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REVIEW ARTICLE

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Umbrella trials as a novel concept of cancer clinical trials — a systematic review

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ABSTRACT

Precision medicine in oncology is a strategy for selecting cancer patients with specific molecular disorders that may be suitable for targeted therapies at the cellular level. With the development of targeted therapies, pharmaceutical companies emphasize the importance of molecular clinical trials in oncology. Umbrella trials are prospective clinical trials that test multiple targeted therapeutic options against specific molecular targets in a single disease entity. In contrast, basket trials recruit patients with different cancers but at the same molecular level. The development of umbrella and basket trials not only reduces the costs of clinical trials but also provides patients with access to modern experimental therapies.

This article aims to present the principles of conducting umbrella and basket studies and present currently ongoing experiments in patients with the most common cancers. The development of oncology requires physicians to follow new developments in diagnostics and therapy, which may directly improve the prognosis of our patients. An individual approach to the patient is the future of precision oncology.

Keywords: umbrella trials, cancer, cancer clinical trials

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Introduction

Precision medicine (PM) has become very popular in recent years for scientific and political reasons [1, 2]. Precision medicine is defined as an approach that uses a person›s genetics, environment, and lifestyle, as well as clinical information, to help determine the best approach to preventing or effectively treating disease. With the development of biomedical technologies, new information regarding, among others, biomarkers allows the expansion of the concepts of PM and use of a full range of PM in each patient [3].

Advances in genomics aim to improve disease treatment by identifying therapies that can specifically affect specific molecular targets (i.e., targeted therapies) [4, 5]. New challenges facing modern oncology and the development of laboratory diagnostics have created the need for umbrella and basket clinical trials.

These designs involve multiple sub-studies that evaluate more than one experimental therapy and/or selected treatment focusing on a specific molecular target in patients with different cancers. The development of umbrella and basket trials has not only reduced the costs of clinical trials but also provided patients with access to modern experimental therapies. The Food and Drug Administration (FDA) has published draft guidelines for the pharmaceutical industry containing recommendations for conducting master protocol studies to ensure the quality and safety of these studies [6].

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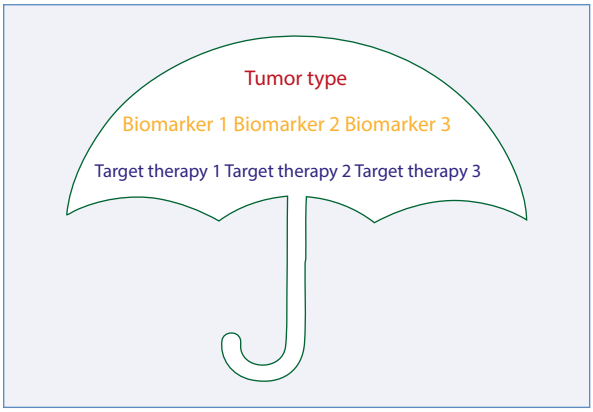

Figure 1. Umbrella trial study model

One of the most critical challenges facing pharmaceutical companies is the intensification of master protocol research, which mainly concerns early phases [7]. The extraordinary progress in molecular test and a reduction in their costs have enabled more frequent and precise examination of tumor biology and adjustments in patient therapies. This extraordinary progress is visible primarily in new clinical trials [8].

Umbrella trials

Umbrella trials are prospective clinical trials that test multiple targeted therapeutic options against specific molecular targets in a single disease entity [9, 10]. An illustration of the umbrella study model is shown in Figure 1.

One of the advantages of umbrella trials is their effectiveness in advanced stages of cancer, in which several molecular changes often occur, and monotherapy is of limited importance. However, in the case of targeted therapies, which have been associated with several molecular changes, a significant percentage of patients show a response to the treatment, sometimes lasting for many months or even years [11, 12]. Umbrella studies have limitations resulting from the study protocol, e.g., in rare diseases, where molecular subsets may need to be more significant to develop patient inclusion criteria effectively. On the other hand, patients with multiple molecular alterations may be eligible for treatment in multiple arms, which may also complicate development of the target group.

