Early drug development in solid tumours: analysis of National Cancer Institute-sponsored phase 1 trials

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Lancet 2022; 400: 512–21

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Summary

Background The low expectation of clinical benefit from phase 1 cancer therapeutics trials might negatively affect patient and physician participation, study reimbursement, and slow the progress of oncology research. Advances in cancer drug development, meanwhile, might have favourably improved treatment responses; however, little comprehensive data exist describing the response and toxicity associated with phase 1 trials across solid tumours. The aim of the study is to evaluate the trend of toxicity and response in phase 1 trials for solid tumours over time.

Methods We analysed patient-level data from the Cancer Therapy Evaluation Program of the National Cancer Institute-sponsored investigator-initiated phase 1 trials for solid tumours, from Jan 1, 2000, to May 31, 2019. We assessed risks of treatment-related death (grade 5 toxicity ratings possibly, probably, or definitely attributable to treatment), all on-treatment deaths (deaths during protocol treatment regardless of attribution), grade 3–4 toxicity, and proportion of overall response (complete response and partial response) and complete response rate in the study periods of 2000–05, 2006–12, and 2013–2019, and evaluated their trends over time. We also analysed cancer type-specific and investigational agent-specific response, and analysed the trend of response in each cancer type over time. Univariate associations of overall response rates with patients' baseline characteristics (age, sex, performance status, BMI, albumin concentration, and haemoglobin concentration), enrolment period, investigational agents, and trial design were assessed using risk ratio based on the modified Poisson regression model.

Findings We analysed 465 protocols that enrolled 13 847 patients using 261 agents. 144 (31%) trials used a monotherapy and 321 (69%) used combination therapies. The overall treatment-related death rate was 0·7% (95% CI 0·5–0·8) across all periods. Risks of treatment-related deaths did not change over time (p=0·52). All on-treatment death risk during the study period was 8·0% (95% CI 7·6–8·5). The most common grade 3–4 adverse events were haematological; grade 3–4 neutropenia occurred in 2336 (16·9%) of 13 847 patients, lymphopenia in 1230 (8·9%), anaemia in 894 (6·5%), and thrombocytopenia in 979 (7·1%). The overall response rate for all trials during the study period was 12·2% (95% CI 11·5–12·8; 1133 of 9325 patients) and complete response rate was 2·7% (2·4–3·0; 249 of 9325). Overall response increased from 9·6% (95% CI 8·7–10·6) in 2000–05 to 18·0% (15·7–20·5) in 2013–19, and complete response rates from 2·5% (2·0–3·0) to 4·3% (3·2–5·7). Overall response rates for combination therapy were substantially higher than for monotherapy (15·8% [15·0–16·8] *vs* 3·5% [2·8–4·2]). The overall response by class of agents differed across diseases. Anti-angiogenesis agents were associated with higher overall response rate for bladder, colon, kidney and ovarian cancer. DNA repair inhibitors were associated with higher overall response rate in ovarian and pancreatic cancer. The rates of overall response over time differed markedly by disease; there were notable improvements in bladder, breast, and kidney cancer and melanoma, but no change in the low response of pancreatic and colon cancer.

Interpretation During the past 20 years, the response rate in phase 1 trials nearly doubled without an increase in the treatment-related death rate. However, there is significant heterogeneity in overall response by various factors such as cancer type, investigational agent, and trial design. Therefore, informed decision making is crucial for patients before participating in phase 1 trials. This study provides updated encouraging outcomes of modern phase 1 trials in solid tumours.

Funding National Cancer Institute.

Introduction

Phase 1 trials are the initial step in early phase oncology drug development. Phase 1 trials evaluate the safety and tolerability of novel investigational agents and combinations, leading to the determination of the recommended phase 2 dose in later-phase studies. However, the debate around treatment intention in these trials has been ongoing. Due to the historical low response rate,[1–5] ethical concerns were raised in offering phase 1 trials as the last resort for patients with advanced cancer who have exhausted other treatment options.[6–9] Overall response rates in a mixed population of solid and haematological

Research in context

Evidence before this study

Previously published analyses of multiple histological solid tumour and haematological malignancy phase 1 trials using the patient-level database generated by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) were published only in 1986 and 2005. The first paper, in 1986, which reported the therapeutic response of 187 phase 1 trials sponsored by CTEP from 1974 to 1982, found an overall response rate of 4·2%. A follow-up study of phase 1 trials from 1991 to 2002, published in 2005, reported a slightly higher response rate of 10·6%. A PubMed search using keywords that included "phase 1", or "phase I", "National Cancer Institute", "National Cancer Institute-sponsored", "efficacy", and "response rate" showed that there has been no single paper published on the analysis of response rate and toxicity from a patient-level phase 1 database containing multiple histologies since 2005. Other recent publications used previously published phase 1 analysis of solid tumours, haematological malignancy, or both using meta-analyses that were subject to publication biases. Due to the historical low response rate, ethical concerns have been raised in offering phase 1 trials to patients with advanced cancer who have exhausted other treatment options. Consequently, we believed further analysis of the CTEP data focusing on only solid tumors was warranted due to the progress in cancer therapeutics since 2002.

Added value of this study

To our knowledge, this study is the first report focusing on trend of toxicity and response rate by solid tumour type leveraging individual patient-level data. We found statistically significant increases in overall response rate in CTEP-sponsored phase 1 trials, without increasing the overall treatment-related death rate over time (2000–19). The response rates in phase 1 trials evaluating combination therapy were substantially higher than monotherapy. The rates and trends of response over time also differed markedly by disease. There were notable improvements in bladder, breast, kidney cancer, and melanoma, whereas no change in the low response of pancreatic and colon cancer. The study highlights the heterogeneity of overall response rate in phase 1 trials by cancer type, investigational agent, and trial design.

