagnostic tests should meet requirements outlined in the May 2022 EU In Vitro Diagnostic Regulation [78], with adequate performance characteristics (e.g. scientific validity, analytical, and clinical performance) and established procedures for sample acquisition, handling and testing [63].

The choice of diagnostic test as part of modified study designs varies according to the biomarker profile to be assessed. Liquid biopsy via circulating tumour DNA may be of use in situations in which limited tissue is available for NGS-based molecular diagnostics or when serial sampling is required to monitor markers of efficacy and resistance over time (serial sampling may increase patient burden and impact willingness to participate in the trial). Notably, the use of liquid biopsy is supported in clinical guidelines for advanced lung cancer and breast cancer, and the assays Guardant 360 CDx and FoundationOne® Liquid CDx have received FDA approval as companion diagnostics across a range of solid tumour types [8,79–82]. However, extending the clinical application of circulating tumour DNA will require recognition of its relevance and value by regulatory agencies; a unified and collaborative approach to transforming clinical trials is needed to facilitate more rapid uptake into clinical practice.

To aid therapy decision-making in personalised oncology, molecular tumour boards (MTBs) including a range of clinical and molecular expertise are critical and should be included as part of modified study designs [83]. This becomes more relevant as the complexity and scale of data generated through NGS increase; a survey of 1281 United States oncologists found that only 38% were very confident in using NGS to inform patient care [84]. Furthermore, a survey of clinicians across 19 European countries found that 39% were concerned with the turnaround times for NGS tests, the reliability of samples and with the interpretation of results [85]. The use of MTBs as a mechanism to support clinical decision-making is therefore key in aiding the education of healthcare professionals and ensuring patients in trials receive the most appropriate treatment based on their molecular profile. MTBs may form part of clinical decision support systems, as seen in the Molecular Tumor Board Portal by Cancer Core Europe [86]. Although the use of MTBs in modified studies may be limited by difficulties in obtaining multidisciplinary expertise or logistical challenges in community practices or small institutions, remote participation at virtual MTBs may provide an innovative solution [87]. For example, the IMPRESS study includes a weekly, virtual, national MTB, consisting of healthcare professionals with broad competencies such as pathology, oncology, haematology, molecular biology and bioinformatics, the referring clinician, and others such as trial coordinators and local clinicians [45].

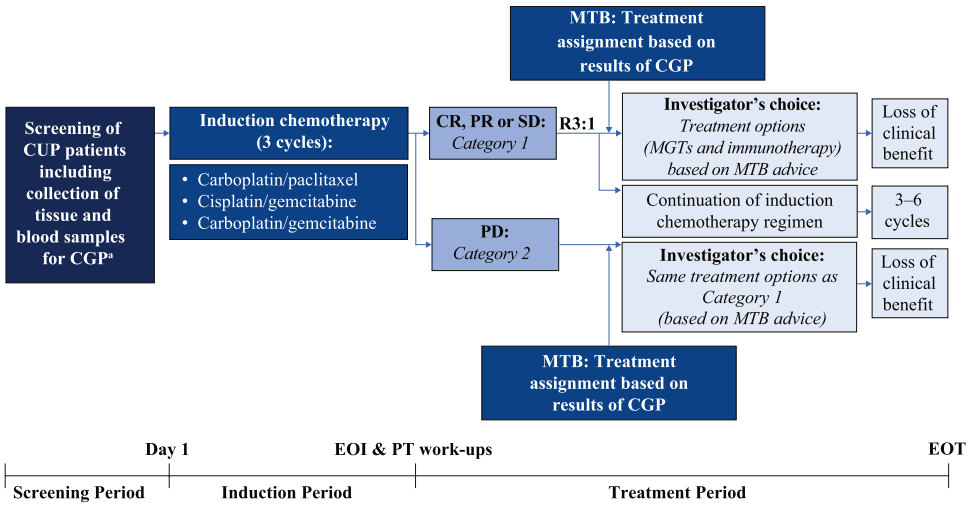

Fig. 2. CUPISCO study design. [a]Based on eligibility criteria that are summarised at ClinicalTrials.gov: NCT03498521. Randomisation is stratified by gender and response during the induction period (CR + PR versus SD). CGP, comprehensive genomic profiling; CR, complete response; CUP, cancer of unknown primary origin; EOI, end of induction; EOT, end of treatment; MGT, molecularly guided therapy; MTB, molecular tumour board; OS, overall survival; PD, progressive disease; PR, partial response; PT, pretreatment; R, randomisation; SD, stable disease.
Used with permission from Ross JS, et al. Comprehensive genomic profiling of carcinoma of unknown primary origin: retrospective molecular classification considering the CUPISCO study design. Oncologist 2021;26:e394-e402. [22]