Methods

In September 2023, a systematic review of umbrella studies from 2013 to 2023 was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model [13].

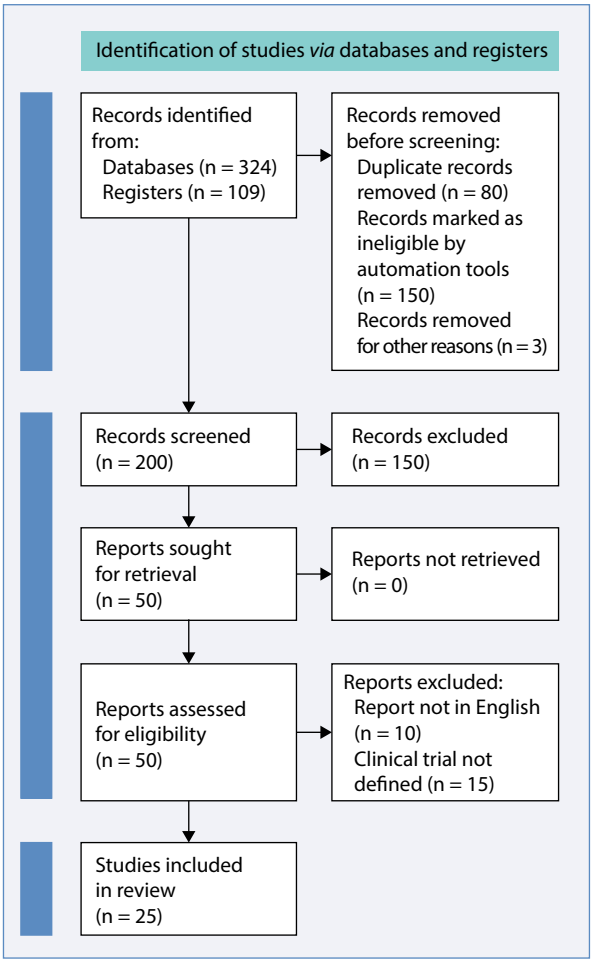

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (from [13])

The systematic review was conducted in four databases: PubMed, Scopus Web of Science, and Google Scholar, and the database registering clinical trials: Clinicsaltrials.gov. Please refers to Figure 2. The database search strategy was defined based on terms in the title or abstract using descriptors related to umbrella trials: umbrella trials, umbrella clinical trials, umbrella basket trials, and umbrella trials. The concept of umbrella study had to be clearly defined in the title or abstract of the study. The results were narrowed in terms of language, and only studies published in English were searched in the databases.

The articles found in the databases were initially screened by their titles and abstracts. Articles deemed relevant to the proposed topic were then read in full. In the following sections, umbrella and basket studies conducted in patients with the most common and rare cancers will be briefly presented.

Table 1. Lung cancer umbrella trials

Clinical trial number	Author	Type of cancer	Phase	Blinding	Screened	Enrolled	Treatment arms	Bio-markers	Inter-vention
NCT02664935	Middleton et al. [15]	Non-small-cell lung cancer (NSCLC)	II	Open-label	5,467	302	8	28	10
NCT02688894	Park et al. [20]	Small cell lung cancer (SCLC)	II	Molecular screening protocol	286	50*	4	3	6
NCT03574402	Maggie Liu et al. [16]	Non-small-cell lung cancer (NSCLC)	II	Open-label	400*	48*	18	2	15
NCT02965378	Aggarwal et al. [19]	Small cell lung cancer (SCLC)	II	Open-label	92	43	1	4	1
NCT00409968	Kim et al [17]	Non-small-cell lung cancer (NSCLC)	II	Open-label	341	255	8	4	4

*Screening/enrollment is still active

Lung cancer umbrella trials

The vast majority of targeted therapies for non-small cell lung cancer (NSCLC) are directed against oncogenic factors, e.g., exposure to tobacco smoke [14]. Umbrella clinical trials in NSCLC are designed to select patients for one of the possible genotype-matched treatment options. This may improve research into genotype-based treatments for multiple genotype alterations. A systematic review of umbrella studies in lung cancer identified three umbrella studies conducted and/or actively recruited (Middleton et al. [15], Maggie Liu et al. [16], Kim et al. [17]). Please refers to Table 1.

