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Review Article

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# Evolution of global clinical trials with adaptive design

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**Review**

Adaptive designs in oncology drug investigation, especially in the clinical trials of anti-cancer agents, have become more and more popular with the advantages of high efficiency and cost-effectiveness. However, potential success of the adaptive trial relies on the thorough understanding of adaptive design, exhaustive pre-protocols backup, proficient statistical skills and support from local regulators. Here We reviewed the definitions of adaptive design trial (ADT) from previous publications, listed the advantages and drawbacks of different ADT approaches compared to traditional RCTs. Next, we collected all the clinical trials with adaptive design, exhibited a landscape of registered ADTs yearly and policies/instructions aiming to accelerate drug approval and commercialization across the world to date. Furthermore, we focus on the utilization of master protocol design in the field of solid tumor and analyzed the pros and cons of multiple key ADT studies around the world. Finally, we proposed an optimal PLATFORM study protocol with adaptive master protocol design based on all the elements we listed above and concluded the importance and potential future applications of adaptive trial design.

## Introduction

Randomized clinical trials ( RCTs ) are well known being the standard solution to provide high-quality evidence for clinical practice. Traditional trail design is characterized by comparing two drugs within a specific disease setting following pre-defined protocols [1,2]. As the growing demand for feasibility, efficiency and flexibility emerges, the concept of "adaptive trial design" has been proposed, which emphasizes on the modification of clinical trial design based on interim data feedback and proleptic decision rules adaptively. The flexible feature of an adaptive trial design derives from specified principles with scrutiny of planed and unplanned clinical details, which separate it from an inadequate prepared trial with uncertain validity and arbitrariness [1]. Adaptive trial design allows investigators to modify toxic/efficacy dosage of a treatment, improve randomization algorism from covariates and response rate, re-define participants number and enrollment criteria and facilitate trial transition meanwhile reduce downtime between phases, based on accumulating feedback and continuous evaluation [3]. With lower expense, faster process and higher likelihood for treatment effect, adaptive trial design displays its advantages in efficiency, flexibility and integrity [4]. Nevertheless, high demands for protocol management, statistical verification and ethical concern remains for the validity of the trial.

Considering different purposes and adaptation methods applied, adaptive trial can be further classified into many types. Several commonly used are: a) adaptive group sequential design [5]; b) sample size re-estimation [6]; c) Phase I/II or II/III two stage seamless design [7]; d) adaptive enrichment [8]; e) master protocol with adaptive design [9]; f) multiple adaptive design [10]; g) adaptive dose escalation [11]; h)Drop-the-loser design [12]; i)Adaptive treatment-switching [13]; j) Adaptive-hypothesis design(Chow, 2014); k)Biomarker-adaptive design{Chen, 2014) ; l) Multi-arm multi-stage(MAMS) [10,14]; It's worth mentioning that different types of adaptive design could be utilized in one trial. Besides, designs like adaptive dose-finding or drop the losers, could be applied in trials independently, or manifested as part of these frequently used adaptive trial designs (Figure 1).

Increasing numbers of adaptive clinical designs have brought an urgent need for guidance, consensus, and regulations due to the notable differences between adaptive trials and traditional trials. Countries or regions like European (medicine agency,2007) and U.S(Food and Drug Administration department,2010) has published guidelines and experience consecutively. In May 2020, China Center for drug evaluation (CDE) initiated guideline on Adaptive Designs for Clinical Trials, recognizing the validity of adaptive trial, and providing references to facilitate the complicated design.

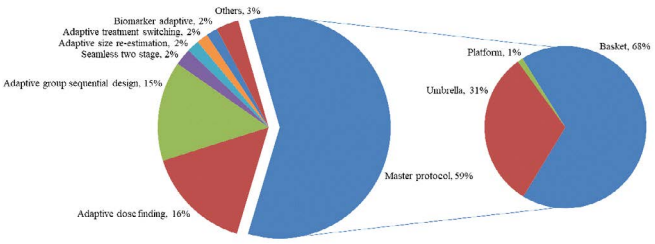


**Figure 1.** Types of adaptive design worldwide (1998-2020. (Left)Numbers of trials in each category followed by its percentage among total trials; (Right) Numbers of trials in each category followed by its percentage in master protocol design trials

