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Hot Topic

Innovation in oncology clinical trial design

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ABSTRACT

Progress in and better understanding of cancer biology causes a shift in cancer drug development: away from the evaluation of drugs in large tumour histology defined patient populations towards targeted agents in increasingly heterogeneous molecularly defined subpopulations. This requires novel approaches in clinical trial design by academia and industry, and development of new assessment tools by regulatory authorities.

Pharmaceutical industry is developing new targeted agents generating many clinical studies, including target combinations. This requires improved operational efficiency by development of innovative trial designs, strategies for early-stage decision making and early selection of candidate drugs with a high likelihood of success. In addition, patient awareness and ethical considerations necessitate that agents will be rapidly available to patients.

Regulatory Authorities such as the European Medicine Agency and national agencies recognise that these changes require a different attitude towards benefit-risk analysis for drug approval. The gold standard of randomised confirmatory Phase III trials is not always ethical or feasible when developing drugs for treatment of small cancer populations. Alternative strategies comprise accelerated approval via conditional marketing approval, which can be granted in the EU based on small non-randomised Phase II trials.

The paper describes innovative trial designs with their pros and cons and efforts of pharmaceutical industry and regulatory authorities to deal with the paradigm shift. Furthermore, all stakeholders should continue to share their experiences and discuss problems in order to understand the position and concerns of the other stakeholders to learn from each other and to progress the field of novel oncology clinical trial design.

Background

Progress in cancer biology resulted in an increased understanding of tumour heterogeneity at multiple levels (genetic, functional, tumour components, signalling pathways), development of targeted agents for small populations of molecularly defined cancer patients and drug assessment in early clinical studies. For example, the safety and efficacy of the pan tropomyosin receptor kinase inhibitor larotrectinib was

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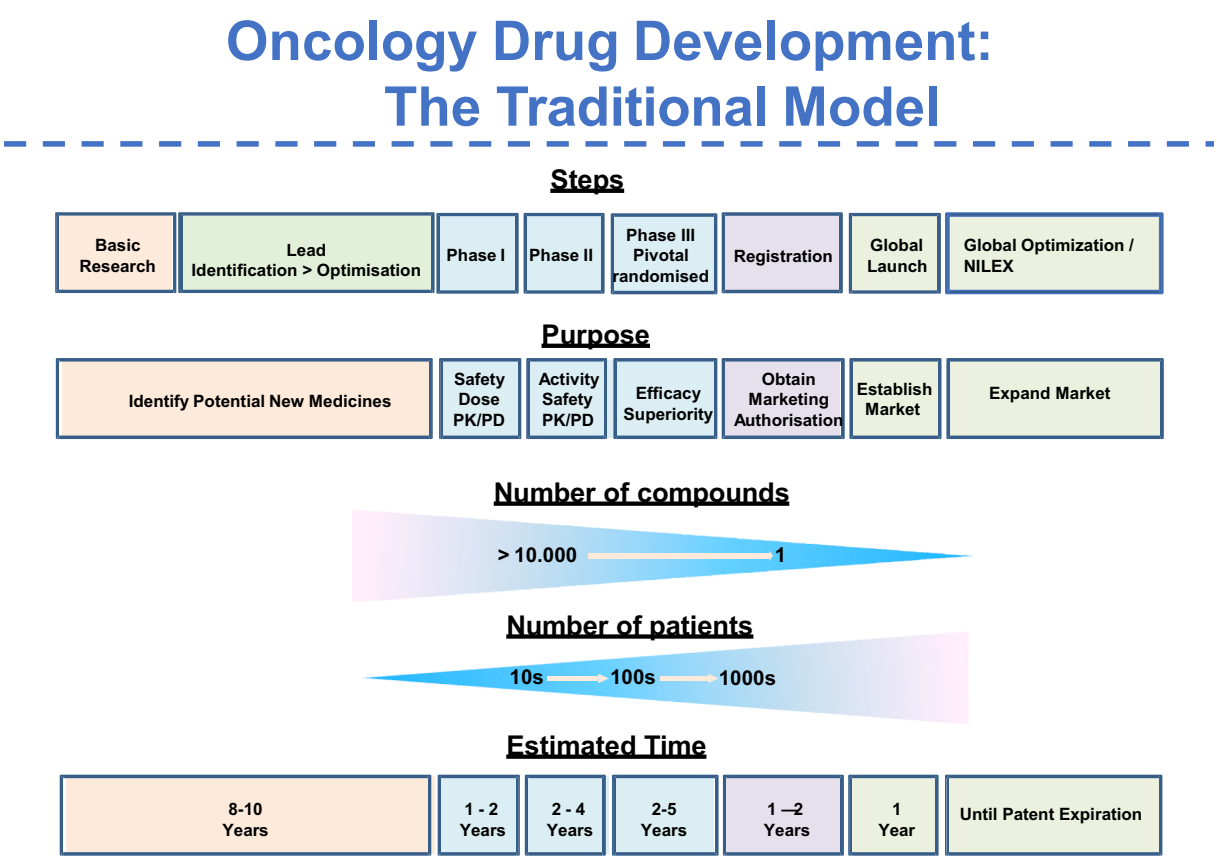