All these studies were conducted in phase II. Regarding the possibility of genotypic matching, the National Lung Matrix Trial (NCT02664935) offered excellent complementarity. At the same time, in the study by Maggie Liu et al. [16] (NCT03574402), the umbrella trial included 18 treatment arms with 14 possible drugs. One of the goals of that study is to develop a multiscale genome database and assess the relationships between genetic variability in NSCLC patients and clinical outcomes.

The BATTLE study (NCT00409968) is the first completed prospective adaptively randomized study in heavily pretreated NSCLC patients that required real-time biopsy tumor profiling. This represented a significant step towards realizing personalized therapy for lung cancer by incorporating real-time molecular testing results to identify specific patient populations for individualized treatment. In the study by Maggie Liu [16], 255 patients were randomized to 8 treatment arms.

In contrast to the therapeutic advances observed in NSCLC, including molecular characterization and targeted therapy (e.g., EGFR, ALK receptor tyrosine kinase), there has been limited progress in approaches to personalized medicine in squamous non-small cell lung cancer (SqNSCLC) [18].

Our search identified one squamous cell carcinoma umbrella study (NCT02965378), Lung-MAP, published by Aggarwal et al. [19]. This phase II/III trial investigated the role of the FGFR inhibitor AZD4547 (AZD4547) in the treatment of patients with stage IV squamous cell lung cancer, who had relapsed after prior radical treatment. Forty-three patients were randomized in the study. Aggarwal et al. [19] found that AZD4547 had an acceptable safety profile but showed minimal activity in this cohort in which FGFR1/FGFR3 amplifications predominated. Other targeted drugs in the Lung-MAP trial are still being evaluated.

The final study included in our analysis was the Molecular Screening for the Umbrella Study (SUKSES) in patients with recurrent small cell lung cancer (SCLC; SUKSES-S, NCT02688894). This study recruited 286 patients with SCLC who had failed platinum therapy and had a known genomic profile based on a previously designed screening test. According to Park et al. [20], this was the first biomarker-driven study in umbrella SCLC trials.

Breast cancer umbrella trials

Precision medicine and targeted therapies have a long history in the treatment of breast cancer

Table 2. Breast cancer umbrella trials

Clinical trial number	Author	Type of cancer	Phase	Blinding	Screened	Enrolled	Treatment arms	Bio-markers	Inter-vention
NCT03805399	Jiang et al. [27]	Tripel negative breast cabcer (TNBC)	Ib/II	Open-label	87	69	7	7	7
NCT01817452	Nitz et al. [25]	Early breast cancer	II	Open-label	220	134	4	2	4
NCT01940497	Zambetti et al. [26]	Breast cancer	IIIb	Open-label	Data not available	240	2	3	1
NCT04395989	Liu et al. [28]	Tripel negative breast cabcer (TNBC)	II	Open-label	Data not available	141	7	4	6
NCT05101564	Stanford University [29]	Breast cancer	II	Open-label	Data not available	150*	14	1	4
NCT04215003	Chen et al. [30]	Breast cancer	I/IIb	Open-label	Data not available	20*	8	Data not available	9

*Screening/enrollment is still active

and continue to hold promise for furthering specialized and individualized care for this disease. PM use ranges from the discovery of hormonal and anti-HER2 therapy through multigene tests for precise selection of patients with hormone-dependent HER2-negative cancer for adjuvant chemotherapy to molecular subtypes and targeted therapies. PM in breast cancer is leaning towards a more individualized course of treatment [21–24]. The studies included in the Table 2 identified six umbrella studies on different types of breast cancer. Two were in early HER2+ breast cancer [25, 26], two in triple-negative breast cancer [27, 28], one in HER2– breast cancer [29], and one was a prospective trial of molecular pathway-based neoadjuvant breast cancer therapy [30].