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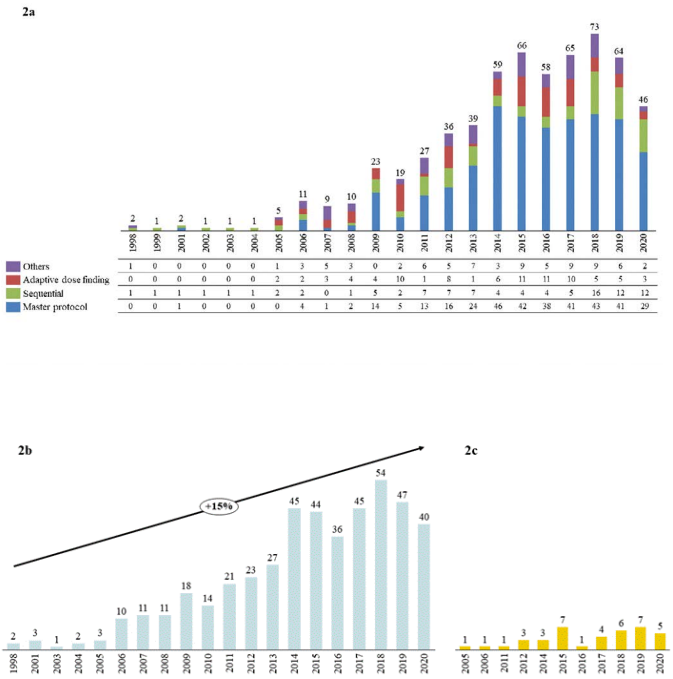


**Figure 2.** Major category of adaptive trial registered per year in regions. Adaptive trials design was divided into master protocol design, adaptive group sequential design, adaptive dose finding and others by quantity and countries (Worldwide:2a, United States:2b and China:2c)

**Table 1.** Comparison of quantity and characters for adaptive clinical trials in US, China, and other country/regions worldwide

| Classification and characteristic of adaptive design trial in the USA, China and elsewhere | | | | | |
|---|---|---|---|---|---|
| Characteristic | Trial type | USA N(%) | China N(%) | Other N(%) | Total |
| Phase | I | 109(42.1) | 3(1.2) | 147(56.7) | 259 |
| | I/II | 119 (42) | 5(1.8) | 284(56.2) | 408 |
| | II | 161(37.8) | 14(3.3) | 251(58.9) | 426 |
| | II/III | 26(37.7) | 7(0.1) | 36(52.2) | 69 |
| | III | 37(38.5) | 8(8.3) | 51(53.2) | 96 |
| | IV | 2(28.6) | 1(14.3) | 4(57.1) | 7 |
| Trial Status | Open | 163(38.9) | 20(4.8) | 236(56.3) | 419 |
| | Closed | 56(41.8) | 3(2.2) | 134(56) | 193 |
| | Completed | 151(38.5) | 14(3.6) | 227(57.9) | 392 |
| | Terminated | 82(42.5) | 1(0.5) | 110(57) | 193 |
| Primary endpoint | Safety | 239(31.5) | 23(4.6) | 496(63.9) | 758 |
| | Efficacy | 255(41.5) | 17(2.8) | 343(55.7) | 615 |

Here, we summarized ongoing and ended adaptive drug clinical studies in oncology field from INFORMA database registered between Jan 1,1998, and Dec 31, 2020 in China, U.S and worldwide. Growing tendency of adaptive design implantation has been witnessed starting from several cases in 1998 to dozens recent years globally and in the US. Compared to US, China still harbors great potential as the adaptive trial number just started to accumulate (Figure 2 and Table 1) [15].

