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Evolving Landscape of Early Drug Development in Solid Tumors: Analysis of National Cancer Institute Sponsored Phase 1 Trials

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Summary

Background—The low expectation of clinical benefit from phase 1 cancer therapeutics trials may negatively impact patient and physician participation, study reimbursement and slow oncology research progress. Advances in cancer drug development, meanwhile, may have favorably improved treatment responses; however, little comprehensive data exist describing the response and toxicity associated with phase 1 trials across solid tumors.

Methods—We analyzed patient-level data from the Cancer Therapy Evaluation Program, National Cancer Institute, sponsored investigator-initiated phase 1 trials for solid tumors, January 2000 to May 2019, and report rates of toxicity and response by cancer type comparing the periods 2000–2005, 2006–2012, and 2013–2019.

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Authors Contributions:

DC and NT designed the study. DC, SRF, LMC, YF and NT collected and cleaned the data. DC and RL analyzed 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 wrote the draft of the paper and all authors contributed to write the final paper.

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Findings—A total of 465 protocols that enrolled 13,847 patients using 261 agents were analyzed. Thirty-one percent of trials comprise a monotherapy and 69% were combination therapies. The overall treatment-related death rate was 0.67% across all periods. Advanced age, performance status 2 and albumin <3.5g/dL were associated with higher risk of treatment-related death. A significant increase in response rate was seen over time; overall response rate increased from 9.6% to 18.0% from 2000–2005 to 2013–2019. Response rates for combination therapy were substantially higher than for monotherapy (15.8% vs 3.5%). The response by class of agents differed across diseases. Anti-angiogenesis agents were associated with higher response rate for bladder, colon, kidney and ovarian cancer. DNA repair inhibitors were associated with higher response rate in ovarian and pancreatic cancer. The rates and trends of response over time differed markedly by disease; there were notable improvements in bladder, breast, kidney cancer, and melanoma, but no change in the low response of pancreatic and colon cancer.

Interpretation—Over the past 20 years, the response rate in phase 1 trials nearly doubled without an increase in the treatment-related death rate. This study provides updated encouraging outcomes of modern phase 1 trials in solid tumors.

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Keywords

Phase I trial; treatment-related death; grade 5 toxicity; efficacy; response rate

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 haematologic malignancies have been reported at 5–10% based on data from previous studies analyzing phase 1 trials in the 1990s to early 2000s,^{1,2,10} confronting patients who are seeking therapeutics options beyond standard treatment with the prospect of high risks 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 monotherapy solid tumor phase 1 clinical trials involving such targeted drugs have demonstrated remarkable responses in patients with selected genomic markers.¹¹ As a result, the risk to benefit ratio of phase 1 trials in particular tumor or genomic driven 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.^{12–16}

It is now recognized that the responses seen in phase 1 trials can vary significantly by disease.^{17,18} A meta-analysis of 346 phase 1 trials conducted between 2011 and 2013 showed that overall response was significantly higher in haematologic malignancies than solid tumors; the median response rate was 21.0% in haematologic malignancies vs. 4.3% in solid tumors.¹⁸ However, these studies were conducted based on meta-analysis of published trials in which the results are prone to various biases. Also, trial results are commonly reported as a summary which makes it challenging to look at disease-specific or agent-specific outcomes. Understanding of disease-specific toxicity and treatment activity requires individual patient-level data and comprehensive analyses which can potentially provide further insights into the characteristics of clinical responses in early phase trials. We recently showed that there has been a meaningful increase in response rate in phase 1 trials for haematologic malignancies;¹⁹ however, a study focusing on solid tumors is lacking.

The National Cancer Institute's (NCI) Cancer Therapy Evaluation Program (CTEP) is the foremost sponsor of early phase clinical trials through the Experimental Therapeutics Clinical Trials Network, which consists of NCI-designated academic cancer centers in the United States and Canada. From 1974 to 1982, the 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 analyzed response and toxicity for trials predominantly using cytotoxic chemotherapy and combined solid tumor and haematologic malignancies. We report here recent trends in treatment-related deaths, and response rates for solid tumors, leveraging the large database of CTEP sponsored phase 1 clinical trials over the last 20 years in recognition of the impact of the National Cancer Act²⁰ on its 50th anniversary.