Fig. 1. Oncology Drug Development: The Traditional Rocket Model.

performed in a Phase I/II study with 55 patients (0.3–76 years in age) comprising seventeen tropomyosin receptor kinase fusion-positive tumour types [1]. These developments are challenging the paradigm of the traditional linear model of cancer drug development (Fig. 1) in which drug assessment occurs in randomised confirmatory Phase III clinical trials (RCTs) of large patient populations with histologically defined tumours. Further challenges to pharmaceutical industry are exponentially increasing development costs [2], decreasing R&D efficiency [3] and high drug attrition rate in Phase III studies [4]. But, how does one develop in precision medicine the right drug for the right patient at the right time? One way is to evolve innovative trial designs early in clinical development. In the industry's perspective, such trials should provide a quick answer on whether a drug is active and in which combinations to decide to continue or to stop with the drug.

Additionally, biomarker research for targeted therapies may lead to companion diagnostics. Given the complexity of the neoplastic process, this will require panels of multiple biomarkers that screen multiple genes and proteins in the same specimen at the same time. Serial tumour biopsies could help but are not always feasible, easily accessible tumour samples like liquid biopsies are therefore preferred [5].

Opportunities and challenges with clinical trial design for early and accelerated development plans

Recent novel clinical trial designs are for instance basket, umbrella, platform, and Phase I trials with expansion cohorts, all aiming for enhanced efficiency and small patient subpopulations. This kind of trials requires a master protocol which describes among others the collection of tissue or blood, biomarker profiling and sub-studies including biomarker-negative patients. The master protocol allows logistic efficiency (centralised screening, budget, stakeholders) and potentially accelerated clinical development than separate studies.

Basket trials

A basket trial is a histology-independent design where each sub-trial enrols multiple tumour types ("the basket") with one common genetic mutation. The hypothesis is that response to the targeted therapy is determined by the molecular variant and (largely) independent of tumour histology. The prerequisites are that the drug sufficiently inhibits the target and the tumour depends on the target. The sub-trials are usually single-arm with a hypothesis-generating objective [6,7].

Benefits are that basket trials determine the efficacy of a targeted agent in different tumour types with the same mutation and are accessible for patients with rare tumours with the respective molecular marker. Disadvantages are that molecular variant(s) may not be the only driver of a tumour and contextual complexities in various histologies may exist, e.g. vemurafenib in mutated BRAF melanoma and colorectal cancer (response rate 50–60% vs. 5%) [8,9]. Examples of Phase II basket trials are the NCI-MATCH study with 30 single-arm substudies [10] and VE-BASKET for mutated $BRAF^{+}$ tumours comprising 7 single-arms [11].

