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Current Perspective

Phase I trials and therapeutic intent in the age of precision oncology: What is a patient's chance of response?

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Abstract The advancement of therapeutic strategies in oncology such as precision oncology has generated significant interest in better estimating the response of modern phase I cancer clinical trials. These estimates have varied widely. In this commentary, we provide an umbrella review of phase I response rates and discuss methodological reasons for variation in prior estimates which include limited use of unpublished data, the inclusion of expansion cohorts that artificially raise response rates of cumulative response rates, varying enrolment of haematologic malignancies, and increased next in class drugs.

1. Introduction

There is widespread interest in estimating the chances a patient enrolling in a phase I cancer clinical trial will experience a tumour response. A low response rate in this setting is offered as evidence of a therapeutic misconception among patients, meaning that participants believe they are likely to receive an effective therapy, but the reality is they are unlikely to benefit (Kimmelman, 2019).[1] Others counter that in the modern era of precision oncology, the response rate in phase I trials is substantial, perhaps as high as 20%, and, as such, these trials can be recommended with therapeutic intent [2]. In this commentary, we set out to address 4 methodological reasons that may account for disagreement in prior estimates of phase I response rates. These are (1) publication bias, (2) inclusion of expansion cohorts, (3) differences in response rates for haematologic and solid malignancies and (4) increasing rates of next in class drugs. We believe that, going forward, these factors should be explicitly communicated

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Table 1
List of phase I response rate studies found through MEDLINE search of the following terms: Phase 1; trials; outcome; response rate; meta-analysis.

#	Series	Period covered	Trials included	Unpublished trials	Solid, haematologic or both	Patients/data points	Agents tested	ORR Solid	ORR Haem	ORR total	Median response rate	Notes
1	Estey *et al.* (1986) [12]	1974 −1982	187	Yes	Both	NR	54	3.2%	12.8%	4.2%	NR	
2	Decoster *et al.* (1990) [13]	1972 −1987	211	No	Both	6639	87	4.3%	17.2%	4.5%	NR	
3	Von Hoff and Turner (1991) [14]	1970 −1983	228	No	Both	7960	113	NR	NR	6%	NR	
4	Itoh *et al.* (1994) [15]	1981 −1991	56	No	Both	2200	38	2.6%	12.6%	4.1%	NR	
5	Shah *et al.* (1998) [44]	1978 −1996	56	No	Both	1606	44	7.4%	8.7%	7.9%	3.8%*	*(calculated by looking at %RR per study drug); paediatric only
6	Yamamoto *et al.* (1999) [16]	1987 −1993	NR	NR	Solid	121	NR	4.2%	–	4.2%	NR	
7	Bachelot *et al.* (2000) [17]	1986 −1993	9	NR	Solid	154	NR	4%	–	4%	NR	
8	Sekine *et al.* (2002) [18]	1976 −1993	399	No	Solid	12,076	174	4.1%	–	4.1%	NR	
9	Horstmann *et al.* (2005) [19]	1991 −2002	460	Yes	Both	11,935	NR	NR	NR	10.6%	NR	
10	Roberts *et al.* (2004) [20]	1991 −2002	213	No	Solid	6474	149	3.8%	–	3.8%	NR	
11	Koyfman *et al.* (2007) [21]	2002 −2004	149	No	Both	4532	NR	NR	NR	3%	NR	
12	Kim *et al.* (2008) [22]	1992 −2005	16	NR	Solid	262	16	4%	–	4%	NR	Paediatric only
13	Italiano *et al.* (2008) [23]	2003 −2006	10	No	Solid	180	NR	7.2%	–	7.2%	NR	
14	Codesido *et al.* (2011) [7]	2004 −2010	31	Yes	Solid	65	18 (only targeted)	14%	–	14%	0%	Melanoma
15	Gupta *et al.* (2012) [24]	2000 −2009	55	NR	Both	1908	NR	7%	14%	8.9%	NR	
16	Levy *et al.* (2013) [25]	2005 −2010	17	NR	Solid	70	NR	17%	–	17%	NR	Non-small-cell lung cancer

(*continued on next page*)

Table 1 (*continued*)