Methods

Study population

We examined data for all patients with solid tumors receiving treatment on CTEP-sponsored, investigator-initiated phase 1 oncology trials conducted between January 2000 and May 2019. Patients with neurological cancers, haematological malignancies, and those treated in phase 1/2 clinical trials were excluded from the study analysis. Also, patients only receiving radiation therapy were not included in the study. CTEP collects comprehensive information at bi-weekly intervals from investigators and actively monitors the trials through regularly scheduled periodic audits. CTEP maintains a patient-level, comprehensive trials data, including patient demographics, agent toxicity, and efficacy data.

Agents used in the trials analyzed were grouped by investigators (D.C., L.M.C, and N.T.) according to the mechanism of action (Supplemental Table 1). Combination therapy consist of investigational new drugs alone, investigational drug and a 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.²¹ 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.

Toxicity grade was based on the Common Terminology Criteria for Adverse Events (CTCAE), 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) 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.²² 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.

Statistical analysis

This study 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 and complete response rate on phase 1 trials. We defined three time periods, 2000–2005, 2006–2012, and 2013–2016, leading to each period having 70 trials initiated and 1500 patients enrolled. For each period, the widths of the 95% confidence interval (CI, calculated based on 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/response rates, respectively. Univariate associations of treatment related deaths and response with patients' variables were assessed using risk ratio (RR) based on the modified Poisson regression model.²³ 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 compared cancer-specific response and toxicity rates among the three periods based on a logistic regression model by including the period as a covariate. A multivariable Poisson regression model was also fitted to adjust for patient baseline variables. All analyses were performed in R Studio version 2022.02.1.

Results

Trial characteristics

A total of 465 protocols that enrolled 13,847 patients using 261 agents (Supplemental Tables 1, 2) were analyzed (Table 1). Ninety percent of the trials focused only on solid tumors. Ten percent of the trials were “all-comer” trials that enrolled solid tumor, haematologic malignancies and/or neurological cancers; for these trials, only patients with solid tumor were included in the study. Common solid tumors included: ovarian cancer (N=1,518), colon cancer (N=1,438), breast cancer (N=1,010), and lung cancer (N=982). Patients without detailed diagnosis (solid tumor not otherwise specified), rare tumors such as sarcomas or other low incidence cancers were pooled and categorized together as “others” (N=6,735). Although information of the dose escalation method of each trial was not available, the majority of trials in the CTEP sponsored trials utilized the 3+3 design. The median age of study patients was 57 years (range: 0–94). The median number of patients treated per trial was 24 (range: 1–431). Thirty-one percent of trials used an agent as a monotherapy, and 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 (Supplemental Figure 1, Supplemental Table 3). Chemotherapy was less frequently used for 10 years after 2004, but its use became more frequent after 2015, involving up to 60% of recent trials in 2018. There was 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, while DNA repair agents became more frequently used.

Toxicity and deaths in phase 1 trials for solid tumors

A total of 1,111 patients died while on study (8.0%, 95%CI: 7.6–8.5%, Table 2), among these, 93 deaths were attributed to treatment (treatment-related death risk: 0.67%, 95%CI: 0.5–0.8%). Advanced age (RR: 1.02 for each one-year increase in age, 95%CI: 1.01–1.04), performance status (PS) 2 (RR: 2.6, 95%CI: 1.2–5.5) and albumin <3.5g/dL (RR: 2.6, 95%: 1.5–4.5) were associated with higher risk of treatment-related deaths (Table 3). The results were consistent with the mixed-effects logistic regression model (Supplemental table 4). Multivariate analysis adjusting cancer type and patient background revealed that albumin <3.5g/dL (RR: 2.5, 95%: 1.5–4.3) was associated with higher risk of treatment-related death (Supplemental table 5). 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; while trials that used receptor/signal transduction pathway agent were associated with a lower risk of treatment-related deaths. The treatment-related death risks for combination trials, were not higher than the risks for monotherapy trials (0.7% for both).