In total, 615 drug trials with adaptive design were searched worldwide. Category of the design also varied among 617 adaptive trials collected, with majority of the trial utilized master protocol (59%), adaptive group sequential design (15%) and adaptive dose finding (15%). Methods like two stage seamless design, adaptive sample re-estimation and drop-the-loser set were employed in a minority of the trials (Figure 2). Non-small cell lung cancer (NSCLC) and checkpoint inhibitor (majorly PD-1/L1) therapy remain to be the focus area of oncolytic trial study, no exception for adaptive design trials (Figure 3 and 4). Furthermore, we investigated the details in phase, status and primary endpoint of adaptive trials in U.S, China and other regions worldwide, details of adaptive trail would help us better overcome the barriers and promote growth of applications in field of oncology trial (Table 1). Current progress of these trials varied significantly, ranging from phase I to phase IV. Besides, the ongoing clinical trials with adaptive design distributed unevenly among regions. In this regard, 109 (42.1%) trials under phase I were conducted in the USA, while only 3 (1.2%) trials were performed in China. 147 (56.7%) clinical trials in phase I were carried out in other regions. 161 (37.8%), 14 (3.3%) and 251 (58.9%) trials were under phase II investigations in the US, China, and other regions respectively. 26 (37.7%), 7 (0.1%) and 36 (52.2%) phase II/III trials, and 37 (38.5%), 8 (8.3%) and 51 (53.2%) phase III trials were carried out in the US, China, and other regions accordingly. However, the distribution of phase IV trials was relatively even among regions, specifically 2 (28.6%) in the US, 1 (14.3%) in China and 4 (57.1%) trials in other regions. For these trials, 163 (38.9%), 20 (4.8%) and 236 (56.3%) studies were still open in the US, China, and other places. 56 (41.8%) and 82 (42.5%) studies were closed or terminated in the US, while 3 (2.2%), 1 (0.5%) and 134 (56.0%), 110 (57.0%) trials were closed and terminated in China and other regions. 151 (38.5%), 14 (3.6%) and 227 (57.9%) studies were completed in the US, China, and other regions respectively. In result, 239 (31.5%) and 255 (41.5%) trials in US have assessed the safety and efficacy of investigated drugs,

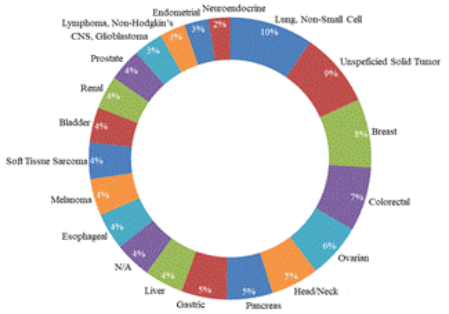


**Figure 3.** Analysis of adaptive design trial by different tumor types. Non-Small cell lung cancer is the leading tumor type with most clinical trials within adaptive trial design. The term "Unspecified solid tumor "were usually seen in stage I trial or drugs with broad treatment indications

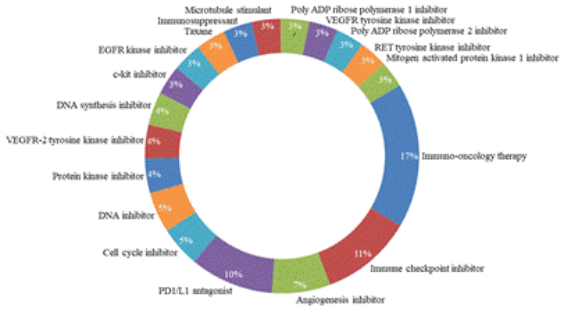


**Figure 4.** Analysis of adaptive design trial by different targeting mechanisms. Checkpoint inhibitor including PD-1/L1 still remains the leading therapy explored with adaptive trial design

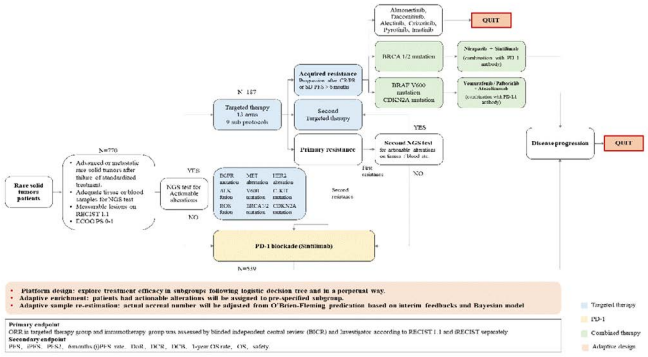


**Figure 5.** Graph illustration of our ongoing rare solid tumor platform trial with adaptive design

**Table 2.** Summary of Key ADTs with master protocol design in solid tumor: Pro and Cons. ADTs: adaptive design trials (DCR=Disease Control Rate, PFS=progression free survival, OS=overall survival, ORR=objective response rate, PR=partial response, QOL=quality of life, PD-L1=programmed death-ligand 1, NSCLC=non-small cell lung cancer.)