Implications of all the available evidence

The findings of this study represent one of the best available references discussing overall and cancer type-specific outcomes of modern phase 1 trials for patients with solid tumours. Patients are encouraged to make informed decision making for participating in phase 1 trials. First-in-human phase 1 trials are underrepresented in this study; therefore, future broader collaboration will provide an opportunity to build more comprehensive data describing modern phase 1 trial outcomes.

malignancies, which generally have a more favourable response to treatment compared with solid tumours,[10] have been reported at 5–10% based on data from previous studies analysing phase 1 trials from the 1990s to early 2000s,[1,2,11] confronting patients who are seeking therapeutics options beyond standard treatment with the prospect of high risks of unknown potential toxicity and unlikely benefit.

With significant advances in understanding cancer molecular biology and the identification of multiple molecular therapeutic targets, cancer drug development has dramatically changed from a focus on cytotoxic chemotherapy to targeted agents, including monoclonal antibodies, small molecules, and immunotherapy. Industry-sponsored, first-in-human phase 1 clinical trials of monotherapies for solid tumours involving such targeted drugs have demonstrated remarkable responses in patients with selected genomic markers.[12] As a result, the risk–benefit ratio of phase 1 trials, in particular tumour-driven or genomic-driven trials, has improved, and the role of phase 1 trials has shifted towards being a tool for signal-finding and identifying an appropriate patient population for further development in addition to evaluating safety and toxicity.[13–17]

It is now recognised that the responses observed in phase 1 trials can vary significantly by disease.[10,18] A meta-analysis of 346 phase 1 trials conducted between 2011 and 2013 showed that overall response was significantly higher in haematological malignancies (21·0%) than in solid tumours (4·3%), particularly with targeted agents.[10,18,19] However, these studies were conducted based on meta-analysis of published trials, the results of which are prone to various biases. Also, understanding disease-specific toxicity and treatment activity requires individual patient-level data and comprehensive analyses; however, trial results are commonly reported as a summary, which makes it challenging to look at disease-specific or agent-specific outcomes. Due to the disease heterogeneity that leads to different drug development pathways in various cancers, disease-specific and agent-specific toxicity and response rate are important information for reference and design of future phase 1 trials. In 2022, we analysed overall and disease-specific toxicity and response in haematological malignancies and showed that there is significant heterogeneity in overall response among different haematological malignancies, but overall we found a meaningful increase in response rate in phase 1 trials over time;[20] however, a study focusing on solid tumours is lacking.

The National Cancer Institute's (NCI) Cancer Therapy Evaluation Program (CTEP) is the foremost sponsor of early-phase clinical trials in both solid and haematological malignancies through the Experimental Therapeutics Clinical Trials Network, which consists of NCI-designated academic cancer centres in the USA and Canada. From 1974 to 1982, the overall response rate in

CTEP-sponsored phase 1 trials was 4·2%.[5] A follow-up CTEP analysis showed that the response rate in phase 1 trials was slightly improved to 10·6% in 1991–2002, with no significant trend observed for improvement within this period.[1] Notably, these studies analysed response and toxicity for trials predominantly using cytotoxic chemotherapy and combined solid tumour and haematological malignancies. In this Article, we report recent trends in treatment-related deaths and response rates for solid tumours, leveraging the large database of CTEP-sponsored phase 1 clinical trials over the past 20 years in recognition of the impact of the National Cancer Act[21] on its 50th anniversary.

Methods

Study population

We examined individual patient-level data for all patients with solid tumours receiving treatment in CTEP-sponsored, investigator-initiated phase 1 oncology trials conducted between Jan 1, 2000, and May 31, 2019. CTEP maintains a patient-level, comprehensive trial database, including patient demographics (age, sex, performance status, BMI, albumin concentration, and haemoglobin concentration), drug toxicity, and response rate. Patients with neurological cancers, haematological malignancies, and those treated in phase 1/2 clinical trials were excluded from the study analysis. Patients who received only radiotherapy were also excluded from this study. CTEP collects comprehensive information at 2 week intervals from investigators and actively monitors the trials through regularly scheduled periodic audits.

Agents used in the trials analysed were grouped by investigators (DC, LMC, and NT) according to the mechanism of action (appendix pp 1–8). Combination therapy consisted of investigational new drugs alone, investigational drug and a US Food and Drug Administration (FDA)-approved agent, and FDA-approved drugs alone aimed at a new clinical indication structured through CTEP agreements with industry partners.[22] The database does not include trial design nor the status of the agent (FDA approved or not at the time of trial conduct) under investigation.

See Online for appendix

Toxicity grade was based on the Common Terminology Criteria for Adverse Events (CTCAE; version depended on the time of the trial), and attribution of all grade 5 adverse events to the intervention was assessed by the phase 1 study investigators when reported to CTEP. The patient's response to treatment was determined based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 introduced in 2000 by the international RECIST Working Group. An updated version, RECIST 1.1, was released in 2009. Concordance between the two versions regarding responses to treatment is high.[23] Best response to the treatment was reported by the investigator for each patient if available according to the standard response criteria used at that time for each disease.

Outcomes

The endpoints of this study were risks of treatment-related death (grade 5 toxicity ratings possibly, probably, or definitely attributable to treatment), all on-treatment deaths (deaths during protocol treatment regardless of attribution), grade 3–4 toxicity, and proportions of overall response (complete response and partial response), complete response rate, and clinical benefit rate (overall response plus stable disease).