The study by Nitz et al. [25] (NCT01817452) regarding hormone-independent HER2-positive early breast cancer (WSG-ADAPT-HER2+/HR–), included four arms of therapy to which 134 patients were randomized. As argued by Nitz et al. [25], the study showed reasonable survival rates in patients with pathological complete response after de-escalation dose of 12 weeks of trastuzumab in combination with pertuzumab with or without weekly paclitaxel.

Another trial in HER2+ breast cancer is the phase IIIb NCT01940497 SCHEARLY trial, which randomized 240 patients and included two treatment arms with four possible chemotherapy combinations. The study aims to assess the safety and tolerability of subcutaneous trastuzumab. According to the primary analysis by Zambetti et al. [26], trastuzumab 600 mg was confirmed to be a safe and tolerable option in the perioperative treatment of patients with HER2+ early breast cancer (EBC), locally advanced breast cancer (LABC).

In the case of HER2-breast cancer, one umbrella study was found, NCT05101564, which aims to test whether adding a new drug targeting a specific genetic change occurring in some breast cancers before surgery will slow tumor growth to a greater extent than standard antihormonal therapy. The study plans to enroll 150 patients, and recruitment is currently underway.

The early phase I/IIa study NCT04215003 by Chen et al. [30] at the Fudan University Cancer Center in Shanghai, plans to recruit 20 early-stage patients to 8 treatment arms; the exact stage of the study is unknown at this time.

Gastric cancer umbrella trials

Gastric cancer was the third leading cause of cancer death in 2018, causing 783,000 deaths worldwide [31]. Molecular targeting studies in advanced gastric cancer offer hope for patients with poor prognosis. Our analysis identified four umbrella studies in gastric cancer.

The first study in Table 3, NCT02951091 [32], aimed to review targeted drugs as second-line treatment in a controlled standard of care (SOC) umbrella trial for the treatment of advanced gastric cancer (AGC). Three hundred eighteen patients were randomized to five arms of the study. The study showed no better survival in the experimental group than in the control group.

The IMMUNOGAST study (NCT04739202) [33] is expected to provide data on the clinical feasibility of biomolecular characterization of gastric adenocarcinomas for routine treatment adjustments. Sixty-eight patients are to be included in the treatment in five arms of therapy. The exact status of the study is unknown at this time.

Table 3. Gastric cancer umbrella trials

Clinical trial number	Author	Type of cancer	Phase	Blinding	Screened	Enrolled	Treatment arms	Bio-markers	Inter-vention
NCT03281369	Ko et al. [35]	Gastroesophageal junction cancer (G/GEJ) or esopha-geal cancer	Ib/II	Open-label	410*	31*	12	1	12
NCT02951091	Lee et al. [32]	Gastric cancer	II	Open-label	Data not available	318	5	4	6
NCT04739202	Hospices Civil de Lyon [33]	Gastric cancer	II	Open-label	Data not available	60*	3	4	3
NCT05270889	Yonsei University [34]	Gastric cancer	II	Open-label	Data not available	50*	1	1	2

*Screening/enrollement is sitll active

Table 4. Cervical and ovarian cancer umbrella trials

Clinical trial number	Author	Type of cancer	Phase	Blinding	Screened	Enrolled	Treatment arms	Bio-markers	Inter-vention
NCT03699449	Lee Jet al. [39]	Ovarian cancer	II	Open-label	104	70	5	4	7
NCT03556839	Grau et al. [41]	Cervical cancer	III	Open-label	404	323*	2	Data not available	4
NCT03267589	Mirza et al. [38]	Ovarian cancer	II	Open-label	ND	25	3	1	4

*Screening/enrollement is sitll active

In the umbrella study conducted by Yonsei University, study NCT05270889 [34], assessing the safety and effectiveness of tislelizumab in combination with zanidatamab in the second-line treatment of patients with advanced HER2-positive gastric cancer is another study included in this analysis. Fifty patients will be recruited for the study, but recruitment has yet to start.

