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Umbrella review of basket and umbrella trials in oncology

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Keywords: basket trial; umbrella trial; tumor agnostic; response rate

Abstract

Introduction: We sought to characterize oncology basket and umbrella trials that have been implemented, determine how many have been completed, and calculate the responses, by tumor types and drug targets.

Methods: We conducted a retrospective, cross-sectional review of PubMed, Embase, and clinicaltrials.gov for all oncology basket and umbrella trials. We included all trials and publications reporting on the results of these trials, and we calculated overall response rates, stratified by tumor type and drug target.

Results: Most basket and umbrella trials are phase II and non-randomized in design. Of the 180 basket trials, 99 (55.0%) had published results and 81 (45.0%) did not. Of the 73 umbrella trials, 28 (38.4%) had published results and 45 (61.6%) did not. The median response rate was 14.0 (IQR: 4.2, 31.2) for basket trials and 17.8 (IQR: 3.8, 40.4) for umbrella trials. These responses varied, depending on tumor type and drug target.

Conclusions: Understanding what is known about these trials, especially given the limited but heterogenous response reported in these trials, provides context about the strengths and limitations of drugs, especially since several drugs have been approved in recent years for tumor-agnostic indications, based on the results of these types of trials.

Introduction

The ease with which tumors can be genetically profiled and the excitement for precision treatment in oncology has necessitated changes in the way that novel drugs are tested. Basket and umbrella trials are two study designs that allow for adaptability in testing multiple tumor types, genetic biomarkers, and/or drug types within a single overarching study.

Basket trials are usually designed so that a single drug, often targeting a specific genetic biomarker, can be tested on multiple tumor types. Conversely, umbrella trials are designed to test multiple drugs on a single tumor type. In some instances, umbrella trials will include drugs that target specific biomarkers, especially if there are biomarkers common in the tumor being tested. The advantage of a basket design is that they allow for smaller sample sizes to be tested for a given tumor type, thus allowing for testing in less common tumor types, whereas umbrella trials allow for a more thorough analysis of treatments for a specific tumor type.[1] A limitation of these trials is that targeting a molecular maker may not always result in similar benefit for different tumor types, or that trials may suffer from poor accrual because of a lack of eligible participants.

Few studies have assessed the landscape of basket and umbrella trials for any health condition,[2] and none, to our knowledge have assessed the landscape of these trials in oncology. In general, the number of basket and umbrella trials was low prior to 2012, but between 2012 and 2019, the number of these trials that were initiated rapidly increased, but little has been reported on the status of these trials. We sought to assemble a comprehensive list of oncology basket and umbrella trials testing an anti-cancer drug and describe the current state of these types of trials, including the overarching findings, if reported.

Methods

Literature search

We systematically searched Embase for all publications on basket trials using the terms "('neoplasm'/exp OR neoplasm) AND basket AND 'clinical trial'/de" and searched for all articles published through our search date (March 16, 2022). We also searched (January 3, 2022) for all basket trials on clinicaltrials.gov by using the terms "basket and oncology" and filtering by "interventional trial". We also searched for basket trials discussed in review articles that came up in our search. Included trials needed to be either a basket or umbrella study design, test an anti-cancer drug, and be an interventional study. Generally, we defined basket trials as those that tested a common drug intervention in multiple tumor types (Figure 1), but we deferred to published authors as to whether a trial was considered a basket trial. We excluded trials that tested a single drug in a single tumor type and studies testing a non-drug and/or non-cancer intervention.

We used a similar search strategy for umbrella trials. For Embase, we used the terms ('neoplasm'/exp OR neoplasm) AND umbrella AND 'clinical trial'/de. For clinicaltrials.gov, we used the search terms: "umbrella and oncology" and filtered by interventional trial. The searches were done on the same day as the searches for basket trials. We defined umbrella trials as those that tested multiple drug interventions in a common tumor type (Figure 1), but again, we deferred to published authors as to whether a trial was considered an umbrella trial.

Data abstraction and coding

We then removed any duplicates, using the trial identification number, and searched for trial information on clinicaltrials.gov or other trial registration website. Trial information that we abstracted included the year the study began, drug name, whether a genomic biomarker was used as an inclusion criterion, tumor types, phase, intervention model (randomized, single arm, etc.), estimated enrollment, and trial group name (if one was listed).