Based on academic basket trials like the WINTHER study [12], the UK National Lung Matrix Trial [13] and the NCI MATCH study [10], Cancer Core Europe developed the novel Basket of Baskets design (Fig. 2). First, the patient's tumour (biopsy, plasma) is molecularly profiled by various multiplexed assays. Cancer patients with an appropriate molecular profile can then participate either in industry-sponsored basket trials or in iBasket, a multi-modular investigator-initiated basket protocol. Modules can be added or dropped based on the results and may have different statistical designs (Bayesian, adaptive). Each module has individual arms with genomically selected patient populations.

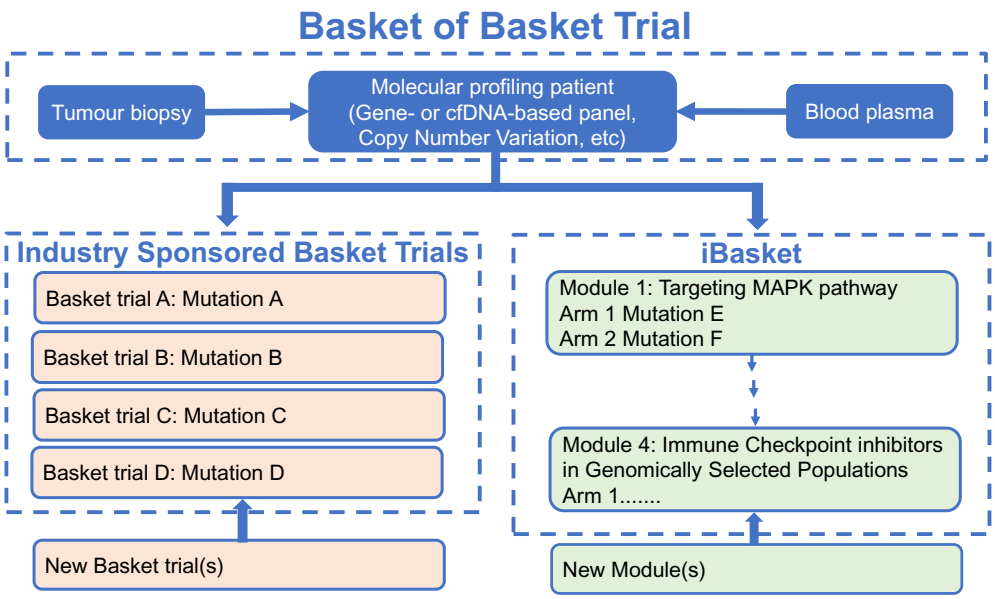

Fig. 2. Study design of the Basket of Baskets trial developed by Cancer Core Europe.

Umbrella trials

An umbrella trial evaluates the efficacy of different targeted agents each against a different genetic mutations (sub-trials) within a single histology ("the umbrella"). A response is assumed to be (primarily) determined by the histological context. Each sub-trial is either single-arm or randomised (treatment vs. standard of care (SoC)). Advantages are a relatively homogeneity (same tumour type) and observed benefit may more credited to the genetic mutation, particularly true when the sub-study was randomised. It supports submission of a marketing authorisation application to regulatory agencies. But, umbrella studies may have difficulty enrolling rare genetic mutations of a single tumour and the introduction of new SoC during trial conduct changes the environment. Examples of umbrella trials are the FOCUS4 Design [14] and the BFAST study (Blood First Assay Screening Trial) [15]. This is a Phase II-III trial in advanced or metastatic non-small cell lung cancer (NSCLC) to evaluate the efficacy and safety of atezolizumab and the association between tumour mutational burden in blood (bTMB), and efficacy in biomarker-unselected patients. NSCLC is considerably heterogeneous and includes many biomarker-driven subsets among others EGFR (15%), ALK (5%) and RET (1.5%) mutations. Blood samples are used to isolate circulating tumour DNA for testing against a panel of somatic mutations and bTMB. Based on the screening results patients will be placed in one of three single-arms (ALK^+, RET^+, bTMB vs. SoC). Additional BFAST cohorts may be added in the future to address other somatic mutations.

Historical controls

Single arm trials are usually more acceptable in situations [16] in which:

- the experimental therapy is strongly believed superior to alternatives (loss of equipoise),
- the rarity of cancer/subtype makes randomisation impossible or unethical,
- the disease has a predictable course,
- the endpoint is objective.