Risks of treatment-related deaths did not change over time (2000–2005 vs. 2006–2012 vs. 2013–2019, $P=0.52$) (Figure 1A) and the RR for the time variable in the multivariable analysis is 0.77 (95%CI, 0.4–1.5, $P=0.43$). Across all cancers analyzed, the treatment-related death risk was <1%, except for pancreatic cancer (1.04%), with no difference between diseases ($P=0.70$). No change in treatment-related deaths over time was seen across all cancer types analyzed except for pancreatic cancer, which showed a decreased trend although with limited number of treatment-related deaths throughout (Supplemental Table 6).

Considering all causes of death including death from disease progression during the trial, patients who were older, male, had PS 2, albumin <3.5 g/dL, and anemia had a higher risk of death. Patients with higher BMI (>30) compared to standard BMI (18.5–25.0) had a lower risk of death (Table 3). Intriguingly, 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 period (Supplemental Table 5: 5.6% in 2000–2005, 9.9% in 2006–2012, and 9.7% in 2013–2019). Progression of disease as a cause of death increased over time (69.5% of deaths in 2000–2005, 84.0% in 2006–2012 and 90.9% in 2013–2019). There was a heterogeneity in risk and trend of death-on-trial across diseases; the highest risk of death was seen with pancreatic cancer (14.9%, 95%CI: 12.0–18.2%) and the lowest risk was seen with prostate cancer (2.4%, 95%CI: 1.0–4.9%) (Table 2).

The most common grade 3/4 toxicities in phase 1 trials for solid tumor were haematologic (Supplemental Table 7). Grade 3/4 neutropenia, lymphopenia, anemia and thrombocytopenia occurred in 16.9%, 8.9%, 6.5% and 7.1% of patients, respectively. Febrile neutropenia was observed in 1.6% of patients. Non-hematologic grade 3/4 toxicities were less common, mostly <5% except for fatigue which was observed in 5.1% of patients. No increasing or decreasing trends of specific toxicities were noted over time, except for the neutropenia, which showed a lower risk in 2013–2019 compared to the prior period.

Response rates in phase 1 trials for solid tumor

Response assessment was available for 9,325 patients (67.3%). The overall and complete response rates for all trials during the study period were 12.2% (95%CI: 11.5–12.8%) and 2.7% (95%CI: 2.4–3.0%), respectively. An increase in overall response and complete response rates were seen over time (Figure 1B). Overall response increased from 9.6% to 18.0%, and complete response rates increased from 2.5% to 4.3% from 2000–2005 to 2013–2019 (Table 4). Intriguingly, there was also an increase of stable disease and a decrease of progressive disease as the best response rate in the phase 1 trials (Figure 1B). Patients who experienced clinical benefit (overall response plus stable disease) increased from 48.3% in 2000–2005 to 61.9% in 2013–2019. Patients who were female, had PS 0–1, albumin 3.5 g/dL, and hemoglobin 12g/dL, experienced higher likelihood of response (Supplemental Table 8). These results were consistent between modified Poisson regression and mixed-effects logistic regression models (Supplemental Table 8). Multivariate analysis adjusting for cancer type and patient background revealed that patients who had albumin 3.5g/dL and PS 0–1 had higher chance of response (Supplemental table 5). The trials that used chemotherapy (18.2%), anti-angiogenesis (20.7%), and DNA repair agents (26.5%) were associated with a higher likelihood of response, while trials using cytokines (6.6%), protein metabolism agents (6.2%), epigenetic modulation (5.3%), and vaccines (2.8%) showed a lower likelihood of response. Trials using checkpoint inhibitors had a high overall response rate of 22.9% although without statistical significance (Supplemental table 8). The overall response rate in trials using combination therapy were higher than trials with monotherapy (overall response; 15.8% vs 3.5%, RR: 4.6, 95%CI: 3.1–6.8, $p<0.001$), and that in all-comer trials was lower than solid tumor focused trials (overall response: 4.1% vs 13.3%, RR: 0.32, 95%CI: 0.2–0.5, $p<0.001$).

The response rate and trend over time differed by disease (Table 4). In the most recent time period of 2013–2019, the response rate was 28.3% in bladder cancer, 16.4% in breast cancer, 25.0% in kidney cancer, 28.2% in lung cancer, 25.6% in melanoma, 16.7% in ovarian cancer, 4.7% in colon cancer and 1.4% in pancreatic cancer. There were improvements in overall and complete response rate over time in bladder, breast, ovary, kidney cancer, and melanoma. No improvement was seen in lung cancer although the response rates were relatively high. In contrast, there was no improvement in response rates and remained notably low for pancreatic and colon cancer.