#	Series	Period covered	Trials included	Unpublished trials	Solid, haematologic or both	Patients/data points	Agents tested	ORR Solid	ORR Haem	ORR total	Median response rate	Notes
17	Hou *et al.* (2013) [26]	1990–2010	41	NR	Solid	602 (120 distinct patients)	30	7.5%	–	7.5%	NR	Gynaecologic malignancies
18	Moreno Garcia *et al.* (2014) [27]	2005–2007	NR	NR	Solid	1182	NR	3%	–	3%	NR	
19	Raphael *et al.* (2014) [28]	2005–2012	20	NR	Solid	45	45	4%	–	4%	NR	Mesothelioma
20	Mahipal *et al.* (2015) [29]	1997–2007	39	NR	Both	1162 (433 >age 64)	NR	NR	NR	15.2% (<age 65), 13.1% (>64)	NR	
21	Gounder *et al.* (2015) [30]	2000–2008	8	No	Solid	327	8	5.5%	–	5.5%	NR	Primary CNS malignancies
22	Zhang *et al.* (2015) [31]	1991–2014	14	No	Haem	119	1	–	73%	73%	NR	Only CD19 CAR-T cells trials
23	Bautista (2015) [32]	2000–2012	12	NR	Solid	106	16	2%	–	2%	NR	Paediatric only
24	Subbiah *et al.* (2015) [33]	2004	31	NR	Solid	61	NR	7%	–	7%	NR	Hepatocellular carcinoma
25	Subbiah *et al.* (2016) [34]	2004–2009	NR	NR	Both	347	NR	NR	NR	18%	NR	
26	Schwaederle *et al.* (2016) [35]	2011–2013	350	No	Both	2655 biomarker driven, 10,548 non-biomarker driven	NR	NR	NR	31.1% per meta-analysis total (42% for biomarker targeted, 5.10% non-biomarker targeted, 4.7 non-biomarker cytotoxic)	*Cytotoxic 0% [4.72%]; Targeted therapy 2.5% [7.84%]; Solid 0% [4.25%]; Haem 16.7% [21.02%]	*Pooled analysis [meta-analysis]
27	Carceller *et al.* (2016) [36]	2006–2015	11	NR	Both	61	NR	NR	NR	7%	NR	Paediatric only
28	Khan *et al.* (2016) [37]	2005–2009	30	NR	Solid	1004 (315 >age 64)	NR	5.2% <age 65, 4.1% > 64	–	5.2% (<age 65), 4.1% (>64)	NR	
29	Massard *et al.* (2017) [38]	2010–2013	NR	NR	Solid	214	NR	5%	–	5%	NR	
30	Dorris *et al.* (2017) [39]	1990–2013	143	No	Solid	3896	53 targeted, 48 cytotoxic	Targeted: 0.031 per patient, cytotoxic 0.066 per patient	–	Targeted: 0.031 per patient, cytotoxic 0.066 per patient	NR	*ORR reported on logit-transformed scale; paediatric only

31	Yeh *et al.* (2017) [40]	1990 −2012	35	No	Both	973	34	NR	NR	9.4%	5%	*Only trials which had progressed to Phase II included; paediatric only
32	Denson *et al.* (2018) [41]	2007 −2013	NR	NR	Solid	243	NR (84% targeted, 42% cytotoxic)	4%	–	4%	NR	Gastrointestinal malignancies
33	Waligora *et al.* (2018) [8]	2004 −2015	170	No	Both	4604	NR	3.17%	27.9%	10.3%	NR	Paediatric only
34	Chakiba *et al.* (2018) [3]	2014 −2015	224	No	Both	NR	224	NR	NR	19.8%	NR	
35	Sundar *et al.* (2018) [42]	2002 −2016	277	NR	Solid	214	219	12%	–	12%	NR	*Limited to ages 15-39
36	Hazim and Prasad (2019) [6]	2015 −2018	175	No	Both	7330	145	NR	NR	15%	5%	
37	Cohen *et al.* (2020) [43]	2012 −2017	109	No	NR	2713	NR	NR	NR	15.3%	NR	Paediatric only
Mean			118			2627	80	5.8%	23.7%	10.4%	4.1%	

NR, not reported; CAR-T, Chimeric antigen receptor T cell therapy; CNS, central nervous system; ORR, overall response rate.

to patients, as they appear to influence the probability of obtaining a tumour response.