These are necessary conditions since in the absence of (randomised) current controls, there is no information about the counterfactual scenario, i.e. what would have been the response rates, had the patients not been treated? It is, therefore, necessary to extract control information from past studies and literature to build a curated dataset of historical controls. The prerequisite is that historical patients should be as similar as possible to the treated population as regards inclusion criteria and confounders (age, gender, clinical history, former treatments, etc). Post-hoc data selection should be avoided and the analysis plan should be pre-specified. However, the main drawbacks of historical controls are a lack of randomisation, a lack of blinding and the impossibility to adjust for unknown confounders (or to access the information). These biases reduce the credibility of the findings and render regulatory assessment of applications based on single-arm trials difficult. To circumvent these hurdles regulators tend to request a larger treatment effect as proof of efficacy when assessing confirmatory single arm trials.

Phase I trial with expansion cohorts

This trial model commonly consists of a dose escalation part to determine the maximum tolerated or biologically active dose, safety and pharmacokinetics, followed by multiple expansion cohorts for either monotherapy, combination therapy, drug-drug interaction or molecular enrichment [17]. Expansion cohorts offer an improved efficiency as they address multiple questions in a single study:

1. single agent activity in a tumour type of interest based on preclinical observations, permits a "quick kill" of the agent, and
2. a biomarker/tailoring hypothesis with corresponding logistics.

They rapidly establish the safety of combination therapy without the need of performing a Phase Ib study or safety lead-in in a Phase II study. The design allows flexibility because new cohorts can be added based on emerging scientific evidence. Since the same study team/site investigator oversees multiple cohorts the experience can be shared and applied in new studies.

Occasionally, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approve drugs on a limited data set e.g. the ALK/MET inhibitor crizotinib in ROS1 rearranged NSCLC with 50 patients in an extension cohort of the Phase I study [18].

Parallel group design with a shared control/Platform trials

A parallel group design with a shared control evaluates two or more

investigational treatment arms relative to a control arm in the same tumour type in a single clinical trial. Instead of having separate trials for SoC treatment versus each investigational compound (+/− SoC) individually, patients are randomly assigned in one study to either one of the investigational arms or SoC as control arm (+/− placebo). This set-up reduces the total sample size by eliminating the need of individual control arms for each investigational arm as it would be required in separate add-on trials. The more investigational arms included the more SoC control arms can be "saved" and the higher is the efficiency of this design. Moreover, the investigational arms don't need to be initiated concomitantly, as long as there is an overlap in the enrolment period. This type of design is called platform trial and provides an additional advantage of this design as it gives some flexibility in timing for drug development programmes that not necessarily can always be synchronized in terms of timing. The rationale and details for such a shared control must be clearly described in the protocol and the statistical analysis plan. This design might be particular advantageous in situations where the number of potential patients is limited, for instance in rare tumour types or in defined molecular subsets of patients with a specific mutation (e.g. ALK, MET exon 14 skipping mutations).

New trials design combinations

Immune checkpoint inhibitors offer many opportunities for combinations in cancer treatment; currently > 1100 PD-1/L1 combination clinical trials are ongoing [19] competing for a restricted number potentially suitable cancer patients. Hence pharmaceutical companies should develop a priority strategy for their immuno-oncology portfolio to focus early in clinical development on candidate drugs with a high probability of success and answer the following questions:

(1) what is a compelling clinical benefit in this setting,
(2) is this a combination where additional evidence is required,
(3) the relevance of historical controls,
(4) what improvement in the endpoint is likely to predict clinical benefit.

When encouraging overall response rate (ORR) and safety (Phase Ib) data are available, the route to registration has to be determined via either innovative trial designs or traditionally Phase II and Phase III trials.