Using the trial identifiers, we searched for published trials reporting on the efficacy of the drug (i.e., response rates), overall and by tumor/mutation type if multiple reports were found. In many cases, this information was provided in articles identified through the Embase search, but other articles were identified through publications listed on the trial registration website. If we could not find published response rates by using these two methods or on the trial registry website, we searched Google Scholar using the trial identifier and in some cases the trial group name. If multiple publications were found for each trial and tumor/mutation type, we prioritized the results coming from larger, more recent publications. We abstracted the median age, the percentage of participants who were male/female, the total number of participants included in the analysis, and the number of people with a response rate (complete and partial) for each tumor type and overall. We considered a study as having published results if an outcome measure (overall survival, progression-free survival, and/or response rate) was reported in the literature or on clinicaltrials.gov.

Statistics

We calculated frequencies for study characteristics for all unique trials. Because some studies had multiple study publications, stratified by tumor or drug type, we also calculated descriptive characteristics and response rates for all unique trial reports. We noted overall response rates, as well as response by tumor (for basket trials) and by drug target (umbrella trials). We used Microsoft Excel and R statistical software for calculating characteristics and creating figures. In accordance with 45 CFR §46.102(f), this study was not submitted for institutional review board approval because it involved publicly available data and did not involve individual patient data.

Results

The Embase search netted 195 results for umbrella trials and 199 for basket trials. The search on clinicaltrials.gov netted 98 basket trials and 75 umbrella trials. After reviewing studies and excluding trials that did not meet the inclusion criteria and removing duplicates, we ended up with 180 unique basket trials/protocols and 73 umbrella trials/protocols.

Of the 180 basket trials, 99 (55.0%) had published results and 81 (45.0%) did not (Table 1). There was a median of 94 participants (IQR: 47, 242). The median year that basket trials were initiated was 2016.

Of the basket trials with published study results (n=99), most (n=71, 71.7%) were phase II trials and single arm studies (n=65, 65.7%). Most included solid tumors of any type (n=73, 73.7%) and 30 (30.3%) were completed trials. Of the basket trials with no published study results (n=81), most (n=61, 75.3%) were phase II trials and single arm studies (n=50, 61.7%). Most included solid tumors of any type (n=60, 74.1%) and two (2.5%) were completed trials.

Of the 73 umbrella trials, 28 (38.4%) had published results and 45 (61.6%) did not (Table 1). There was a median of 5 arms (IQR: 3, 8) per study and 240 participants (IQR: 82, 411). The median year that umbrella trials were initiated was 2017.

Of the umbrella trials with published study results (n=28), 13 (46.4%) were phase II trials and non-randomized with multiple arms (n=9, 32.1%). Lung was the most common tumor type (n=12, 42.9%) and four (14.3%) targeted a genetic biomarker. Eight (28.6%) were completed trials. Of the umbrella trials with no published study results (n=45), 27 (60.0%) were phase II trials and non-randomized with multiple arms (n=22, 48.9%). Lung was the most common tumor type (n=8, 17.8%) and 11 (24.4%) targeted a genetic biomarker. Three (6.7%) were completed trials.

The figure shows the number of studies published by year and the number of studies with published results. The number of studies with most published results had a study start date of 2016 for basket studies and 2017 for umbrella studies (Figure).

Table 2 shows basic demographic characteristics and response for basket and umbrella studies with published results. The median age was 60 (IQR: 56, 63) for basket trials and 62 (IQR: 57, 66) for umbrella trials. The median response rate was 14.0 (IQR: 4.2, 31.2) for basket trials and 17.8 (IQR: 3.8, 40.4) for umbrella trials. For basket trials, the single tumors with the highest and lowest responses were, respectively, breast (28.6%) and pediatric (1.9%) For umbrella trials, the tumors with the highest and lowest responses were, respectively, rare cancers (48.7%) and head and neck cancers (0%). Figure 3 shows the responses by tumor type for basket trials and drug target for umbrella trials.

Discussion

We found that while there has been an increase in oncology basket and umbrella trials in recent years, the number has generally plateaued since about 2016 for basket trials and 2017 for umbrella trials. Further, a large percentage of trials have yet to publish any efficacy results on trial data. For those studies that have published data, the response rate is modest for both basket (14%) and umbrella trials (18%).