| Trial Name | | NCT00409968（Battle study） | NCT01248247(Battle-2) | NCT01771458(SHIVA) |
|---|---|---|---|---|
| Phase | | II | II | II |
| Adaptive design | | Umbrella | Umbrella | Basket |
| Trial design | Purpose | Treatment Investigational | Treatment Investigational | Proof of concept |
| | Randomization | Yes | Yes | Yes |
| | Tumor type | NSCLC | NSCLC | Tumor types included breast (5), lung (3), ovary (2), cervix (2) |
| | Drug | Erlotinib, vandetanib, erlotinib plus bexarotene, or sorafenib | MK-2206,selumetinib,erlotinibsorafenib | Erlotinib,trastuzumab,letrozole,tamoxifen… |
| | Biomarker | Mutation of EGFR/cyclin D1/BEGF receptor/KRAS/BRAF/CCND2 | KRAS mutation | Molecular alterations in PI3K/AKT/mTOR pathway and RAF/MEK pathway |
| | Study population | Patients with either stage IIIB, stage IV, or advanced, incurable NSCLC, and failed at least one front-line metastatic NSCLC | Patients with previously treated patients with advanced non-small cell lung cancer | Patient with recurrent or metastatic solid tumor who failed or are not candidate for treatments usually proposed in first intentions |
| Results | Primary endpoint | 8-week DCR | 8 week DCR/PFS/OS | PFS |
| | Results | Completed. Successful | Completed, primary endpoint(s) not met | Completed, primary endpoint(s) not met |

while the amount of trials assessing safety and efficacy in China and other regions are 23 (4.6%), 17 (2.8%) and 496 (63.9%), 343 (55.7%) accordingly. To summarize, large regional disparity was observed in the amount of clinical trials with adaptive design, with the numbers of studies in US and other regions are significantly higher than in China, indicating adaptive design trial is a relatively novel drug development strategy in China with great potential to facilitate local drug discovery.

Six key studies with adaptive trial design are discussed in detail (Table 2), namely NCT00409968 (Battle study), NCT01248247 (Battle-2), NCT01771458 (SHIVA), NCT02154490 (Lung-Map-S1400), NCT01042379 (I-SPY 2), and NCT02693535 (TAPUR). All studies enrolled stage II/III cancer patients, with adaptive design including umbrella and basket designs. The primary purposes of these trials are treatment investigations and proof of concept, and all but NCT02693535 (TAPUR) are randomized trials.

The investigated tumor type is NSCLC in the trial of NCT00409968 (Battle study). Drugs including erlotinib, vandetanib, erlotinib plus bexarotene, and sorafenib were tested. The biomarkers used were *EGFR*, *BEGF* receptor, *KRAS*, *BRAF*, *CCND2* and cyclin D1 mutations. The studied population was a group of patients with the diagnosis of either stage IIIB, stage IV, or advanced incurable NSCLC, and who failed at least one front-line metastatic NSCLC chemotherapy. Primary endpoint was 8-week Disease Control Rate (DCR), and the trial was completed successfully [16]. Reviewing this trial, it was the first completed prospective study in heavily pretreated NSCLC patients that mandated tumor profiling with core needle biopsies, providing the evidence to develop specific predictive biomarkers-based approach and associated treatments for subsequent definitive clinical testing. However, pre-defined biomarker group has diluted predicative value than unique biomarkers like *EGFR* mutations [17].

NCT01248247(Battle-2) mainly enrolled previously treated patients with advanced non-small cell lung cancer. The biomarkers utilized were *KRAS* mutations, and drugs assessed included MK-2206, selumetinib and erlotinibsorafenib. The primary endpoint is 8-week DCR/PFS/OS. The trial was currently completed, though without meeting the primary endpoint(s) [18]. One highlight of this study is it further confirmed the feasibility of real-time biopsy-sequenced, biomarker-based, adaptively platform trial design in patients with pretreated advanced NSCLC. Nonetheless it failed to show clear association between clinical drug decision or tumor response and limited set of biomarkers (*KRAS* mutation here). Further exploration of biomarker-based immunotherapy is needed [18].

