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Predicting Success in Regulatory Approval From Phase I Results

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Abstract

Drug development in oncology is resource intensive and has a high failure rate. In this exploratory analysis, we aimed to identify the characteristics and outcomes of published Phase I studies associated with future Food and Drug Administration (FDA) approval. Phase I studies of 88 anticancer agents, treating a total of 4423 subjects between 2000 and 2013 were retrospectively examined. Fisher's Exact and Chi-square tests were used to compare the potential predictive measures. The median number of patients in Phase I trials of approved and non-approved agents were 44.5 and 32 respectively. A total of 423 subjects (86 reporting studies) had a complete responses (CR) and 342 subjects (80 reporting studies) had a partial responses (PR). A higher number of PRs ($P<0.001$), PR rate ($P=0.003$), and longer PR duration ($P=0.001$) were predictive of regulatory success.

The development of effective new treatments for cancer remains expensive and challenging. This is because a majority of new agents in oncology do not succeed in gaining FDA approval [1, 2]. A high failure rate in oncology drug development, highlights the severe limitations of current methods of prediction for future regulatory approval [3]. Some difficulties in oncology drug development are due to a shift from cytotoxic to molecularly targeted agents, availability of several new potential drug combinations, and a plethora of newly recognized pathways that could be therapeutically targeted. A high number of negative Phase III studies and regulatory setbacks has a negative impact on the confidence level of investigators as well investors in the pharmaceutical industry. Considering the high cost involved in developing new therapeutics, a prediction tool to guide which agents proceed forward after completion of Phase I study is needed. However, Phase I trials are not statistically designed for efficacy analysis and therefore, differ from Phase II or III studies in several respects including the primary endpoint; dose range; patient population; baseline characteristics such as disease status, severity and age. With all the pitfalls, still there is a

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None

growing interest to extrapolate efficacy findings from these data. Therefore, the purpose of our analysis was to identify the characteristics and outcomes of published Phase I studies associated with future FDA approval.

We compared the characteristics of published Phase I studies of both FDA approved and non-approved agents. Phase I studies of cytotoxic drugs between 2000 and 2013 were identified by searching PubMed, relevant oncology journals, and the oncologic drugs advisory committee (ODAC) website. Supplementary Appendix summarizes the literature search and agent identification process (as of November 2013). Agents which had not proceeded to Phase III testing because of lack of clinical activity were excluded. This would screen out agents which had not demonstrated an efficacy signal or abandoned due to other reasons without further development. The selected agents (listed in Supplementary Appendix) were placed into approved or non-approved categories, based on their FDA regulatory status.[4] Agents with approval in multiple tumor types were included only once at the time of their initial FDA approval. Phase Ib trials, Phase I trials of radiopharmaceuticals, supportive drugs, drug devices, endocrine agents and vaccines were excluded. For the included agents, details on the number of patients in study, response rates (complete, confirmed partial, stable disease), duration of response, dose at which the response occurred were retrieved. Responses were classified according to the description in the published study (RECIST or WHO criteria) [5–7]. We then examined trial characteristics and outcomes associated with future FDA-approval or non-approval. Fisher's Exact and Chi-square tests were used to compare the potential predictive measures.

Phase I results of 88 new agents treating a total of 4423 subjects met the eligibility criteria (54 approved and 34 non-approved by the FDA). The median number of patients in Phase I trials of approved and non-approved agents were 44.5 and 32 respectively. A total of 423 subjects (from 86 reporting studies) had a CR and 342 subjects had a PR (from 80 reporting studies). A higher number of PRs ($P<0.001$), PR rate ($P=0.003$) and longer PR duration ($P=0.001$) were predictive of regulatory success (Table 1). A positive trend towards higher regulatory success was observed for studies with larger sample size ($P=0.053$), higher CR rate ($P=0.049$), and number of patients with stable disease ($P=0.047$). There were no statistically significant differences in stable disease rate and duration of CRs between the two groups. Studies that had 3 subjects with a PR ($p<0.001$) or 3% of subjects with a PR ($p=0.001$) in Phase I trials were more likely to eventually receive FDA approval.

If an agent had no response in the Phase I trial, our study showed that it has a low likelihood of being approved. Eribulin mesylate (Halaven®), Pemetrexed (Alimta®), and vandetanib (Caprelsa®) are the only three approved agents in this analysis without an objective response in the first Phase I trials.[8–10] However, confirmed partial responses were observed in the subsequent Phase I trials of these agents using similar or different schedules. [11–13] Previously Von Hoff et al. in an analysis of 113 chemotherapeutic agents from 1970–1983 reported that the FDA approved agents were associated with a median of six responses in the Phase I trials. [14].