To put the response rates in context, previous analyses have estimated the response for patients in phase 1 trials to be about 20%[3] and as high as 41%[4] for drugs that have received FDA approval. Our analysis indicates that for tumors like breast, ovarian, leukemia, and rare types, the response rate is much higher, but for other tumor types, such as pediatric, sarcoma, and head and neck, the responses can be much lower.

In the past few years, there have been six tumor agnostic FDA approvals that have been based on data from basket trials. Availability of a greater number of drugs for patients, especially for those with rare tumor types with few treatment options, may seem advantageous, but this assumes that all patients with a given molecular marker benefit from these drugs. We have previously found that for all six drugs approved for tumor agnostic indications, the response to these drugs can vary, ranging from 0 to 100%, depending on tumor type. (data/manuscript under review) For some patients, treatment with these drugs may be detrimental because of a delay in other drugs with a known benefit.

We found that the number of umbrella trials was smaller than for basket trials, which is consistent with what has been previously reported about these trials for all health outcomes.[5] We did note that umbrella trials were more likely to be randomized (20.5% vs. 2.8%) and to have a phase III component

(8.2% vs 0%) than basket trials, which suggests stronger study design, but we also found fewer publications for umbrella trials, which may be partly due to these studies having a more recent time of initiation. The higher percentage of randomized trials among umbrella trials is not surprising given that it is easier to determine an appropriate control for trials with the same tumor type, compared to trials with multiple tumor types.[6]

Limitations

There are several limitations to our analysis. First, because our searches required that study authors identify their study as either “basket” or “umbrella”, we may not have fully captured all basket and umbrella trials that have been proposed or conducted, thus our results may not be generalizable to all basket and umbrella trials. Second, our estimation of trials with published findings may be underestimated because we were not able to find trials reports. We used several methods, including searches with clinical trial name and identifier on clinicaltrials.gov, Embase, and Google Scholar, to locate any published trial findings. Third, because we deferred to the authors as to whether the trials were basket or umbrella, the definition may not have been standardized, and some trials may have been categorized differently if adhering to different definition.

Conclusion

Basket and umbrella trials have become common types of oncology drug studies in recent years, with 38% and 55%, respectively, with published results. At the current moment, basket trials appear to be more than twice as common (180 vs 73). Among completed trials, the median response rate in basket trials is 14%, and 18% in umbrella trials, and response rates vary widely, depending on tumor type and drug target.

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Table 1. Characteristics of oncology basket and umbrella trial protocols registered on clinical trial registry sites, overall and by result status[1]

	Studies with no published results	Studies with published results	All studies
Basket Trials			
Number of studies	81 (45.0)	99 (55.0)	180
Number of study participants, median (IQR)	85 (38, 162)	108 (52, 284)	94 (47, 242)
Phase, n (%)			
I	5 (6.2)	13 (13.1)	18 (10.0)
I/II	14 (17.3)	16 (16.2)	30 (16.7)
II	61 (75.3)	71 (71.7)	131 (72.8)
Not indicated	1 (1.2)	0	1 (0.6)
Randomization, n (%)			
Randomized	1 (1.2)	4 (4.0)	5 (2.8)
Non-randomized with multiple groups	30 (37.0)	29 (29.3)	59 (32.8)
Single arm	50 (61.7)	65 (65.7)	115 (63.9)
Not indicated	0	1 (1.0)	1 (0.6)
Tumor category, n (%)			
Gynecologic cancers	5 (6.2)	3 (3.0)	8 (4.4)
Hematologic and solid malignancies	1 (1.2)	3 (3.0)	4 (2.2)
Hematologic malignancies	0	1 (1.0)	1 (0.6)
Solid tumor – limited indication	13 (15.0)	11 (11.2)	24 (13.3)
Solid tumor – broad indication	60 (74.1)	73 (73.7)	133 (73.9)
Rare cancers	1 (1.2)	5 (5.1)	6 (3.3)
Pediatric cancers	1 (1.32)	3 (3.0)	4 (2.2)
Targets a genetic biomarker, n (%)			
Yes	42 (51.9)	54 (54.5)	96 (53.3)
No	37 (45.7)	36 (36.4)	73 (40.6)
Some arms/baskets	2 (2.5)	9 (9.1)	11 (6.1)
Trial status, n (%)			
Complete	2 (2.5)	30 (30.3)	32 (17.8)
Ongoing/unknown	72 (88.9)	64 (64.6)	136 (75.6)
Terminated/withdrawn	7 (8.6)	5 (5.1)	12 (6.7)
Umbrella trials			
Number of studies	45 (61.6)	28 (38.4)	73
Number of arms	5 (2, 7)	7 (4, 10)	5 (3, 8)
Number of study participants, median (IQR)	160 (54, 350)	344 (156, 1000)	240 (82, 411)
Phase, n (%)			