Patient attrition rates

Molecularly defined subgroups of patients are inherently small. Only 5–20% of patients enrolled in recent clinical trials were eligible for treatment with targeted therapy [20–23]. This high attrition rate is a serious concern, in the first place for the non-eligible patients but also regarding manpower, time and finances. Endeavours to offer biomarker-negative patients treatment matching their molecular profile is a solution for a minority. Because data from the ONCOKB database [24] and the MSK-IMPACT study [25] show that 36% of cancer patients has at least one actionable mutation of which 20% can be treated by FDA approved targeted drugs (< 5% will have clinical benefit [26]) and 80% with targeted drugs with evidence for activity. The remaining 64% with no actionable mutations qualifies for chemotherapy. This is in line with the ONCO-T-Profiling collaborative project results, in which 66% (87/131) of the patients were treated according to their molecular profile: 7% received targeted therapy, 6% hormone receptor blockers, and the large majority chemotherapy [27].

Statistics in innovative clinical trials designs to accelerate development and approval

Statistics in adaptive trial designs

An option to accelerate approval by regulatory authorities is moving a drug directly from Phase I to Phase III. Two case examples are discussed.

Extensive data exist on the antibody-drug conjugate trastuzumab emtansine in various $HER2^+$ solid tumours but not in $HER2^+$ gastric cancer. Trastuzumab is, however, an approved first-line therapy in that tumour type. Based on these data, a decision has been taken to move the conjugate directly into a pivotal trial. There is residual uncertainty on the optimal dose for trastuzumab emtansine as gastric cancer patients have lower plasma levels of monoclonal antibodies than patients with other types of solid tumours. To cope with this, an adaptive seamless adaptive Phase II/III trial design with dose selection at an interim analysis was implemented to address this residual uncertainty. The patients in the Phase II were randomly assigned to three treatment groups: trastuzumab emtansine 3.6 mg/kg every 3 weeks, 2.4 mg/kg weekly or physician's choice of docetaxel or paclitaxel. At the interim analysis, 2.4 mg/kg weekly was selected by the independent data monitoring committee for the Phase III, in which patients were then randomly assigned (2:1) to trastuzumab emtansine or a taxane. The outcome showed that trastuzumab emtansine was not superior to taxane in patients with previously treated $HER2^+$ advanced gastric cancer [28].

This adaptive design allowed to address residual uncertainty in dose, enabled savings in time and costs by reducing patient numbers and the ability to use stage 1 patients for the confirmatory part of the study. But this type of trial is also operationally more challenging and require complex simulations to understand design characteristics (type I error, power and any bias in estimates).

The second example concerns the VALOR Phase III trial design, in which the efficacy of the combination vosaroxin-cytarabine was compared with placebo-cytarabine in relapsed/refractory acute myeloid leukaemia [29]. A decision to move to Phase III have been made based on promising data from a single arm Phase II trial (69 patients) [30]. As setting a target treatment effect based on the single arm data and previous trials of cytarabine for the Phase III sample size determination is challenging and associated with uncertainty, an adaptive design has been chosen to be able to adjust sample size at an interim analysis shall the assumed treatment effect be incorrect [31]. Depending on the results observed at interim analyses, three scenarios can occur: 1) continue the trial as designed, 2) increase the sample size if results are promising, and 3) stop early for overwhelming efficacy or futility.

The message is thus: no one-fits-all approach exists, each approach should be tailored, preferably early in drug development to allow sufficient time for trial design refinement.

Subgroup analysis

Subgroup analyses for a survival benefit in heterogeneous populations aim to identify groups of patients for other treatments in precision medicine. Subgroup analysis depends on the relationship between drug and target. If the relationship is strong then trials in subgroups can be performed (umbrella, basket, RCT in selected patients, etc.). When the relation is plausible, a Phase II trial in unselected patients followed by subgroup analyses or a Phase III in subgroups using adaptive designs are options. Here, seamless Phase II-III trials for selection of subgroups is potentially a very powerful tool to speed up cancer drug development. In the case of a questionable relationship, a Phase III study in unselected patients is feasible to determine whether a positive or negative outcome in the subgroup analyses is detected.

Classical problems in subgroup analysis are methodological (retrospective vs. prospective, planned vs. unplanned, bias) and statistical.