Overall, modified studies have been mostly used in exploratory/signal-seeking settings.

CUPISCO (NCT03498521) is a fully powered, randomised controlled trial of targeted therapy/cancer immunotherapy versus platinum-based chemotherapy in patients with previously untreated, unfavourable CUP (defined per the ESMO guidelines [19]), and with features of an adaptive umbrella design (e.g. multiple targeted therapies or immunotherapies that can be added to/removed; Fig. 2) that could help the development of drugs in CUP [88]. CUPISCO has included some of the considerations above, thus helping to inform the design of future studies of molecularly guided therapies in CUP and other tumour types, as detailed in the next section. More efficient study designs, such as that of CUPISCO, are needed, depending on sample sizes, to inform regulatory approval of existing molecularly guided therapies in CUP.

4. CUPISCO: helping inform the design of future studies

As shown in Fig. 2, CUPISCO is comparing the efficacy and safety of multiple targeted therapies or cancer immunotherapies, guided by genomic profiling, with platinum-based standard chemotherapy, in patients with newly diagnosed, unfavourable CUP. CUPISCO assesses the effectiveness of a personalised oncology treatment approach and, depending on sample size, results from CUPISCO may be used to inform regulatory approvals of targeted therapies in CUP. All enrolled patients received genomic profiling using the latest comprehensive genomic profiling (CGP)-based diagnostic tests (i.e. FoundationOne® CDx or FoundationOne® Liquid CDx), both of which have been approved for all solid tumour types [81,89]. After three rounds of induction platinum-based chemotherapy, patients experiencing disease control (partial or complete response, or stable disease) were randomised in a 1:3 ratio to either standard chemotherapy continuation or experimental treatment with molecularly guided therapies, following assignment by a global, interdisciplinary MTB. The use of an MTB ensures that all patients receive the most appropriate treatment based on their molecular profile. Patients not responding to induction chemotherapy also undergo MTB-based treatment assignment for the same molecularly guided therapies, but in a non-randomised fashion and without a control arm. Patients were treated until loss of clinical benefit and were monitored for progression-free survival (primary endpoint), as well as overall survival, clinical benefit duration and safety (secondary endpoints). The use of an exploratory arm in patients experiencing disease control will provide insight into whether CGP-informed therapies are superior to standard platinum-based chemotherapy in CUP.

Therapies included in CUPISCO are from different biopharmaceutical partners, helping to tackle newly described molecular alterations based on suggestions made by the MTB. For example, pemigatinib (Incyte) and ivosidenib (Servier) were added as experimental treatment arms after a retrospective analysis of CUP specimens referred for NGS demonstrated that 3.6% and 3.3% of patients with CUP harbour alterations in *FGFR2* and *IDH1*, respectively [22]. The same analysis showed ~32% of patients to be eligible for targeted therapy in CUPISCO [22], similar to the 38% of 5954 patient tumour biopsies in the analysis discussed previously [11], shedding further light on the proportion of

patients with CUP harbouring potentially targetable genomic alterations, which is informative for recruitment into trials in this setting.