Response rates by class of investigational agents for each cancer are shown in Supplemental Table 9. After chemotherapy, 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. Interestingly, a protein metabolism agent was 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.

Discussion

Expectations of direct clinical benefit by participating in phase 1 clinical trials have been historically low for cancer patients, which may influence patients and physicians considering phase 1 trials as therapeutic options. Although meta-analysis studies suggested a potential increase in response rate in more recent phase 1 trials, particularly with targeted agents,^{17,18,24} these studies were prone to publication bias and were unable to assess individual patient-level characteristics that influence outcomes. These studies also included patients with haematologic malignancies, who generally have a more favorable response to treatment compared to solid tumors. Due to the disease heterogeneity that leads to different drug development pathways in different cancers, disease-specific toxicity and response rate are critical for reference and design for future phase 1 trials. This 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 <1% across the entire study period in patients with solid tumors enrolled in CTEP sponsored phase 1 trials. Notable heterogeneity of rate and trend in response by trial design (combination vs monotherapy and solid tumor focused vs all-comer), by class of investigational agents and by cancer types was observed. The response rate in the most recent years of 2013–2019 was 18%, which is almost doubled from 9.6% in 2000–2005. 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 paradigm-shifting treatment innovations were introduced during the study period, such as monoclonal antibodies, signaling pathway inhibitors, with one of the most dramatic being immune checkpoint inhibitors.²⁵ The agents evaluated in phase 1 trials in this study reflected the path of drug development in the last 20 years. The response rate in trials using regimens involving anti-angiogenesis agents, checkpoint inhibitors, and DNA repair agents exceeded 20%, while the response in trials testing treatments encompassing protein metabolism agents, cytokine, and vaccine were low with <10%. Although chemotherapy is still the most common agent used, almost all are combined with other targeted treatments; checkpoint inhibitors are now used in over 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 (3.5%), underscoring the difficulty in developing such regimens for the at large cancer patient populations who do not have a treatment selection biomarker.

This comprehensive analysis of response and toxicity in CTEP sponsored phase 1 trials also demonstrated profound 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 era. A common feature of these tumor types is that response may be attributed to rapidly evolving treatment paradigms 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 indicated 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 in the most recent era. Patients with pancreatic and 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 generalizability 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 The general perception of phase 1 trials is equivalent to a first-in-human single-agent trials. Such 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, there may present other unobserved confounders which need more sensitivity analyses. Therefore, 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 may impact response rate including whether patients were treated in dose escalation cohort or in dose expansion cohort, the number of lines of treatment patients received prior to the investigational agents, and whether patients were selected by biomarkers. 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 cohort with hundreds of patients since expansion cohort in CTEP sponsored phase 1 trials is not designed to evaluate clinical efficacy.^{29,30} The database lack 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 tumor phase 1 trials has almost doubled without increasing treatment related death rate over 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 tumors and provides an important framework for oncologists to discuss participation with patients. To further characterize outcomes of modern phase 1 trials, collaborative work to build a more comprehensive and complete real-world database is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict-of-interest Disclosure:

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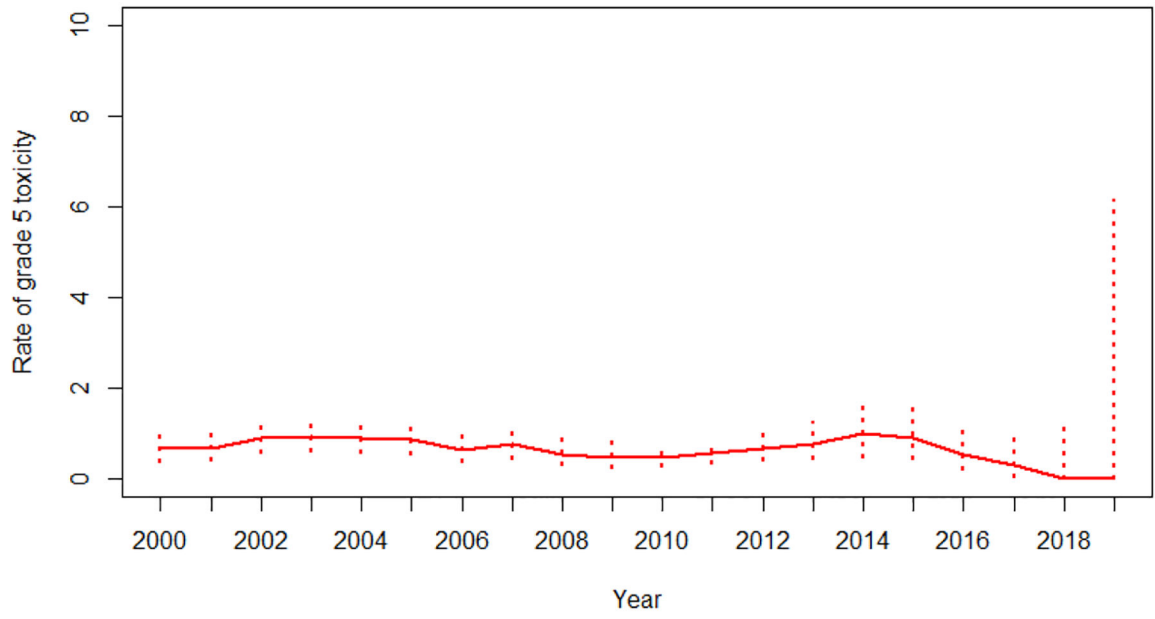


Figure 1A:
Trend of treatment-related death between 2000 to 2019 with 95% exact confidence interval

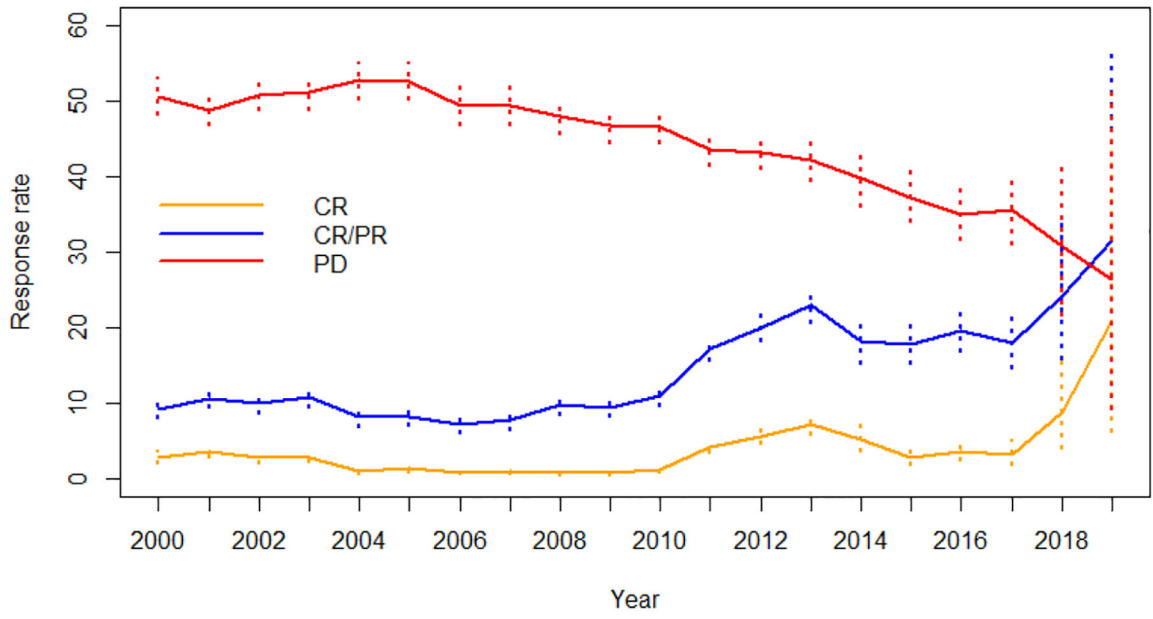


Figure 1B:
Response trends between 2000 to 2019 with 95% exact confidence interval

Table 1.