Statistical analysis

We analysed the trends of study outcomes over time. We defined three time periods, 2000–05, 2006–12, and 2013–19, leading to each period having at least 70 trials initiated and at least 1500 patients enrolled. For each period, the widths of the 95% CI (calculated using the exact method) are at most 24·4% for study-level endpoints (such as the rate of combination trials) and 5·1% for patient-level toxicity or response rates. Univariate associations of treatment-related deaths, all on-treatment deaths, and overall and complete response rates with patients' demographic characteristics (age, sex, Eastern Cooperative Oncology Group performance status, BMI, albumin concentration, haemoglobin concentration, enrolment period, investigational agents, and trial design) were assessed using risk ratio (RR) with 95% CIs with the modified Poisson regression model.[24] Each protocol was treated as a cluster, and the p-value of the Wald test was computed based on the sandwich variance estimator for clustering. The results were also verified by the mixed-effects logistic regression model. We also assessed cancer type-specific overall and complete response and toxicity rates and compared rates among the three time periods based on a logistic regression model by including the period as a covariate. Because toxicity is agent specific, it is likely that cancer type does not affect the characteristics of toxicity, but response rate changes significantly by cancer type due to difference in biology and what agents are used. A multivariable Poisson regression model was also fitted to adjust for patient baseline variables (same as listed for univariate associations of deaths and response) and was performed for treatment-related death and overall response.

p values of less than 0·05 were considered statistically significant. All analyses were performed with R Studio, version 2022.02.1.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We analysed 465 protocols that enrolled 13 847 patients using 261 agents (appendix pp 9–30, table 1). 418 (90%) trials focused only on solid tumours. 47 (10%) trials were all-comer trials that enrolled patients with solid tumours,

	Patients (n=13 847)	Trials (n=465)
Sex		
Female	7531 (54·4%)	..
Male	6316 (45·6%)	..
Eastern Cooperative Oncology Group performance status		
0–1	6460 (46·7%)	..
≥2	404 (2·9%)	..
Unknown	6983 (50·4%)	..
Race		
American Indian or Alaska Native	64 (0·5%)	..
Asian	514 (3·7%)	..
Black or African American	1164 (8·4%)	..
More than one race	32 (0·2%)	..
Native Hawaiian or other Pacific Islander	35 (0·3%)	..
Not reported or unknown	370 (2·6%)	..
White	11 668 (84·3%)	..
Types of cancer		
Bladder	257 (1·9%)	66 (14%)
Breast	1010 (7·3%)	130 (28%)
Colon	1438 (10·4%)	156 (34%)
Kidney	310 (2·2%)	69 (15%)
Lung	982 (7·1%)	146 (31%)
Melanoma	779 (5·6%)	101 (22%)
Ovary	1518 (11·0%)	113 (24%)
Pancreas	530 (3·8%)	123 (26%)
Prostate	288 (2·1%)	63 (14%)
Others	6735 (48·6%)	356 (77%)
Median age of patients (IQR)	57 (46–65)	..
Median BMI of patients (IQR)	26·3 (23·1–30·3)	
Type of phase 1 trial		
Solid tumor focused trial*	..	418 (90%)
All-comers trial†	..	47 (10%)
Median number of patients on trial (IQR)	..	24 (14–37)
Trial activation year		
2000–05	5882 (42·5%)	214 (46%)
2006–12	6220 (44·9%)	180 (39%)
2013–19	1745 (12·6%)	71 (15%)
(Table 1 continues in next column)		
(Continued from previous column)		
Median days to study completion (IQR)	..	1517 (1079–2138)
Types of agents		
Anti-angiogenesis	2689 (19·4%)	71 (15%)
Checkpoint inhibitor	817 (5·9%)	24 (5%)
Chemotherapy	6981 (50·4%)	225 (48%)
Cytokine	367 (2·7%)	20 (4%)
DNA repair	1791 (12·9%)	35 (8%)
Gene or cellular therapy	1255 (9·1%)	8 (2%)
Epigenetic modulation	132 (1·0%)	39 (8%)
Monoclonal antibody	468 (3·4%)	19 (4%)
Protein metabolism	1126 (8·1%)	41 (9%)
Receptor or signal transduction pathway agent	4029 (29·1%)	136 (29%)
Vaccine	773 (5·6%)	30 (6%)
Others (eg, apoptosis and immunotoxin)	2953 (21·3%)	113 (24%)
Number of agents used on trial (IQR)	..	2 (1–3)
Monotherapy	4108 (29·7%)	144 (31%)
Combination	9739 (70·3%)	321 (69%)

Data are n (%), unless stated otherwise. *Trials that enrolled only patients with solid tumours. †Trials that enrolled patients with solid tumors, haematological malignancies, or neurological cancers.

Table 1: **Characteristics of the phase 1 clinical trials and enrolled patients**

haematological malignancies, and neurological cancers; for these trials, only patients with solid tumours were included in the study. Common solid tumours included: ovarian cancer (n=1518), colon cancer (n=1438), breast cancer (n=1010), and lung cancer (n=982). Patients without detailed diagnosis (solid tumour not otherwise specified), rare tumours such as sarcomas, or other low incidence cancers were pooled and categorised together as others (n=6735). Although information of the dose escalation method of each trial was not available, the majority of trials in the CTEP sponsored trials used the 3+3 design. The median age of study patients was 57 years (46–65). The median number of patients treated per trial was 24 (IQR 14–37). 144 (31%) of trials used an agent as a monotherapy, and 321 (69%) of trials used combination therapy. Overall, the most used class of agents was chemotherapy; however, the class of agents used in the trials changed over time (appendix pp 31–33). Chemotherapy was less frequently used for 10 years after 2004, but its use became more frequent after 2015, involving up to 42 (59%) of 71 of trials in 2013–19. There has been increased use of checkpoint inhibitors since the late 2000s, with approximately one-third of trials using checkpoint inhibitors recently. Anti-angiogenesis agents became less frequently used recently since 2014, whereas DNA repair agents became more frequently used from 2014.