The development of CUPISCO has also involved collaboration with patient advocacy groups and educational efforts to raise awareness of the relevance of personalised oncology in CUP among healthcare professionals, patients, and the general public. Such partnership when designing modified studies is key to ensure that the efficacy evidence generated from such trial designs is aligned with the perspectives of multiple stakeholders and can impact/expedite the regulatory approval of molecularly guided therapies. Studies designed as proof-of-concept might not necessarily be seen as unproblematic for cost-effectiveness decisions. Yet, HTA bodies and payers deal with limited data in different ways, but it is generally acknowledged that, in certain disease areas, evidence expectations need to be adjusted. It is less a question of sufficient amounts of data (in terms of sample sizes), but rather the ability to substantiate the relative effectiveness (and clinical relevance to patients) and potential long-term trends. If the strength of evidence on the natural history of the condition, clinical relevance of outcomes and the ability to contextualise is sufficiently available (in some situations, external contextualisation might be acceptable as the only viable option), innovative study designs can be considered sufficient to allow reimbursement under large uncertainty (see the below example of IMPRESS). Another example, DRUP, a multidrug, pan-tumour trial, is aiming to identify signals of clinical benefit of approved drugs used outside their label in rare, molecularly defined subsets of patients with cancer and also involves treatments from different biopharmaceutical companies [37]. The Dutch Healthcare Institute and insurance agencies have now embraced a pay-for-performance model inside DRUP for stage III cohorts; positive results from the first stage III cohort have led to reimbursement of nivolumab in patients with microsatellite instability-high tumours [37]. In collaboration with the DRUP trial, the Regional Health Authorities in Norway have also recently decided to reimburse patients who are included in the expansion cohorts in the IMPRESS-Norway trial (starting with olaparib for patients with biallelic *BRCA1* and/or *BRCA2* inactivation), according to a similar pay-for-performance model [90]. These examples stress the importance of biopharmaceutical and multistakeholder collaboration in order to enhance patient access to molecularly guided therapies.

CUPISCO and DRUP are two positive examples of clinical trials that involve treatments from different biopharmaceutical companies. There are challenges associated with this approach, especially in the contractual and legal setup of clinical trials and in the definition of sponsorship, that need to be solved before this will become main practice. However, as shown in Table 2, all stakeholders should work together to overcome these challenges and provide the community with learnings from the experiences with CUPISCO, DRUP and other trials.

In terms of regulatory approvals, the FDA and EMA have recognised the value of modified studies to accelerate drug development [63,91], and such studies have already resulted in approvals of molecularly driven therapies in rare indications, for example, in tumour-agnostic therapies [40]. Conditional approval, which allows for expedited drug access while further data are generated, is an important strategy by which regulatory bodies deal with uncertainty. This demonstrates how modified study designs are beginning to challenge the status quo of regulatory decisions by showing the benefit of molecularly guided therapies as a treatment approach rather than as individual molecules. However, to fulfil the full potential of modified study designs, their designs and definitions should be aligned with regulatory guidance, which has been shown to be lacking [92]. Furthermore, to translate regulatory approvals of targeted therapies from modified study designs into positive HTA decisions, discussions with HTA bodies are needed to ensure that the design of modified studies, including any treatment comparators, is acceptable from their perspective [93].

Despite the potential learnings that CUPISCO can bring, insights from other studies are also critical (Table 1). A feeder layer of rapid and complementary exploratory approaches will be critical to substantiate prioritising (or deprioritising) candidates for confirmatory trials, which will almost certainly take longer to generate statistically valid outcomes.

5. Conclusions and future outlook

Modified study designs that increase operational and, potentially, statistical efficiency, are needed for evidence generation in small molecular-based patient subgroups and to support decision-making in personalised oncology. Such study designs should incorporate a multistakeholder perspective (regulatory bodies, patient representatives, treating physicians, principal investigators, HTA bodies, industry) [29] to ensure that the evidence generated can be used for regulatory approval, HTA body reimbursement decisions and/or clinical treatment decisions. Learnings from current modified studies can inform various methodological considerations for others in the future, including borrowing of information in basket trials, choice of a control, use of centralised or investigator-assessed profiling, choice of diagnostic test and inclusion of an MTB. For example, as the number of molecular cancer subclassifications and tumour-agnostic therapies continues to increase, the choice of a control arm for modified study designs becomes more relevant, particularly regarding the use of each patient as their own control. Overall, a change in trial designs is required to

evaluate targeted therapies as a treatment approach rather than as individual molecules, as seen in CUPISCO, in order to help realise the numerous opportunities of personalised oncology.

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