Although in the past unplanned subgroup analyses had a negative connotation, today the methodology is standardised as a result of guidelines [32] and education [33]. Unfortunately, not everyone follows the standard methodology [34].

New types of subgroup analyses are early failures vs. average progression free survival (PFS) [35] and long-term survivors vs. average survivors [36,37].

The estimand framework

Patients differ in response to treatment, also in clinical trials. Randomised trials are expected to be free from baseline confounding but, in trials as in clinical practice, post baseline certain events will occur that complicate the description and interpretation of the outcome and hence the treatment effects. These events are denoted as intercurrent events and include among others rescue medication, treatment switching, discontinuation, and death. A new framework to discuss with stakeholders which treatment effect to be estimated (the estimand) was therefore developed and released in 2017 for consultation as draft ICH E9 (R1) guidance [38]. It addresses issues on the definitions of population, variable (endpoint), intercurrent events, and summary measure with which the treatment effect will be assessed.

Time-to-event endpoints are used in oncology as primary endpoints to measure treatment effect, for example overall survival or PFS and event free survival. For PFS and event free survival, different censoring rules are typically applied which lead to inherently different estimands. A standardised definition of treatment effect to be estimated (the estimand) is, however, lacking, which will cause problems comparing different trial results. Recommendations for standardised definitions of time-to-event endpoints in cancer clinical trials are provided by the DATECAN project [39,40].

For better interactions, the estimand framework offers the possibility to all stakeholders to speak a common language.

Regulatory agents and innovative clinical trial design

For regulators, RCTs remain the gold standard to evaluate the benefit-risk ratio of cancer drugs, but early clinical trials offer opportunities for early access to the market. The EMA has approved drugs based on early clinical trial data since 1995 on a case-by-case basis. As of 2006 conditional marketing approval (CMA) can be granted on limited data to drugs that address unmet medical need. The data must show high clinical benefit over existing therapies and the benefit of rendering the drug available earlier outweigh the associated risks. The sponsor has also to show that more comprehensive data are likely to become available later on in order to complement the assessment. The US counterpart of the CMA is since 1992 the Accelerated Approval (AA). An important prerequisite for CMA/AA is that the applicant should be able to timely provide comprehensive clinical data, either in the same or more typically in a closely related clinical setting of the disease following the CMA/AA [41].

A pitfall of CMA/AA is that it can hamper postapproval RCTs due to a) low diligence by industry, because there is little incentive to enrol in trials when the drug is approved and reimbursed, b) ethical implications to randomise patients to a “less effective” control group and c) RCTs are problematic for rare diseases [42]. FDA experience over the period 1992–2017 shows that 55% (51/93) of the AAs in haematology and oncology verified benefit in the postmarketing RCT with a median of 3.4 years (0.5–12.6 years) [43].

Seventeen CMAs in oncology have been granted over the period 2006–2016, > 50% based on single-arm Phase I/II and IIb studies. The primary endpoints were generally time-related [44]. ORR was the preferred endpoint for regulatory agents in single-arm trials. Significant ORR had however to be combined with durable responses that exceeded those of existing therapies. CMA/AA examples based on single-arm data in 2010–2015 for chemo- and targeted therapies show an ORR ≥ 30% with durable responses (≥6 months) vs. an ORR of 15% and very durable responses of 9–12 months or more for immuno-oncology drugs in 2016–2017 [45].

Conclusions

Advances in cancer biology are resulting in development of numerous novel targeted agents for specific genetic mutations, present in small groups of patients selected by molecular profiling of their tumour. Standard RCTs are not always best suited for the evaluation of these drugs. Patients with unmet needs could benefit from innovative clinical trials designs and alternative regulatory pathways by rapid access to novel drugs and potential clinical outcome. In addition to developing new targeted agents, pharmaceutical industry aims to improve its efficiency by developing strategies for early-stage decision making and early selection of candidate drugs. To learn from each other and to continue improving oncology trial designs, a continuous dialogue between all stakeholders is needed.

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Contributions

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Conflict of interest

The authors declare no conflict of interest.

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