The most recent study, the MORPHEUS-gastric and esophageal cancer trial (NCT03281369) [35], randomized 404 patients. When writing the article, the research is in the active phase. The MORPHEUS study includes multiple open-label, randomized, umbrella Phase Ib/II trials aimed at early identification of the efficacy and safety of cancer treatment combinations. Atezolizumab [anti-programmed cell death ligand 1 (PD-L1)] was evaluated in combination with PEGylated recombinant human hyaluronidase (PEGPH20).

The analysis also included the MORPHEUS-pancreatic study (NCT03193190), based on the same primary protocol, in patients with prostate cancer.

Cervical and ovarian cancer umbrella trials

Ovarian cancer ranks fifth in cancer deaths among women, causing more deaths than any other cancer of the female reproductive system. The risk of developing ovarian cancer during a woman's lifetime is approximately 1 in 78 [36]. Ovarian cancer response to immunotherapy is limited; however, assessment of target therapy sensitive/resistant subpopulations based on tumor biomarker stratification may improve the predictability of response to immunotherapy [37]. Future directions for clinical trials of new ovarian cancer therapies include using biomarkers.

The two ovarian cancer umbrella studies in the Table 4, NSGO-OV-UMB1/ENGOT-OV30 (NCT-03267589) [38] and AMBITION (NCT03699449) [39] were included in this analysis. These studies were conducted in phase II, and 25 and 70 patients were randomized. The AMBITION study was the first biomarker-driven umbrella study in patients with recurrent platinum-resistant ovarian cancer.

Table 5. Other cancer umbrella trials

Clinical trial number	Author	Type of cancer	Phase	Blinding	Screened	Enrolled	Treatment arms	Bio-markers	Inter-vention
NCT03784014	Italiano et al. [42]	Soft-tissue sarcomas (STS)	II/III	Open-label	960*	Data not available	3	19	10
NCT03193190	Ko et al. [43]	Pancreatic ductal adenocarcinoma	Ib/II	Open-label	340*	117*	12	1	15
NCT03158389	Wick et al. [44]	Glioblastoma	I/Iia	Open-label	Data not available	228	7	10	7
NCT03292250	Keam et al. [45]	Head and neck squamous cell carcinoma (HNSCC)	II	Open-label	Data not available	180*	5	ND	6
NCT04072107	Sun Yat-sen University [46]	Nasopharyngeal carcinoma	II	Open-label	Data not available	110*	2	ND	2
NCT05722886	Cancer Research UK [47]	Cancers with actionable genomic alterations	II/III	Open-label	Data not available	825*	5	ND	5
NCT05768178	Cancer Research UK [48]	*BRAF*-positive cancers	II/III	Open-label	Data not available	30*	1	1	2

*Screening/enrollement is sitll active

Cervical cancer is the fourth most common cancer in women worldwide, with an estimated 604,000 new cases and 342,000 deaths in 2020. About 90% of new cases and deaths worldwide in 2020 occurred in low- and middle-income countries income [40, 41]. In patients with recurrent or metastatic cervical cancer, the prognosis is usually unfavorable, and therapeutic options are severely limited.

The BEATcc trial (NCT03556839) [41] is the only umbrella trial included in the analysis assessing overall survival in patients with metastatic, recurrent, or persistent cervical cancer. The study is in the active phase, with plans to enroll 404 patients in two study arms with four possible therapeutic options.

Other cancer umbrella trials

The analysis in Table 5 also showed umbrella studies in the following cancers: soft tissue sarcomas [42], prostate cancer [43], glioblastoma [44] head and neck cancer [45, 46], and cancers with actionable changes in the genome [47, 48].