1.1. Publication bias

Publication bias—that more optimistic or positive phase I studies are selectively published—is a threat to estimates of response rates in phase I trials. If authors perform traditional literature-based systematic reviews, including only published studies, it is likely that these groups collect only a subset of phase I trials performed.

We performed an umbrella review of phase I response rates, as shown in Table 1. Only 3 of 37 analyses (8%) include unpublished phase I studies. In a recent article, Chakiba et al [3] report a response rate of 20% for phase I studies in the era of precision medicine. However, this study only includes PubMed indexed, published research articles, which are likely an unrepresentative sample of all articles. Decullier *et al.* [4] have shown that many phase I studies go unpublished, with lower than rates of publication than phase II-IV studies (21/127 [17%] versus 93/218 [43%]). As such, the most relevant estimates for patients will include unpublished studies.

1.2. Cumulative versus median response rates

The primary question that faces patients who are choosing to enrol in a phase I study is what is my chance of responding if I decide to enrol? This probability is markedly different for a patient considering joining an expansion cohort of an already highly promising phase I trial, such as the the one with more than 1000 patients included in the phase I trial of pembrolizumab [5], versus a patient considering joining a clinical trial for which nothing a priori is known. Expansion cohorts do not occur at random and are far more likely to be added to phase I trials with extraordinary response rates.

As shown in Table 1, the majority of studies estimate the response rate by dividing total responders by the total number of patients to calculate a cumulative response rate. Yeh *et al.* [40] went further as to only include therapies which had gone to phase II trials in their analyses of phase 1 trials. As depicted in Fig. 1, response rates may be inflated by selectively expanding only promising phase I trials. The specific numbers in the figure are compatible to observed values seen in the study by Hazim and Prasad [6].

The difference between cumulative response rate (total responders/total patients) and median response rate (response rate seen in the 50th percentile phase I trial) is shown in the figure. In each of the studies that report both cumulative and median response rates, the median is the lesser figure. This is perhaps most clearly demonstrated in the series by Blanco Codesido *et al.* [7] in which the overall response rate (ORR) is 14%,