Characteristics of the phase 1 trials

	N	
Total number of protocols	465	
Total number of patients	13,847	
Number of patients with disease		
Bladder	257	(1.9%)
Breast	1010	(7.3%)
Colon	1438	(10.4%)
Kidney	310	(2.2%)
Lung	982	(7.1%)
Melanoma	779	(5.6%)
Ovary	1518	(11.0%)
Pancreas	530	(3.8%)
Prostate	288	(2.1%)
Others	6735	(48.6%)
Median age of patients (range, 1Q-3Q)	57	(0–94, 46–65)
Type of phase I		
Solid tumor focused trial *	418	(89.9%)
Basket trial **	47	(10.1%)
Median number of patients on trial (range, 1Q-3Q)	24	(1–431, 14–37)
Trial activation year		
2000–2005	214	(46.0%)
2006–2012	180	(38.7%)
2013–2019	71	(15.3%)
Median days to study completion (range, 1Q-3Q)	1517	(4–4794, 1079–2138)
Number of trials agents used		
Antiangiogenesis	71	(15.3%)
Checkpoint inhibitor	24	(5.2%)
Chemotherapy	225	(48.4%)
Cytokine	20	(4.3%)
DNA repair	35	(7.5%)
Gene/cellular therapy	8	(1.7%)
Epigenetic modulation	39	(8.4%)
Monoclonal antibody	19	(4.1%)
Protein metabolism	41	(8.8%)
Receptor/signal transduction pathway agent	136	(29.2%)
Vaccine	30	(6.5%)
Others (Apoptosis, Immunotoxin, etc.)	113	(24.3%)
Number of agents used on trial (range, 1Q-3Q)		
Monotherapy	144	(31.0%)
Combination	321	(69.0%)

* Trials that enrolled only patients with solid tumors

** Trials that enrolled patients with solid tumors, hematologic malignancies and/or neurological cancers

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Table 2.

Treatment-related death and all cause death rate during trials by cancer types

		Number of patients	Number of events	%	95%CI
Treatment-related death	All patients	13847	93	0.67	(0.54, 0.82)
	Bladder	257	1	0.39	(0.01, 2.15)
	Breast	1010	7	0.69	(0.28, 1.42)
	Colon	1438	11	0.76	(0.38, 1.36)
	Kidney	310	1	0.32	(0.01, 1.78)
	Lung	982	9	0.92	(0.42, 1.73)
	Melanoma	779	1	0.13	(0, 0.71)
	Ovary	1518	9	0.59	(0.27, 1.12)
	Pancreas	530	3	0.57	(0.12, 1.65)
	Prostate	288	3	1.04	(0.22, 3.01)
	Others	6735	48	0.71	(0.53, 0.94)
Death during trial*	All patients	13847	1111	8.02	(7.58, 8.49)
	Bladder	257	34	13.23	(9.34, 17.99)
	Breast	1010	84	8.32	(6.69, 10.19)
	Colon	1438	120	8.34	(6.97, 9.9)
	Kidney	310	13	4.19	(2.25, 7.06)
	Lung	982	78	7.94	(6.33, 9.81)
	Melanoma	779	59	7.57	(5.82, 9.66)
	Ovary	1518	43	2.83	(2.06, 3.8)
	Pancreas	530	79	14.91	(11.98, 18.23)
	Prostate	288	7	2.43	(0.98, 4.94)
	Others	6735	594	8.82	(8.15, 9.52)

* Death during trial: all death regardless of attribution

Abbreviations: CI, confidence interval computed using the exact method

Table 3.