One of the studies in the active recruitment phase is the MULTISARC study (NCT03784014) [42], which is a prospective study that aims to provide high-quality evidence supporting the implementation of next-generation exome sequencing (NGS) into routine clinical practice in advanced soft-tissue sarcomas (STS) participants on a large scale.

However, in glioblastoma multiforme, the umbrella study is the NCT Neuro Master Match-N^{2}M^2 (NOA-20) (N^{2}M^2) (NCT03158389) [44], which included 228 patients in seven treatment arms.

The KCSG HN 15-16 TRIUMPH trial (NCT-03292250) [45] is the first biomarker-driven umbrella trial in patients with platinum-resistant head and neck squamous cell carcinoma (HNSCC) using molecularly targeted molecules.

The last umbrella studies included in our analysis are the DETERMINE studies (NCT05722886, NCT05768178) [47, 48]. They are aimed at adults, teenagers, and children with rare cancers and are conducted in the United Kingdom (UK). The research aims to determine the role of anticancer therapies already used in treating certain cancers in new diagnoses. If the effectiveness of the treatment is satisfactory, the Cancer Drugs Fund (CDF) review and National Health Service (NHS) approval will be accelerated.

Discussion

Precision medicine in oncology is a strategy for selecting oncological patients with specific molecular disorders for targeted therapies, which can significantly improve their prognosis. With the development of targeted therapies, pharmaceutical companies emphasize the importance of molecular clinical trials even more. Umbrella clinical trials are one of the models enabling

the development of targeted therapies in various groups of cancer patients. Our analysis has shown that umbrella trials in oncology are mainly at the early stages, with long-term effects of such experiments yet to be demonstrated. Most umbrella studies are in the second phase, where the safety of a given therapy is only confirmed but not the final therapeutic effect, whose final confirmation will take place in the third phase.

Maximizing benefits and minimizing harm to clinical trial participants is one of the critical ethical requirements. Umbrella trial designs are believed to be more flexible than traditional designs by allowing multiple treatment options to be evaluated simultaneously and providing trial participants with a better risk-to-benefit ratio [49].

Our analysis indicates the enormous potential of umbrella research in oncology, which is confirmed by the number of biomarkers tested in the presented studies. The central advantage of the umbrella study is the possibility of testing many therapeutic options in one disease entity, which, on the one hand, results in a reduction in the costs of conducting clinical trials and, on the other hand, provides patients with even more comprehensive access to the most modern therapies.

As innovative concepts of clinical trials in oncology, umbrella and basket trials pose an ethical challenge regarding the complexity of the protocols and, consequently, the creation of informed consent for the patient, who should understand the essence of these trials [50]. Another ethical challenge is the risk-benefit ratio when testing multiple therapeutic options for one condition. Both types of research, umbrella and basket trials, require intensive work by ethical teams who will develop precise standards of conduct in these projects.

One of the last significant challenges facing the world of medicine is artificial intelligence (AI). The convergence of artificial intelligence and PM can revolutionize healthcare. Artificial intelligence uses advanced computation and reasoning to generate insights, including genotype analyses. Active research in both artificial intelligence and PM points to a future in which the health-related tasks of both healthcare professionals and patients are expanded to include highly personalized medical diagnostic and therapeutic information. The use of AI in clinical trials creates development opportunities that we did not know about before; expanding the methods of genotype identification by AI can be used in umbrella and basket trials.

Considering the possibilities of umbrella research and the use of AI, we are in the moment of dynamic development of these clinical trial concepts.

Conclusions

Umbrella-type trials in oncology are mainly early phase I/II trials. These studies can test many biomarkers in one disease entity and use molecularly targeted therapies, which may benefit a narrow group of patients. Modern diagnostics at the cellular and lower levels allow us to determine the tumor's molecular profile and adapt the therapy to the patient's needs, especially the biology of the tumor.

Article Information and Declarations

Author contributions

M.B., J.K.-G., P.B.: contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. All authors discussed the results and commented on the manuscript.

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Conflict of interest

Authors declare no conflict of interest.

Supplementary material

None.

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