The trial of NCT01771458 (SHIVA) is the only one with the purpose of proof of concept in all trials focusing on tumor types including breast cancer (5), lung cancer (3), ovary cancer (2) and cervix cancer

**Continued Table 2.** Summary of Key ADTs with master protocol design in solid tumor: Pro and Cons. ADTs: adaptive design trials

| Trial Name | | NCT02154490(Lung-Map-S1400) | NCT01042379(I-SPY 2) | NCT02693535 (TAPUR) |
|---|---|---|---|---|
| Phase | | II/III | II | II |
| Adaptive design | | Umbrella | Umbrella | basket |
| Trial design | Purpose | Treatment Investigational | Treatment Investigational | Treatment Investigational |
| | Randomization | Yes | Yes | No |
| | Tumor type | NSCLC | Stage II/III breast cancer | Breast; Colorectal; Liver; Lung, Non-Small Cell; Lymphoma, Non-Hodgkin's;. Multiple Myeloma; Ovarian;Pancreas: Unspecified Solid Tumor |
| | Drug | Erlotinib,tremelimumab,rilotumumab,palbociclib… | Carboplatin,paclitaxel,pertuzumab,neratinib,metformin | Cetuximab,erlotinib,trastuzumab,pembrolizumab… |
| | Biomarker | Mutation of PI3KCA/CDK4/6, CCND1, CCND2, and CCND3/FGFR1, FGFR2, and FGFR3 / HGF/c-MET | Mutation of ER/PGR/HER-2/NEU gene | KRAS/NRAS/BRAF |
| | Study population | Patients with squamous cell carcinoma of the lung. | Newly diagnosed patients with histologically confirmed invasive, high-risk clinical stage breast cancer | Patients with advanced or metastatic solid tumor no longer responding to standard anti-cancer treatment or not available |
| Results | Primary endpoint | ORR/OS/PFS | QOL/OS/PFS/RR/PCR | ORR/PR |
| | Results | Continue with major change(add PD-L1 therapy) | Ongoing, demonstrated response in subgroups | Ongoing,failed to demonstrated response in subgroups |

(2). Patients with recurrent or metastatic solid tumor who failed or were not candidates for treatments usually proposed in first intentions. The biomarkers included molecular alterations in the *PI3K*/*AKT*/*MTOR* pathway and *RAF*/*MEK* pathway, and tested drugs included erlotinib, trastuzumab, letrozole, tamoxifen *etc*. The primary endpoint of the trial result was PFS. Similarly, the trial was already completed without meeting the primary endpoints [19]. The trial emphasized the importance of biomarkers in treatment selection and response prediction and urged for more biomarkers to be explored in the field of tumor immunology, proving that use of molecular targeted agent outside its indication needed further exploration. Nevertheless, it failed to show treatment difference (PFS) between physician recommended therapy and molecular targeted therapy in heavily pretreated patients.

In the trial of NCT02154490 (Lung-Map-S1400), the study population was patients with squamous cell carcinoma of the lung, using the biomarkers encompassing mutations in *PI3KCA*/*CDK4*/*6*, *CCND1*, *CCND2*, and *CCND3*/*FGFR1*, *FGFR2*, and *FGFR3*/*HGF*/*c-MET*. Evaluated drugs included erlotinib, tremelimumab, rilotumumab, palbociclib, etc. The primary endpoint of trial results is ORR/OS/PFS. The trial was eventually continued with a major change (add PD-L1 therapy) [20]. In this study, grouping biomarker-driven targeted drug studies with adaptive design under a single trial reduced the screen failure rate, making the screening efficiently and less costly. However, the importance of an explicit pre-defined protocols with consideration on consistent update for new drug indications and biomarkers was seen in the trial design [21].

NCT01042379 (I-SPY 2), focused on newly diagnosed stage II/III breast cancer patients with histologically confirmed invasive, high-risk clinical stage breast cancer. The biomarkers included mutations in *ER*/*PGR*/*HER-2*/*NEU* genes, and assessed drugs mainly included carboplatin, paclitaxel, pertuzumab, neratinib and metformin. The primary endpoint was QOL/OS/PFS/RR/PCR. To date, the study was underway, demonstrating response in subgroups [22]. It proved the advantage of target inhibition in women with early-stage, high-risk, *ERBB2*-negative breast cancer. However, whether pCR is a validated surrogate to predict long-term outcome remains debatable [23].