1111 (8·0%, 95% CI 7·6–8·5; table 2) patients died while on study; among these, 93 deaths were attributed to treatment (treatment-related death risk 0·7%, 95% CI 0·5–0·8). Advanced age (RR 1·02 for each 1-year increase in age, 95% CI 1·01–1·04), performance status of 2 or higher (2·6, 1·2–5·5), and albumin concentration of less than 3·5 g/dL (2·6, 1·5–4·5) were associated with higher risk of treatment-related deaths (table 3). No other associations were found. The results were consistent with the mixed-effects logistic regression model (appendix pp 34–36). Multivariate analysis adjusting for cancer type and patient baseline characteristics (age, sex, performance status, BMI, and albumin and haemoglobin

	Number of patients	Number of events	Rate, % (95% CI)
Treatment-related death			
All patients	13 847	93	0·7% (0·54–0·82)
Bladder	257	1	0·4% (0·01–2·2)
Breast	1010	7	0·7% (0·3–1·4)
Colon	1438	11	0·8% (0·4–1·4)
Kidney	310	1	0·3% (0–1·8)
Lung	982	9	0·9% (0·4–0·7)
Melanoma	779	1	0·1% (0–0·7)
Ovary	1518	9	0·6% (0·3–1·1)
Pancreas	530	3	0·6% (0·1–1·7)
Prostate	288	3	1·0% (0·2–3·0)
Others	6735	48	0·7% (0·5–0·9)
Death during trial*			
All patients	13 847	1111	8·0% (7·6–8·5)
Bladder	257	34	13·2% (9·3–18·0)
Breast	1010	84	8·3% (6·7–10·2)
Colon	1438	120	8·3% (7·0–9·9)
Kidney	310	13	4·2% (2·3–7·1)
Lung	982	78	7·9% (6·3–9·8)
Melanoma	779	59	7·6% (5·8–9·7)
Ovary	1518	43	2·8% (2·1–3·8)
Pancreas	530	79	14·9% (12·0–18·2)
Prostate	288	7	2·4% (1·0–4·9)
Others	6735	594	8·8% (8·2–9·5)

*Death during trial: all deaths regardless of attribution.

Table 2: **Treatment-related death and all-cause death rates during trials by cancer types**

concentrations) showed that albumin concentration of less than 3·5g/dL was associated with higher risk of treatment-related death (2·5, 1·5–4·3; appendix p 37) than those with albumin ≥3·5 g/dL. No other associations were found. Trials that used anti-angiogenesis and protein metabolism agents, such as heat shock protein inhibitors and proteasome inhibitors, were associated with a higher risk of treatment-related deaths, whereas trials that used receptor or signal transduction pathway agents were associated with a lower risk of treatment-related deaths. No other agents were shown to increase or decrease the risk of death. The treatment-related death risk for combination trials (0·7%, 0·5–0·8) was not higher than the risk for monotherapy trials (0·7%, 0·5–1·0).

Risks of treatment-related deaths did not change over time (p=0·52; figure A) and the RR for the time variable in the multivariable analysis was 0·8 (95% CI 0·4–1·5; p=0·43). Across all cancers analysed, the treatment-related death risk was less than 1%, except for pancreatic cancer (1·0%; table 2), with no difference between cancer types (p=0·70). No change in treatment-related deaths over time was seen across all cancer types analysed except for pancreatic cancer, which showed a decreasing trend although with limited number of treatment-related deaths throughout (appendix pp 39–41).

Considering all causes of death including death from disease progression during the trial, advanced age (RR 1·0 for each 1-year increase in age, 95% CI 1·0–1·0), had performance status of 2 or higher (3·2, 2·5–4·0), albumin concentration of less than 3·5 g/dL (3·4, 2·8–4·1), and haemoglobin concentration of less than 12 g/dL (2·2, 1·8–2·6) were associated with a higher risk of death (table 3). Patients with high BMI (≥30 kg/m²) had a lower risk of death than those with a BMI 18·5–25·0 kg/m² (table 3). No other associations were found. Trials that used chemotherapy and cytokines showed a lower risk of death. The overall risk of all causes of death during phase 1 trial increased over the study period (RR 5·6% [95% CI 5·0–6·2] in 2000–05, 9·9% [9·1–10·6] in 2006–12, and 9·7% [8·4–11·2] in 2013–19; appendix p 37). Progression of disease as a cause of death increased over time (98 [70%] of 141 deaths in 2000–05, 184 [84%] of 219 in 2006–12, and 90 [91%] of 99 in 2013–2019). There was a heterogeneity in risk of death-on-trial across diseases; the highest risk of death was observed for pancreatic cancer (RR 14·9%, 95% CI 12·0–18·2) and the lowest risk was seen for prostate cancer (2·4%, 1·0–4·9; table 2).

The most common grade 3–4 adverse events in phase 1 trials for solid tumour were haematological events (appendix pp 40–41). Grade 3–4 neutropenia occurred in 2336 (16·9%) of 13 847 patients, lymphopenia in 1230 (8·9%), anaemia in 894 (6·5%), and thrombocytopenia in 979 (7·1%). Febrile neutropenia was observed in 222 (1·6%) patients. Non-haematological grade 3–4 adverse events were less common, mostly less than 5% except for fatigue, which was observed in 708 (5·1%) patients. No increasing or decreasing trends of specific adverse events were noted over time, except for the neutropenia, which showed a lower risk in 2013–19 compared with the previous period.