Risk factor table for treatment-related death or death during trial

	N (%)	Treatment-related death				Death during protocol treatment			
		Number toxicities (%)	RR	95%CI	p-value	Number events (%)	RR	95%CI	p-value
Age									
Continuous (with 1 increase)			1.02	(1.01–1.04)	0.006		1.01	(1.00–1.01)	0.009
< 18	1169 (8.4)	3 (0.3)	0.45	(0.15, 1.40)	0.169	85 (7.3)	0.95	(0.69, 1.30)	0.739
18–59	6899 (49.8)	39 (0.6)	Ref			528 (7.7)	Ref		
60	5778 (41.7)	51 (0.9)	1.58	(1.02, 2.41)	0.041	498 (8.6)	1.13	(1.00, 1.27)	0.050
Sex									
Female	7531 (54.4)	47 (0.6)	Ref			529 (7.0)	Ref		
Male	6316 (45.6)	46 (0.7)	1.21	(0.80, 1.83)	0.370	582 (9.2)	1.17	(1.03, 1.33)	0.370
PS									
0–1	6460 (94.1)	43 (0.7)	Ref			482 (7.5)	Ref		
2	404 (5.9)	7 (1.7)	2.62	(1.24, 5.54)	0.011	110 (27.3)	3.16	(2.52, 3.97)	<0.001
BMI									
Continuous			1.01	(0.97, 1.06)	0.554		0.97	(0.95, 0.98)	<0.001
<18.5	257 (3.7)	1 (0.4)	0.56	(0.08, 3.80)	0.556	36 (14.0)	1.41	(1.00, 1.98)	0.052
18.5–25	2489 (35.6)	18 (0.7)	Ref			257 (10.3)	Ref		
25–30	2395 (34.2)	15 (0.6)	0.88	(0.46, 1.67)	0.688	196 (8.2)	0.84	(0.68, 1.04)	0.104
30	1858 (26.5)	16 (0.9)	1.18	(0.57, 2.44)	0.652	115 (6.2)	0.62	(0.50, 0.78)	<0.001
Albumin									
Continuous			0.47	(0.30, 0.72)	0.001		0.32	(0.29, 0.37)	< 0.001
3.5 g/dL	3856 (68.7)	20 (0.5)	Ref			190 (4.9)	Ref		
< 3.5 g/dL	1757 (31.3)	23 (1.3)	2.62	(1.51, 4.54)	<0.001	300 (17.1)	3.38	(2.80, 4.08)	< 0.001
Hemoglobin									
Continuous			1.01	(0.84, 1.21)	0.925		0.79	(0.75, 0.83)	< 0.001
12.0 g/dL	3513 (52.3)	22 (0.6)	Ref			185 (5.3)	Ref		
< 12.0 g/dL	3209 (47.7)	27 (0.8)	1.32	(0.79, 2.20)	0.288	395 (12.3)	2.15	(1.76, 2.64)	< 0.001
Study Activation Year									

	N (%)	Treatment-related death				Death during protocol treatment				
		Number toxicities (%)	RR	95%CI	p-value	Number events (%)	RR	95%CI	p-value	
2000–2005	5882 (42.5)	44 (0.7)	Ref			327 (5.6)	Ref			
2006–2012	6220 (44.9)	37 (0.6)	0.76	(0.48, 1.21)	0.249	614 (9.9)	1.49	(1.13, 1.98)	0.005	
2013–2019	1745 (12.6)	12 (0.7)	0.94	(0.47, 1.82)	0.830	170 (9.7)	1.65	(1.15, 2.36)	0.006	
Investigational Agent										
Antiangiogenesis	2689 (19.4)	32 (1.2)	2.19	(1.41, 3.39)	<0.001	224 (8.3)	1.06	(0.77, 1.47)	0.725	
Checkpoint inhibitor	817 (5.9)	5 (0.6)	0.95	(0.41, 2.21)	0.909	70 (8.6)	1.12	(0.66, 1.90)	0.681	
Chemotherapy	6981 (50.4)	48 (0.7)	1.03	(0.66, 1.59)	0.912	432 (6.2)	0.68	(0.52, 0.89)	0.005	
Cytokine	367 (2.7)	1 (0.3)	0.39	(0.06, 2.50)	0.320	12 (3.3)	0.49	(0.26, 0.90)	0.021	
DNA repair	1791 (12.9)	12 (0.7)	0.91	(0.47, 1.79)	0.790	152 (8.5)	1.17	(0.76, 1.80)	0.480	
Epigenetic modulation	1255 (9.1)	7 (0.6)	0.82	(0.41, 1.66)	0.582	139 (11.1)	1.34	(0.92, 1.94)	0.129	
Gene/cellular therapy	132 (1.0)	0 (0.0)	NA	NA	NA	8 (6.1)	1.00	(0.29, 3.49)	1.000	
Monoclonal antibody	468 (3.4)	2 (0.4)	0.66	(0.16, 2.71)	0.562	25 (5.3)	0.56	(0.34, 0.93)	0.024	
Protein metabolism	1126 (8.1)	16 (1.4)	2.39	(1.41, 4.06)	0.001	81 (7.2)	0.94	(0.66, 1.33)	0.731	
Receptor/signal transduction pathway	4029 (29.1)									
agent		18 (0.4)	0.60	(0.36, 1.00)	0.051	362 (9.0)	1.21	(0.95, 1.54)	0.128	
Vaccine	773 (5.6)	1 (0.1)	0.19	(0.03, 1.29)	0.089	46 (6.0)	0.93	(0.46, 1.88)	0.847	
Others	2953 (21.3)	22 (0.7)	1.17	(0.69, 1.96)	0.559	210 (7.1)	1.00	(0.72, 1.39)	0.992	
Combination Therapy										
Monotherapy	4108 (29.7)	28 (0.7)	Ref			391 (9.5)	Ref		0.685	
Combination Therapy	9739 (70.3)	65 (0.7)	0.99	(0.61, 1.60)	0.958	720 (7.4)	0.95	(0.72, 1.24)		
Trial type										
Solid tumor focused trial	12179 (88.0)	85 (0.7)	Ref			923 (7.6)	Ref			
All-comer trial	1668 (12.0)	8 (0.5)	0.70	(0.33, 1.52)	0.371	188 (11.3)	1.48	(1.10, 1.97)	0.008	