As recently reported, we observed that it involved an average of 6 years from the start of Phase I study until approval of the agent.[15] Given the high unmet need in oncology, new

drugs with a favorable benefit-to-harm balance should become available to patients more rapidly. Newer FDA initiatives such as breakthrough therapy designation and the accelerated approval program may expedite the future drug approval process. However, the rapid approval and withdrawal of some drugs recently illustrate ongoing challenges of these programs.[16, 17] Some observers have proposed routine adoption of randomized designs in Phase I and II trials to make the development process more efficient.[18] Admittedly, the extent of therapeutic benefit from uncontrolled studies is difficult to interpret accurately, it could be argued at the same time that Phase I studies only offer basic guidance for the design of subsequent randomized trials.

There are several limitations of our analysis including retrospective methodology, heterogeneity of agents, a possibility of publication bias due to our reliance on published data only, preselection of agents with positive track record, non-uniform data collection and reporting among published studies. To ameliorate the effect of publication bias, a serious effort should be made to publish all clinical trial results in a consistent manner, regardless of outcome. We have identified some areas of future work as these data lead to an interesting but challenging future direction. These findings could be extended to different types of cancers, similar review of Phase II studies, and development of a prediction model by incorporating all the characteristics of drug response in the target population. This may allow a more formal synthesis of the data and knowledge available at the end of Phase I or II study and contribute to a better and more successful drug development, from a regulatory, industry and academic standpoint.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Von Hoff DD. There are no bad anticancer agents, only bad clinical trial designs--twenty-first Richard and Hinda Rosenthal Foundation Award Lecture. Clin Cancer Res. 1998; 4(5):1079–1086. [PubMed: 9607564]
2. Czerepak EA, Ryser S. Drug approvals and failures: implications for alliances. Nat Rev Drug Discov. 2008; 7(3):197–198.
3. Walker I, Newell H. Do molecularly targeted agents in oncology have reduced attrition rates? Nat Rev Drug Discov. 2009; 8(1):15–16. [PubMed: 19008887]
4. U.S. Food and Drug Administration. <http://www.accessdata.fda.gov/Scripts/cder/drugsatfda/index.cfm>
5. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer. 1981; 47(1):207–214. [PubMed: 7459811]

6. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000; 92(3): 205–216. [PubMed: 10655437]
7. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009; 45(2):228–247. [PubMed: 19097774]
8. Goel S, Mita AC, Mita M, et al. A phase I study of eribulin mesylate (E7389), a mechanistically novel inhibitor of microtubule dynamics, in patients with advanced solid malignancies. *Clin Cancer Res.* 2009; 15(12):4207–4212. [PubMed: 19509177]
9. Holden SN, Eckhardt SG, Basser R, et al. Clinical evaluation of ZD6474, an orally active inhibitor of VEGF and EGF receptor signaling, in patients with solid, malignant tumors. *Ann Oncol.* 2005; 16(8):1391–1397. [PubMed: 15905307]
10. McDonald AC, Vasey PA, Adams L, et al. A phase I and pharmacokinetic study of LY231514, the multitargeted antifolate. *Clin Cancer Res.* 1998; 4(3):605–610. [PubMed: 9533527]
11. Mukohara T, Nagai S, Mukai H, et al. Eribulin mesylate in patients with refractory cancers: a Phase I study. *Invest New Drugs.* 2012; 30(5):1926–1933. [PubMed: 21887501]
12. Tamura T, Minami H, Yamada Y, et al. A phase I dose-escalation study of ZD6474 in Japanese patients with solid, malignant tumors. *J Thorac Oncol.* 2006; 1(9):1002–1009. [PubMed: 17409986]
13. Rinaldi DA, Kuhn JG, Burris HA, et al. A phase I evaluation of multitargeted antifolate (MTA, LY231514), administered every 21 days, utilizing the modified continual reassessment method for dose escalation. *Cancer Chemother Pharmacol.* 1999; 44(5):372–380. [PubMed: 10501910]
14. Von Hoff DD, Turner J. Response rates, duration of response, and dose response effects in phase I studies of antineoplastics. *Invest New Drugs.* 1991; 9(1):115–122. [PubMed: 1827432]
15. Sherman RE, Li J, Shapley S, et al. Expediting drug development--the FDA's new "breakthrough therapy" designation. *N Engl J Med.* 2013; 369(20):1877–1880. [PubMed: 24224621]
16. Suspension of Marketing and Sales: Iclusig (ponatinib). US Food and Drug Administration website. <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm373072.htm>
17. Food and Drug Administration. Mylotarg (gemtuzumab ozogamicin): market withdrawal. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm216458.htm>
18. Djulbegovic B, Hozo I, Ioannidis JP. Improving the drug development process: more not less randomized trials. *JAMA.* 2014; 311(4):355–356. [PubMed: 24449311]

Table 1

Characteristics and outcomes of Phase I studies of FDA approved and non-approved agents (n=88)