I	3 (6.7)	1 (3.6)	4 (5.5)
I/II	11 (24.4)	5 (17.9)	16 (21.9)
II	27 (60.0)	13 (46.4)	40 (54.8)
II/III	0	4 (14.3)	4 (5.5)
III	1 (2.2)	1 (3.6)	2 (2.7)
Not indicated	3 (6.7)	4 (14.3)	7 (9.6)
Randomization, n (%)			
Randomized	7 (15.6)	8 (28.6)	15 (20.5)
Non-randomized with multiple groups	22 (48.9)	9 (32.1)	31 (42.5)
Single arm	11 (24.4)	35 (17.9)	16 (21.9)
Observational	3 (6.7)	6 (21.4)	9 (12.3)
Not indicated	2 (4.4)	0	2 (2.7)
Tumor category, n (%)			
Brain	2 (4.4)	0	2 (2.7)
Breast	6 (13.3)	3 (10.7)	9 (12.3)
Gastrointestinal	6 (13.3)	2 (7.1)	8 (11.0)
HNSCC	5 (11.1)	1 (3.6)	6 (8.2)
Leukemia	1 (2.2)	1 (3.6)	2 (2.7)
Lung	8 (17.8)	12 (42.9)	20 (27.4)
Multiple	7 (15.6)	4 (14.3)	11 (15.1)
Myeloma	2 (4.4)	0	2 (2.7)
Ovarian	2 (4.4)	3 (10.7)	5 (6.8)
Pancreatic	1 (2.2)	0	1 (1.4)
Prostate	3 (6.7)	0	3 (4.1)
Rare cancers	0	1 (3.6)	1 (1.4)
Urothelial	1 (2.2)	1 (3.6)	2 (2.7)
Uterine	1 (2.2)	0	1 (1.4)
Targets a genetic biomarker, n (%)			
Yes	11 (24.4)	4 (14.3)	15 (20.5)
No	30 (66.7)	23 (82.1)	53 (72.6)
Some arms/baskets	4 (8.9)	1 (3.6)	5 (6.8)
Trial status, n (%)			
Complete	3 (6.7)	8 (28.6)	11 (15.1)
Ongoing/unknown	40 (88.9)	20 (71.4)	60 (82.2)
Terminated/withdrawn	2 (4.4)	0	2 (2.7)

1. Considered as having published results if an outcome measure (overall survival, progression-free survival, and/or response rate) was reported in the literature or on clinicaltrials.gov for the basket or umbrella group

Table 2. Characteristics of basket and umbrella trial reports in oncology registered on clinical trial registry sites with reported results[1]

	Umbrella trials (n=51)	**Basket trials (n=167)**
Age, median (IQR)	62 (57, 66)	60 (56, 63)
Percent male, median (IQR)	56 (46, 67)	44 (28, 57)
Percent female, median (IQR)	44 (33, 54)	53 (40, 65)
Overall response rate, median (IQR)	17.8 (3.8, 40.4)	14.0 (4.2, 40.4)
Response rate, by tumor type, median (IQR)		
Brain	-	16.5 (8.2, 24.8)
Breast	35.8 (27.5, 56.8)	28.6 (20.2, 34.4)
Endometrial	-	-
Gastrointestinal	20.0 (6.1, 19.5)	11.5 (5.4, 27.4)
Gynecologic (ovarian, ovarian, endometrial, cervical, vulvar)	-	18.7 (10.9, 27.0)
Head and neck	0 (0, 0)	14.1 (5.8, 29.1)
Leukemia	40.8 (37.5, 42.9)	-
Lung	5.2 (0, 13.8)	25.0 (11.7, 28.0)
Multiple	16.4 (13.7, 45.2)	15.9 (4.2, 30.2)
Neuroendocrine	-	23.0 (15.9, 30.5)
Other	-	36.0 (24.4, 36.8)
Ovarian	46.5 (43.2, 49.8)	-
Pediatric	-	0 (0, 1.9)
Rare cancers	48.7 (48.7, 48.7)	-
Sarcoma	-	4.4 (3.6, 13.4)
Solid tumors	-	7.7 (2.4, 26.5)
Urothelial	25.2 (25.2, 25.5)	31.0 (17.4, 42.0)
Results reported in abstract form only, n (%)	34 (43.6)	94 (47.2)