Response assessment was available for 9325 (67·3%) of 13 847 patients. The overall response rate for all trials during the study period was 12·2% (95% CI 11·5–12·8; 1133 of 9325 patients) and complete response rate was 2·7% (2·4–3·0; 249 of 9325 patients). An increase in overall response and complete response rates were observed over time (p<0·0001 for overall response rate and p=0·018 for complete response rate; figure B, table 4). Overall response increased from 9·6% (95% CI 8·7–10·6) in 2000–05 to 18·0% (15·7–20·5) in 2013–19, and complete response rates from 2·5% (2·0–3·0) to 4·3% (3·2–5·7; table 4). There was also an increase of stable disease from 38·7% (37·2–40·2) in 2000–05 to 43·9% (40·8–46·9) in 2013–19 and a decrease of progressive disease as the best response rate in the phase 1 trials (figure B). Patients who had clinical benefit (overall response plus stable disease) increased from 48·3% (95% CI 46·8–49·9) in 2000–05 to 61·9% (58·9–64·8) in 2013–19.

	Number of patients (%)	Treatment-related deaths			Deaths during protocol treatment		
		Number of events (%)	RR (95% CI)	p value	Number of events (%)	RR (95% CI)	p value
Age, years							
Continuous (with 1-year increase)	13 846	93 (6·7%)	1·0 (1·0–1·0)	0·0062	1111 (8·0%)	1·0 (1·0–1·0)	0·0095
<18	1169 (8·4%)	3 (0·3%)	0·5 (0·2–1·4)	0·17	85 (7·3%)	1·0 (0·7–1·3)	0·74
18–59	6899 (49·8%)	39 (0·6%)	Ref	..	528 (7·7%)	Ref	..
≥60	5778 (41·7%)	51 (0·9%)	1·6 (1·0–2·4)	0·041	498 (8·6%)	1·1 (1·0–1·3)	0·050
Sex							
Female	7531 (54·4%)	47 (0·6%)	Ref	..	529 (7·0%)	Ref	..
Male	6316 (45·6%)	46 (0·7%)	1·2 (0·8–1·8)	0·37	582 (9·2%)	1·2 (1·0–1·3)	0·37
Performance status							
0–1	6460 (94·1%)	43 (0·7%)	Ref	..	482 (7·5%)	Ref	..
≥2	404 (5·9%)	7 (1·7%)	2·6 (1·2–5·5)	0·011	110 (27·3%)	3·2 (2·5–4·0)	<0·0001
Body-mass index, kg/m²							
Continuous	6999	50 (0· 7%)	1·0 (1·0–1·1)	0·55	604 (8· 6%)	1·0 (1·0–1·0)	<0·0001
<18·5	257 (3·7%)	1 (0·4%)	0·6 (0–3·8)	0·56	36 (14·0%)	1·4 (1·0–2·0)	0·052
18·5–25	2489 (35·6%)	18 (0·7%)	Ref	..	257 (10·3%)	Ref	..
25–30	2395 (34·2%)	15 (0·6%)	0·9 (0·5–1·7)	0·69	196 (8·2%)	0·8 (0·7–1·0)	0·10
≥30	1858 (26·5%)	16 (0·9%)	1·2 (0·6–2·4)	0·65	115 (6·2%)	0·6 (0·5–0·8)	<0·0001
Albumin concentration, g/dL							
Continuous	5613	43 (0· 8%)	0·5 (0·3–0·7)	0·0006	490 (8· 7%)	0·3 (0·3–0·4)	<0·0001
≥3·5	3856 (68·7%)	20 (0·5%)	Ref	..	190 (4·9%)	Ref	..
<3·5	1757 (31·3%)	23 (1·3%)	2·6 (1·5–4·5)	0·0006	300 (17·1%)	3·4 (2·8–4·1)	<0·0001
Haemoglobin concentration, g/dL							
Continuous	6722	49 (0·7%)	1·0 (0·8–1·2)	0·93	580 (8· 6%)	0·8 (0·8–0·8)	<0·0001
≥12·0	3513 (52·3%)	22 (0·6%)	Ref	..	185 (5·3%)	Ref	..
<12·0	3209 (47·7%)	27 (0·8%)	1·3 (0·8–2·2)	0·29	395 (12·3%)	2·2 (1·8–2·6)	<0·0001
Study activation year							
2000–05	5882 (42·5%)	44 (0·7%)	Ref	..	327 (5·6%)	Ref	..
2006–12	6220 (44·9%)	37 (0·6%)	0·8 (0·5–1·2)	0·25	614 (9·9%)	1·5 (1·1–2·0)	0·0053
2013–19	1745 (12·6%)	12 (0·7%)	0·9 (0·5–1·8)	0·83	170 (9·7%)	1·7 (1·2–2·4)	0·0061
Investigational agent							
Anti-angiogenesis	2689 (19·4%)	32 (1·2%)	2·2 (1·4–3·4)	0·0046	224 (8·3%)	1·1 (0·8–1·5)	0·73
Checkpoint inhibitor	817 (5·9%)	5 (0·6%)	1·0 (0·4–2·2)	0·91	70 (8·6%)	1·1 (0·7–1·9)	0·68
Chemotherapy	6981 (50·4%)	48 (0·7%)	1·0 (0·7–1·6)	0·91	432 (6·2%)	0·7 (0·5–0·9)	0·0052
Cytokine	367 (2·7%)	1 (0·3%)	0·4 (0·1–2·5)	0·32	12 (3·3%)	0·5 (0·3–0·9)	0·021
DNA repair	1791 (12·9%)	12 (0·7%)	0·9 (0·5– 1·8)	0·79	152 (8·5%)	1·2 (0·8–1·8)	0·48
Epigenetic modulation	1255 (9·1%)	7 (0·6%)	0·8 (0·4–1·7)	0·58	139 (11·1%)	1·3 (0·9–1·9)	0·13
Gene or cellular therapy	132 (1·0%)	0	NA	NA	8 (6·1%)	1·0 (0·3–3·49)	1·00
Monoclonal antibody	468 (3·4%)	2 (0·4%)	0·7 (0·2–2·7)	0·56	25 (5·3%)	0·6 (0·3–0·9)	0·024
Protein metabolism	1126 (8·1%)	16 (1·4%)	2·4 (1·4–4·1)	0·0012	81 (7·2%)	0·9 (0·7–1·3)	0·73
Receptor or signal transduction pathway agent	4029 (29·1%)	18 (0·4%)	0·6 (0·4–1·0)	0·051	362 (9·0%)	1·2 (1·0–1·5)	0·13
Vaccine	773 (5·6%)	1 (0·1%)	0·2 (0–1·3)	0·089	46 (6·0%)	0·9 (0·5–1·9)	0·85
Others	2953 (21·3%)	22 (0·7%)	1·2 (0·7– 2·0)	0·56	210 (7·1%)	1·0 (0·7–1·4)	0·99
Combination therapy							
Monotherapy	4108 (29·7%)	28 (0·7%)	Ref	..	391 (9·5%)	Ref	..
Combination therapy	9739 (70·3%)	65 (0·7%)	1·0 (0·6–1·6)	0·96	720 (7·4%)	1·0 (0·7–1·2)	0·69
Trial type							
Solid tumour-focused trial	12 179 (88·0%)	85 (0·7%)	Ref	..	923 (7·6%)	Ref	..
All-comers trial	1668 (12·0%)	8 (0·5%)	0·7 (0·3–1·5)	0·37	188 (11·3%)	1·5 (1·1–2·0)	0·0085