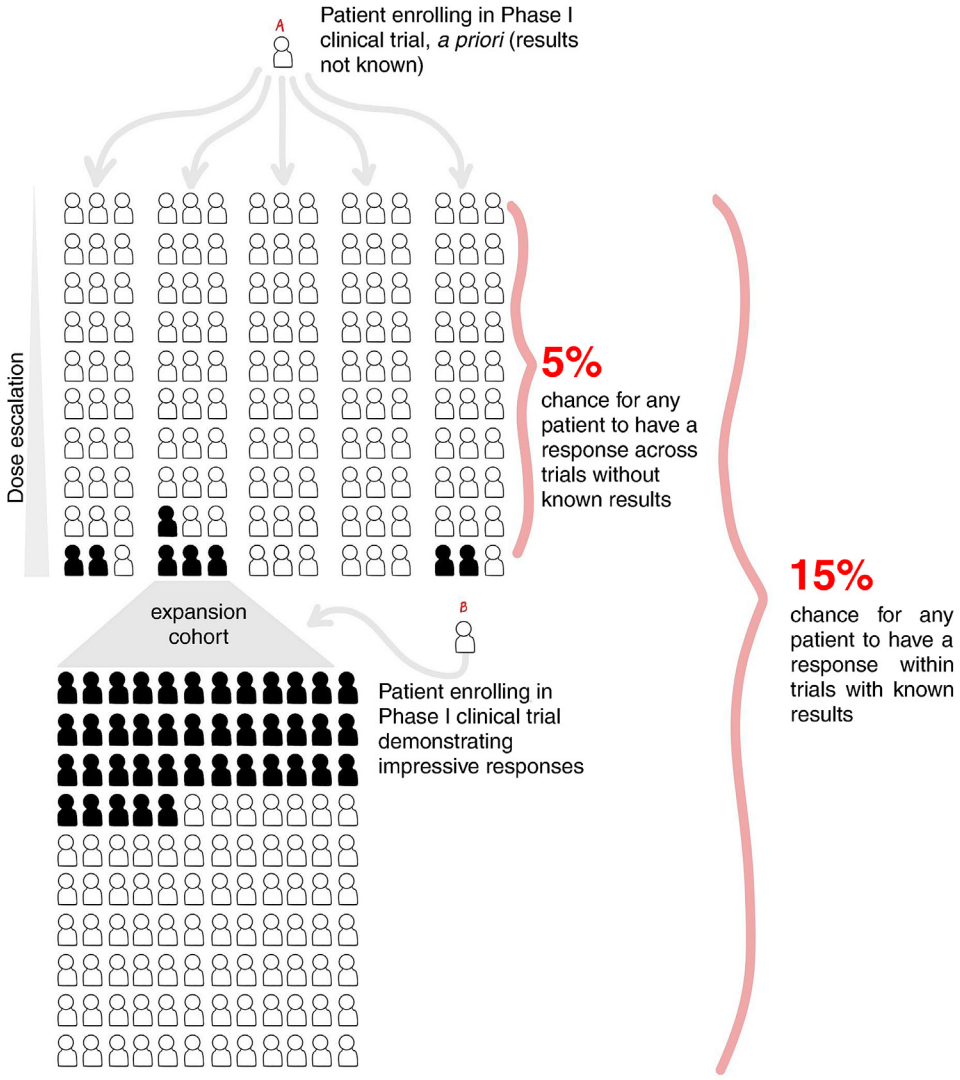

Fig. 1. Visual comparison of response rates for patients enrolling in phase I clinical trials with unknown results vs promising results and an expansion cohort.

despite a number of trials which had no response leading to a median response rate of 0%.

The best estimate for a patient enrolling in a de novo phase I trial run on a compound for which nothing is known is the median response rate. Yet, in our review, only five of the studies had reported a median response rate or provided the data to calculate the median response rate. Across 647 trials analysed in those articles, the median response rate averages 4.1% (refer Table 1).

1.3. Haematologic malignancies and solid tumours

Another cause of variation in estimates of response rates is the varying rates of haematologic malignancy, which often has higher response rates than solid malignancy. In the analysis by Waligora *et al.* [8], researchers found that solid tumour phase I trials had a median response rate of 3.2%, while this figure surpassed 27% for haematologic malignancies. It is well known that haematologic cancers, likely due to favourable biology and drug delivery, are more likely settings for successful drug development [9]. We found that the ratio of haematologic and solid malignancies is not uniformly reported in the analyses we examined.

1.4. Next in class molecules

An analysis of all genome-targeted drugs (as of 2018) reveals 31 US Food and Drug Administration–approved agents with 17 unique cellular or extracellular targets [10]. This is roughly 1.8 drugs per target, although some targets now have at least 7 unique agents (e.g. HER2 breast cancer). The studies we examined do not distinguish between response rates among first in class and next in class drugs. Of course, a patient with Anaplastic lymphoma kinase gene

rearranged non-small cell lung cancer (ALKr NSCLC) enrolling on a phase I trial of a novel inhibitor may face better odds than a patient enrolling on a phase I trial for a hitherto untested target. Future work should disambiguate the response rate for novel targets/novel drugs versus the response rate for next in class agents developed for known oncogenes and those that limit enrolment to a single tumour type.

2. Conclusion

While tumour response is not in and of itself a measure of benefit, the absence of tumour response has long been used to deem therapies ineffective [11]. As such, low response rates in phase I trials have generally been accepted as evidence these are not therapeutic studies, i.e. not realistically meant to help participants, and enrolment is instead an act of altruism. Recent analyses have sought to question this model; however, common distortions in estimating the response rate include the use of published data only, the inclusion of expansion cohorts, which artificially raise response rates if cumulative as opposed to the median response rate is reported, the rate of enrolment of patients with haematologic malignancies and the rate of next in class compounds. We encourage greater transparency across each of these dimensions in future research on this topic.

Conflict of interest statement

V.P. reports receiving research funding from Arnold Ventures royalties from Johns Hopkins Press, Medscape; honoraria for Grand Rounds/lectures from universities, medical centres and non-profit and professional societies consulting fees from United Healthcare speaking fees from Evicorereports being a member of Plenary Session podcast, which has Patreon backers.

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