1. Considered as having published results if an outcome measure (overall survival, progression-free survival, and/or response rate) was reported in the literature or on clinicaltrials.gov for the basket or umbrella group

Figure 1. Schematic of basket and umbrella trial basic study design. Figures adapted[7,8]

Figure 2. Distribution of published and unpublished findings from oncology basket and umbrella trials.

Figure 3. Median response rates, by tumor type for oncology basket studies (A) and by drug target for oncology umbrella studies (B).

Figure 1. Schematic of basket and umbrella trial basic study design. Figures adapted(7,8)

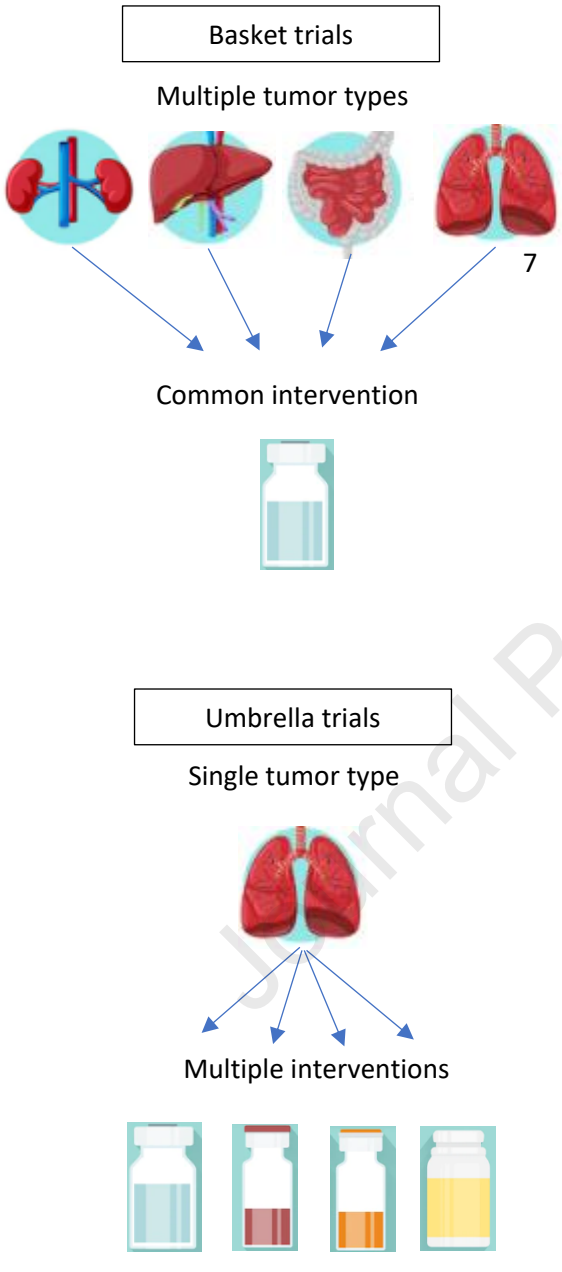


Figure 2

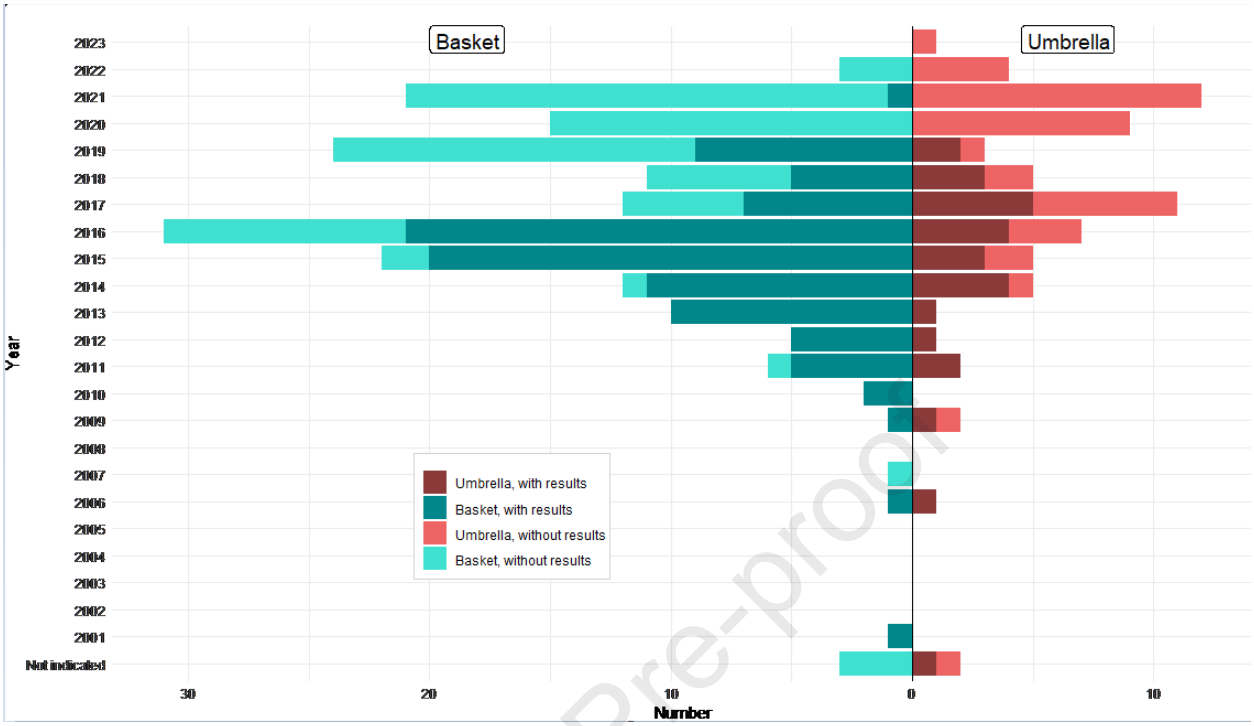
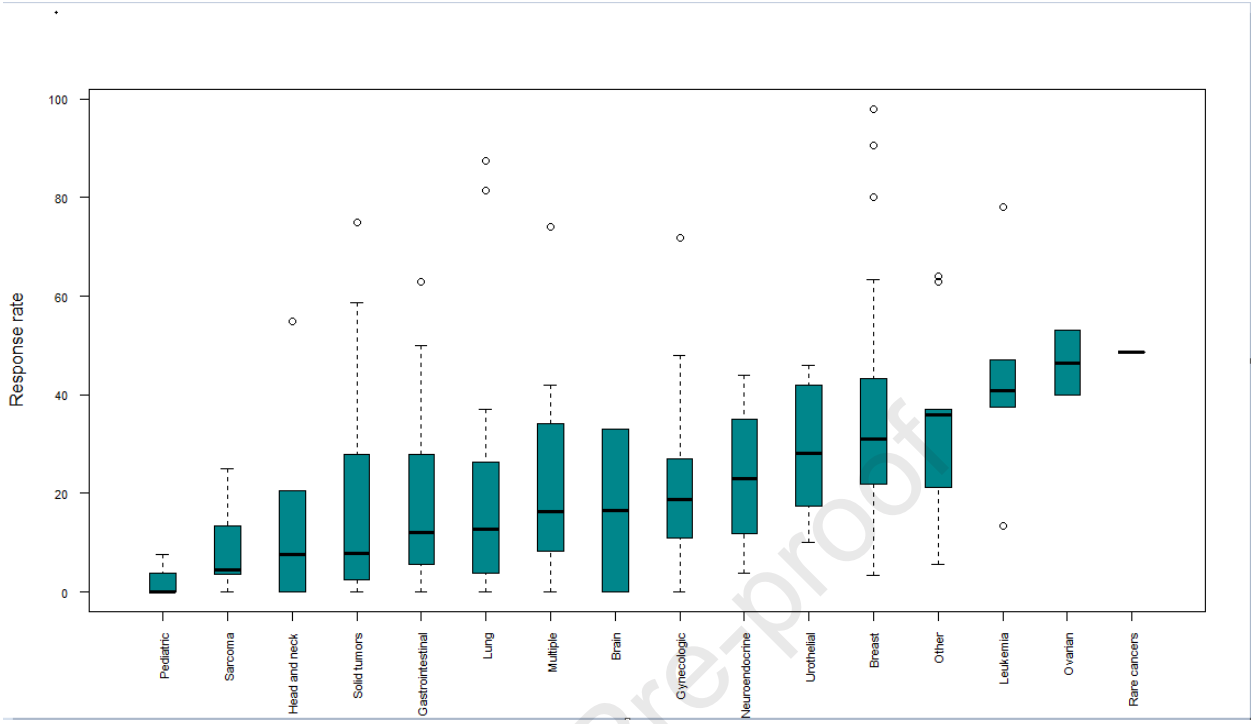
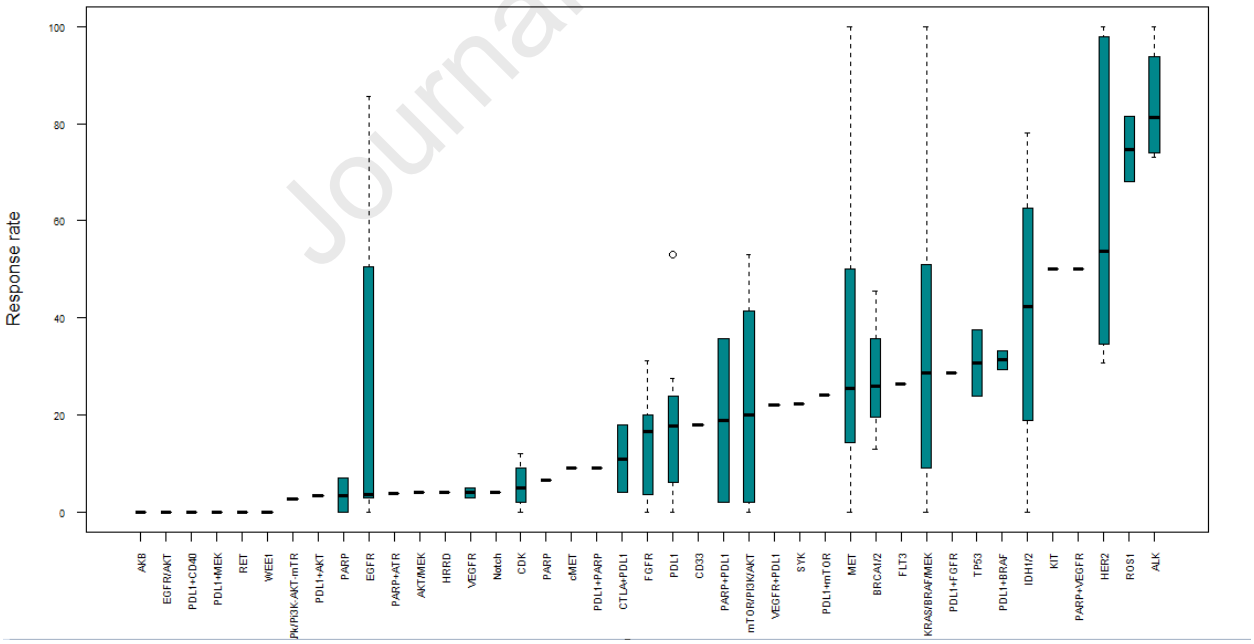


Figure 3a and 3b





Highlights

- Of the 180 basket trials, 55% had published results and a median response rate of 14%
- Of the 73 umbrella trials, 38% had published results and a median response rate of 18%
- Response rates varied by tumor type and drug target

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Vinay Prasad's Disclosures. (Research funding) Arnold Ventures (Royalties) Johns Hopkins Press, Medscape, and MedPage (Honoraria) Grand Rounds/lectures from universities, medical centers, non-profits, and professional societies. (Consulting) UnitedHealthcare and OptumRX. (Other) Plenary Session podcast has Patreon backers, YouTube, and Substack. All other authors have no financial nor non-financial conflicts of interest to report.