NA=not applicable. RR=risk ratio.

Table 3: **Treatment-related death or death during trial according to risk factors**

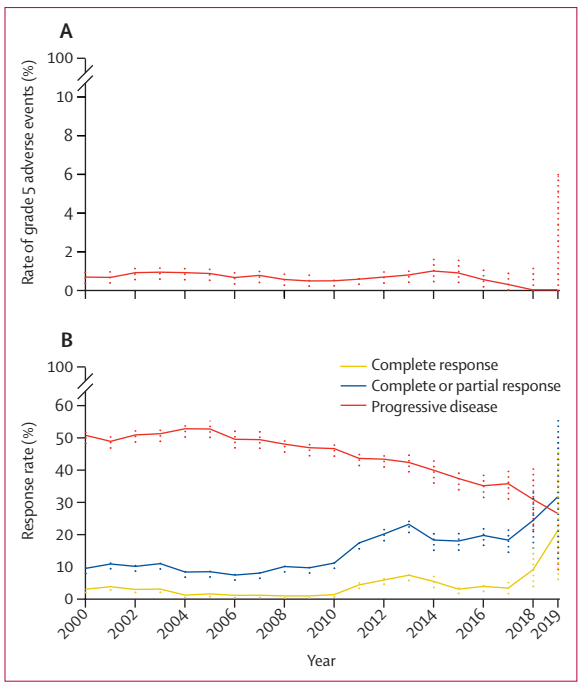

Figure: **Treatment-related deaths (A) and response (B) trends between 2000 and 2019 with 95% exact CI**
Dots represent 95% CIs.

Patients who had a performance status of 0–1, were female, had an albumin concentration of at least 3·5 g/dL, or a haemoglobin concentration 12 g/dL or higher, had an increased likelihood of overall response (appendix pp 42–43). These results were consistent between modified Poisson regression and mixed-effects logistic regression models (appendix pp 44–45). Multivariate analysis adjusting for cancer type and patient baseline characteristics showed that patients who had albumin concentration of at least 3·5 g/dL and performance status 0–1 had higher likelihood of response (appendix p 37). The trials that used chemotherapy (799 [18%]) and DNA repair agents (323 [27%]) were associated with an increased likelihood of response, whereas trials using cytokines (16 [7%]), protein metabolism agents (56 [6%]), and vaccines (12 [3%]) showed a decreased likelihood of response. The overall and complete response rate in trials using combination therapy were higher than trials with monotherapy (overall response 15·8% [95% CI 15·0–16·8] *vs* 3·5% [2·8–4·2], RR 4·6 [95% CI 3·1–6·8], p<0·0001; complete response 3·7% [95% CI 3·3–4·2] *vs* 0·3% [0·1–0·5], RR 10·7 [95% CI 4·3–26·5], p<0·001), and that in all-comer trials was lower than solid tumour-focused trials (overall response overall response 4·1% [95% CI 3·0–5·3] *vs* 13·3% [12·6–14·1], RR 0·3 [95% CI 0·2–0·5], p<0·001; complete response 0·3% [95% CI 0·1–0·9] *vs* 3·0% [2·6–3·4], RR 0·1 [95% CI 0·03–0·3], p<0·001).

The response rate over time differed by tumour type (table 4). There were improvements in overall and complete response rate over time in bladder, breast, and kidney cancer and melanoma. No improvement was observed in lung cancer, although the overall response rates were relatively high (>20% during the study period). In contrast, there was no improvement in response rates, which remained notably low for pancreatic and colon cancer.

Response rates by class of investigational agents for each cancer are shown in the appendix (pp 46–51). In non-chemotherapy agents, anti-angiogenesis agents were associated with higher response rates for bladder, colon, kidney, and ovarian cancer; and DNA repair inhibitors were associated with higher response rates in ovarian and pancreatic cancer. Protein metabolism agents were associated with lower response rate in breast and colon cancer. In all diseases other than pancreatic and prostate cancer, combination therapy was associated with higher response rates. Due to the small number of cases in each group for this cancer type, investigational agent-specific, minor differences in p-value were seen between modified Poisson regression and mixed-effect logistic regression model; however, the trend remained consistent.