Study Characteristic	Approved	Not approved	Total	Pval
Total number of studies	54	34	88	
Total number of patients enrolled	3144	1279	4423	
Number of patients in study (in quartiles)				0.053 ²
Number of reporting studies	54	34		
<=28	12 (22.22%)	11 (32.35%)	23 (26.14%)	
29–40	13 (24.07%)	11 (32.35%)	24 (27.27%)	
41–63	11 (20.37%)	9 (26.47%)	20 (22.73%)	
>63	18 (33.33%)	3 (8.82%)	21 (23.86%)	
Number of patients with Complete Response (CR) (in quartiles)				0.35 ²
Number of Reporting Studies	52	34	86	
0	32 (61.54%)	26 (76.47%)	58 (67.44%)	
1	10 (19.23%)	3 (8.82%)	13 (15.12%)	
2–5	3 (5.77%)	3 (8.82%)	6 (6.98%)	
>5	7 (13.46%)	2 (5.88%)	9 (10.47%)	
NA	2 (3.7%)	0 (0%)	2 (2.27%)	
Percentage of patients with CR (in quartiles)				0.049 ²
Number of Reporting Studies	52	34	86	
0	32 (61.54%)	26 (76.47%)	58 (67.44%)	
0–2.9	10 (19.23%)	1 (2.94%)	11 (12.79%)	
2.9–11.5	3 (5.77%)	5 (14.71%)	8 (9.3%)	
>11.5	7 (13.46%)	2 (5.88%)	9 (10.47%)	
NA	2 (3.7%)	0 (0%)	2 (2.27%)	
Number of patients with Partial Response (PR) (in quartiles)				< 0.001 ²
Number of Reporting Studies	47	33	80	
<=1	7 (14.89%)	25 (75.76%)	32 (40%)	
2	7 (14.89%)	4 (12.12%)	11 (13.75%)	
3–5	16 (34.04%)	3 (9.09%)	19 (23.75%)	
>5	17 (36.17%)	1 (3.03%)	18 (22.5%)	
NA	7 (12.96%)	1 (2.94%)	8 (9.09%)	
Percentage of patients with Partial Response (PR) (in quartiles)				0.003 ²
Number of Reporting Studies	47	20	67	
<=3.1	7 (14.89%)	11 (55%)	18 (26.87%)	
3.1–6.6	11 (23.4%)	5 (25%)	16 (23.88%)	
6.6–13.45	13 (27.66%)	3 (15%)	16 (23.88%)	
>13.45	16 (34.04%)	1 (5%)	17 (25.37%)	
NA	7 (12.96%)	14 (41.18%)	21 (23.86%)	

Study Characteristic	Approved	Not approved	Total	Pval
Number of patients with Stable Disease (SD) (in quartiles)				0.0472
Number of Reporting Studies	35	29	64	
<=7	7 (20%)	12 (41.38%)	19 (29.69%)	
8–12	11 (31.43%)	8 (27.59%)	19 (29.69%)	
13–20	9 (25.71%)	1 (3.45%)	10 (15.62%)	
>20	8 (22.86%)	8 (27.59%)	16 (25%)	
NA	19 (35.19%)	5 (14.71%)	24 (27.27%)	
Percentage of patients with Stable Disease (SD) (in quartiles)				0.84 ³
Number of Reporting Studies	35	29	64	
<=18.7	9 (25.71%)	8 (27.59%)	17 (26.56%)	
18.7–30	10 (28.57%)	6 (20.69%)	16 (25%)	
30–43	7 (20%)	8 (27.59%)	15 (23.44%)	
>43	9 (25.71%)	7 (24.14%)	16 (25%)	
NA	19 (35.19%)	5 (14.71%)	24 (27.27%)	
Duration of Complete Response (CR), in weeks (in quartiles)				0.19 ²
Number of Reporting Studies	17	8	25	
<=27	5 (29.41%)	2 (25%)	7 (28%)	
27–48	6 (35.29%)	2 (25%)	8 (32%)	
48–80	4 (23.53%)	0 (0%)	4 (16%)	
>80	2 (11.76%)	4 (50%)	6 (24%)	
NA	37 (68.52%)	26 (76.47%)	63 (71.59%)	
Duration of Partial Response (PR), in weeks (in quartiles)				0.001 ²
Number of Reporting Studies				
<=18	8 (19.51%)	9 (56.25%)	17 (29.82%)	
18–24	11 (26.83%)	1 (6.25%)	12 (21.05%)	
24–41	14 (34.15%)	0 (0%)	14 (24.56%)	
>41	8 (19.51%)	6 (37.5%)	14 (24.56%)	
NA	13 (24.07%)	18 (52.94%)	31 (35.23%)	
Number of Patients with a Partial Response				<0.001 ²
<3	14 (29.79%)	29 (87.88%)	43 (53.75%)	
3	33 (70.21%)	4 (12.12%)	37 (46.25%)	
Total number of reporting studies	47	33	80	
Percentage of Patients with a Partial Response				<0.001 ³
<3	5 (10.64%)	10 (50%)	15 (22.39%)	
3	42 (89.36%)	10 (50%)	52 (77.61%)	
Total number of reporting studies	47	20	67	

* P-value < 0.05

¹ Mann-Whitney U test.

² Fisher's exact test.

³ Chi-squared test.

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