Abbreviations: RR, risk ratio; CI, confidence interval; PS, performance status; BMI, body mass index; p-values are obtained using Wald test

Table 4:

Overall and complete response rate with trends by cancer type during 2000 to 2019

	Number of patients	Year											
		2000–2005				2006–2012				2013–2019			
		%	95%CI	%	95%CI	%	95%CI	%	95%CI	%	95%CI	%	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)	<0.001		
	Bladder	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)	0.006		
	Breast	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)	0.003		
	Colon	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)	0.002		
	Kidney	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)	<0.001		
	Lung	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)	0.255		
	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)	0.006		
	Ovary	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)	0.03		
	Pancreas	375	2.9	(1.5, 5.2)	1.8	(0.4, 5.3)	5.1	(2.1, 10.2)	1.4	(0.0, 7.4)	0.788		
	Prostate	212	6.1	(3.3, 10.3)	3.3	(1.1, 7.5)	14.6	(6.5, 26.67)	0.0	(0, 60.2)	0.03		
	Others	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	186	4.8	(2.2, 9.0)	0.0	(0, 7.6)	0.0	(0, 8.8)	9.1	(4.2, 16.6)	0.001		
	Breast	855	2.6	(1.6, 3.9)	0.0	(0, 1.8)	3.2	(1.9, 4.9)	5.5	(1.1, 15.1)	0.004		
	Colon	1092	0.5	(0.2, 1.1)	0.9	(0.3, 2.0)	0.0	(0, 0.9)	0.0	(0, 4.2)	0.012		
	Kidney	276	0.7	(0.1, 2.6)	0.0	(0, 2.5)	0.0	(0, 4.4)	4.6	(0.6, 15.5)	0.006		
	Lung	632	1.6	(0.8, 2.9)	1.8	(0.6, 3.8)	0.7	(0, 3.7)	2.1	(0.4, 6.1)	0.944		
	Melanoma	474	1.5	(0.6, 3.0)	1.3	(0.4, 3.2)	0.0	(0, 3.1)	7.0	(1.5, 19.1)	0.112		
	Ovary	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)	0.590		
	Pancreas	375	0.0	(0, 1.0)	0.0	(0, 2.2)	0.0	(0, 2.6)	0.0	(0, 4.9)	1.000		
	Prostate	212	0.0	(0, 1.7)	0.0	(0, 2.4)	0.0	(0, 6.5)	0.0	(0, 60.2)	1.000		
	Others	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)	0.114		

Abbreviations: CI, confidence interval computed using the exact method; p-values are derived from the likelihood ratio test using the logistic regression model