Discussion

Expectations of direct clinical benefit by achieving overall response by participating in phase 1 clinical trials have been historically low for patients with cancer, which might discourage patients and physicians from considering phase 1 trials as therapeutic options. Our study showed that there has been a statistically significant improvement in response rates without an increase in the risk of treatment-related death, which remained less than 1% across the entire study period (2000–19), in patients with solid tumours enrolled in CTEP-sponsored phase 1 trials. Notable heterogeneity of rate and trend in response by trial design (combination *vs* monotherapy and solid tumour focused *vs* all-comer), by class of investigational agents, and by cancer type was observed. The overall response rate in the most recent years of 2013–19 was 18·0%, which is almost the double from 9·6% in 2000–05. This study demonstrates that phase 1 trials in the most recent era offer improved likelihood of response with very low likelihood of treatment-related deaths.

Many treatment innovations were introduced during the study period, such as monoclonal antibodies, signalling pathway inhibitors, and one of the most impactful ones—immune checkpoint inhibitors.[25] The agents evaluated in phase 1 trials in this study reflected the path of drug development in the past 20 years. The response rate in trials using regimens involving anti-angiogenesis agents, checkpoint inhibitors, and DNA repair agents exceeded 20%, whereas the response in trials testing treatments encompassing protein metabolism agents, cytokine, and vaccine were low (<10%). Although chemotherapy is still the most

	Number of patients	Year				p value
		2000–19	2000–05	2006–12	2013–19	
		Response rate, % (95% CI)	Response rate, % (95% CI)	Response rate, % (95% CI)	Response rate, % (95% CI)	
Overall response						
All patients	9325	12·2% (11·5–12·8)	9·6% (8·7–10·6)	13·1% (12·1–14·2)	18·0% (15·7–20·5)	<0·0001
Bladder cancer	186	22·0% (16·3–28·7)	8·5% (2·4–20·4)	22·5% (10·8–38·5)	28·3% (19·7–38·2)	0·0061
Breast cancer	855	15·8% (13·4–18·4)	7·9% (4·6–12·5)	18·4% (15·4–21·8)	16·4% (7·8–28·8)	0·0030
Colon cancer	1092	5·4% (4·1–6·9)	7·7% (5·7–10·2)	2·4% (1·1–4·3)	4·7% (1·3–11·5)	0·0017
Kidney cancer	276	11·6% (8·1–16·0)	3·4% (1·1–7·7)	19·3% (11·4–29·4)	25·0% (13·2–40·3)	<0·0001
Lung cancer	632	21·2% (18·1–24·6)	21·3% (17·1–26·0)	14·3% (9·1–21·0)	28·2% (21·0–36·3)	0·26
Melanoma	474	7·8% (5·6–10·6)	6·7% (4·2–10·1)	4·2% (1·4–9·6)	25·6% (13·5–41·2)	0·0065
Ovary cancer	656	30·5% (27·0– 34·2)	14·6% (9·0–21·9)	36·4% (32·1–41·0)	16·7% (7·9–29·3)	0·030
Pancreatic cancer	375	2·9% (1·5–5·2)	1·8% (0·4–5·3)	5·1% (2·1–10·2)	1·4% (0–7·4)	0·79
Prostate cancer	212	6·1% (3·3–10·3)	3·3% (1·1–7·5)	14·6% (6·5–26·7)	0% (0–60·2)	0·030
Other cancer	4567	10·3% (9·5–11·2)	10·1% (8·8–11·5)	9·2% (8·0–10·5)	16·9% (13·5–20·7)	0·012
Complete response						
All patients	9325	2·7% (2·4–3·0)	2·5% (2·0–3·0)	2·4% (2·0–3·0)	4·3% (3·2–5·7)	0·018
Bladder cancer	186	4·8% (2·2–9·0)	0% (0–7·6)	0% (0–8·8)	9·1% (4·2–16·6)	0·0006
Breast cancer	855	2·6% (1·6–3·9)	0% (0–1·8)	3·2% (1·9–4·9)	5·5% (1·1–15·1)	0·0042
Colon cancer	1092	0·5% (0·2–1·1)	0·9% (0·3–2·0)	0% (0–0·9)	0% (0–4·2)	0·012
Kidney cancer	276	0·7% (0·1–2·6)	0% (0–2·5)	0% (0–4·4)	4·6% (0·6–15·5)	0·0064
Lung cancer	632	1·6% (0·8–2·9)	1·8% (0·6–3·8)	0·7% (0–3·7)	2·1% (0·4–6·1)	0·94
Melanoma	474	1·5% (0·6–3·0)	1·3% (0·4–3·2)	0% (0–3·1)	7·0% (1·5–19·1)	0·11
Ovary cancer	656	9·3% (7·2–11·8)	4·6% (1·7–9·8)	11·4% (8·7–14·7)	1·9% (0·1–9·9)	0·59
Pancreatic cancer	375	0% (0–1·0)	0% (0–2·2)	0% (0–2·6)	0% (0–4·9)	1·00
Prostate cancer	212	0% (0–1·7)	0% (0–2·4)	0% (0–6·5)	0% (0–60·2)	1·00
Other cancers	4567	2·9% (2·4–3·4)	4·1% (3·2–5·1)	1·4% (0·9–2·0)	5·4% (3·5–7·9)	0·11

Table 4: **Overall and complete response rate from 2000 to 2019 according to type of cancer**

common agent used, almost all are combined with other targeted treatments; checkpoint inhibitors are now used in more 30% of trials. This study suggests that newer agent regimens evaluated in phase 1 trials and rationally designed therapeutic combinations are contributing to increasing response rates without increasing toxicity. However, the response rate in CTEP-sponsored monotherapy trials remains low (4%), underscoring the difficulty in developing such regimens for the at large patients within cancer populations who do not have a treatment selection biomarker.