Multiple tumor types were investigated simultaneously in the trial of NCT02693535 (TAPUR), namely breast cancer, colorectal cancer, liver cancer, lung cancer, non-small cell carcinoma, lymphoma, non-Hodgkin's lymphoma, multiple myeloma, ovarian cancer, pancreatic tumors, and unspecified solid tumor. It enrolled patients with advanced or metastatic solid tumor which no longer responded or not available to standard anti-cancer treatment. Utilized biomarkers included *KRAS*/*NRAS*/*BRAF* mutations, and the tested drugs included cetuximab, erlotinib, trastuzumab, pembrolizumab, *etc*. The primary endpoint of trial results was ORR/PR. Currently the trial is still ongoing but failed to demonstrate response in subgroups. It proved that Cetuximab does not have clinical activity in patients with advanced BC, NSCLC, and OC without *KRAS*, *NRAS*, or *BRAF* mutations. Nevertheless, it failed to show potential genomic biomarker role of *KRAS/NRAS/BRAF* in predicting cetuximab treatment activity and response [24].

Solid tumor, with its disorganized architecture that hinders the delivery of anti-cancer reagents, brings unique challenges for selection of molecule-profile based treatment. Master protocol design could be further divided into basket (explores the indication of certain therapy within multiple diseases or subtypes), umbrella (utilizes different therapies for defined subtypes within same disease category) and platform (studies and compares various treatments in a specific disease setting whereas pre-defined principles allow for optimal outcome in a perpetual manner), showing its great benefit in drug discovery and efficacy comparison in the field of solid tumor. Here we reviewed master protocol designed trials in this area (Table 2). There are 18 master protocol designed clinical trials exploring oncolytic therapies in the field of solid tumor with available progress records (12 with interim analysis feedbacks and 6 have completion results). Category of the master protocol design was basket (9), umbrella (8) and platform (1, focus on radiotherapy). Success rate was 66.7% among 6 completed trials with 2 trials couldn't met their primary endpoint. Major focus of the trials were stage III/IV patients who failed standard first-line therapy, or with refractory / metastasis solid tumors, utilizing molecular information including biomarkers to guide treatment group selection. The only platform trial registered focused on the radiotherapy

Based on the advancement of adaptive design and peculiar presence of platform trials in the area of solid tumor, we proposed a PLATFROM study on rare tumors in Chinese population. In our previous study, we classified rare tumors in China into three main types: entities with rare histo-molecular phenotypes with an annual incidence of "2.5/100,000" driven by mutations of a rare cell type, entities with rare histology but a common cell origin, and entities with common histology but a rare molecular alteration [25]. We applied next generation sequencing in rare tumor patients, and then separated them into two treatment subgroups according to the results of genetic testing, and two types of treatments will be used differently in the two groups in this study. After gene detection and failure to standardized treatment, patients with advanced rare tumors who carry the actionable alterations (EGFR mutation (exon 19 deletion mutation, L858R replacement mutation or T790M mutation), ALK gene fusion, Ros-1 gene fusion, MET gene amplification or mutation, BRAF mutation (V600), BRCA1/2 mutation, HER-2 positive (mutation or overexpression or amplification), c-kit mutation and CDK4 amplification or CDKN2A mutation will be separated into 13 study groups in which the corresponding targeted drugs (almonertinib, dacomitinib, alectinib, crizotinib, vemurafenib, niraparib, pyrotinib, imatinib, palbociclib) will be administered Figure 5. In this study, adaptive design was widely used such as sample size re-estimation; adaptive enrichment; master protocol with adaptive design; multiple adaptive design. We believe the Platform Study could solve the problem of rare tumor research to a large extent through the mode of cross-tumor multi-drug simultaneous screening and bring this population the benefit.

In conclusion, the experience from the previous success and failure has exhibited that adaptive design is a promising novel strategy for accelerating drug development for cancer treatment yet awaiting more explorations and standardization. The practice of adaptive design trials might be an effective way to facilitate the findings of new drugs, boost the translation of drugs from bench to bed and accelerate novel drug commercialization. Remarkably, master protocol in adaptive design helps in conducting multi-arm trials simultaneously to include multiple tested drugs and utilize clinical resource optimally, improving the efficiency while decreasing the cost in novel drug development. It might be one of the essential strategies for rare cancer drug development in the future.

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## Disclosure

The authors declare no conflict of interest.

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