This comprehensive analysis of response and toxicity in CTEP-sponsored phase 1 trials also demonstrates heterogeneity in response rate among different cancer types. The response rate was the highest in bladder, kidney, lung cancer, and melanoma in the most recent years. A common feature of these tumour types is that response might be attributed to rapidly evolving treatment frameworks, including combination therapy regimens incorporating anti-angiogenesis inhibitors, immune checkpoint inhibitors, and DNA repair inhibitors. In the meantime, there has been no improvement in pancreatic and colon cancer. Our data indicate that there is an unmet need for novel therapeutics in high-risk colorectal cancer,[26] and pancreatic cancer, which had a less than 2% response rate between 2013 and 2019. Patients with pancreatic or colon cancer who benefit from recent novel agents such as checkpoint inhibitors beyond standard combination chemotherapy are limited. These results indicate an unmet need for patients requiring additional understanding of disease biology and the development of agents with new mechanisms of action for these cancers.

This analysis has limitations related to study selection and generalisability of the results. The study summarized CTEP-sponsored phase 1 trials that often involved combination trials structured through CTEP agreements with industry partners and conducted by academia collaborators.[21] CTEP attempts to fill in the many critical gaps in the national cancer research effort and avoid duplication of ongoing industry partners' efforts. CTEP encourages investigators to propose and design rational combination studies based on compelling in-vitro and in-vivo preclinical data. These trials were funded based on the strength of preclinical studies.[27] In the general population, the overall perception is that all phase 1 trials are mostly first-in-human trials, but many other types of phase 1 trials are available. Such first-in-human trials are underrepresented in the current study. The current

study is descriptive in nature. Although we did multivariable analyses to adjust for few patient baseline characteristics, other unobserved confounders might have affected the outcomes, which needs to be addressed with more sensitivity analyses. Therefore, the increasing response rates seen in this study need to be interpreted with caution. Analyses examining cancer type and investigational agent-specific response had small numbers of patients and were subject to sparse-data bias.[28] In addition, we could not assess several important factors that might affect treatment response rate, including whether patients were treated in dose escalation cohorts or in dose expansion cohorts, the number of lines of treatment patients received before the investigational agents, and whether patients were selected based on biomarker analysis. Many recent CTEP-sponsored phase 1 trials include one or more tissue-agnostic dose-expansion cohorts after dose determination. However, CTEP generally limits expansion cohorts to 12–15 patients unlike some industry-sponsored trials that have large expansion cohorts with hundreds of patients since expansion cohorts in CTEP sponsored phase 1 trials are not designed to evaluate clinical efficacy.[29,30] The database lacks details to further assess clinical outcomes, such as duration of response, progression-free survival, and overall survival.

In summary, our data showed that response in CTEP-sponsored, solid tumour, phase 1 trials has almost doubled without increasing treatment-related death rate during the past 20 years, although with significant heterogeneity in response rate by trial characteristics and disease. This study presents encouraging safety and response data in modern phase 1 trials for solid tumours and provides an important framework for oncologists to discuss participation with patients. To further characterise outcomes of modern phase 1 trials, collaborative work to build a more comprehensive and complete real-world database is warranted.

Contributors

DC and NT designed the study. DC, SRF, LMC, YF, and NT collected and cleaned the data. DC and RL analysed the data. SRF, EPH, LVR, SPI, and JHD contributed in quality control of the data. All authors contributed to interpret the results of analyses. DC, CRF, and NT wrote the draft of the paper and all authors contributed to write the final paper. DC and NT were responsible for submission. All authors agreed with the last version of the paper. All authors had access to all of the data in the study, and DC, RL, and NT verified the raw data.

Declaration of interests

RL has served as a consultant for Monte Rosa Therapeutics. CRF has served as a consultant for AbbVie, AstraZeneca, Bayer, BeiGene, Bristol Meyers Sqibb/Celgene, Denovo Biopharma, Genentech/Roche Pharma, Genmab, Gilead Sciences, Karyopharm Therapeutics, Morphosys, Pharmacyclics/Janssen, Seagen, and Spectrum Pharmaceuticals; and has received research funding paid to the institution from 4D, AbbVie, Acerta Pharma, Adaptimmune, Allogene Therapeutics, Amgen, Bayer, Celgene, Cellectis, EMD, Gilead Sciences, Genentech/Roche, Guardant, Iovance Biotherapeutics, Janssen, Kite Pharma, MorphoSys, Nektar Therapeutics, Novartis, Pfizer, Pharmacyclics, Sanofi, Takeda, TG Therapeutics, Xencor, Ziopharm, Burroughs Wellcome Fund, Eastern Cooperative Oncology Group, National Cancer Institute, V Foundation for Cancer Research, and the Cancer Prevention and Research Institute of Texas where he is a CPRIT Scholar in Cancer Research. LJN has received research support from BMS/Celgene, Caribou Biosciences, Epizyme, Genentech, Gilead/Kite, IGM Biosciences, Janssen, Novartis, Takeda, and TG Therapeutics; and has served as consultant for ADC Therapeutics, Bayer, BMS/Celgene, Epizyme, Genentech, Gilead/Kite, Janssen, Morphosys, Novartis, Takeda, and TG Therapeutics. All other authors declare no competing interests.

Data sharing

All of the available data are shown in the Article and appendix. No genomic or other clinical or radiological data sharing is available. The raw data used in this study are not open to the public.

Acknowledgments

This research was supported by the Intramural Research Program of the National Cancer Institute–National Institutes of Health and by the Division of Cancer Treatment and Diagnosis, Cancer Therapy Evaluation Program and Biometrics Research Program. We thank the researchers and investigators, who were responsible for conducting each of the trials reported here, as well as the patients and their families, who contributed significant information.

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