Title

Relationship Between Response and Dose in Published, Contemporary Phase I Oncology Trials.

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Relationship Between Response and Dose in Published, Contemporary Phase I Oncology Trials

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ABSTRACT

Background: As progress continues in oncology drug development, this study aimed to examine whether the previously established association between drug dose and efficacy in the era of cytotoxic therapies remains true in today's phase I dose-escalation oncology trials. **Methods:** A systematic review of early-phase dose-finding trials of single-agent oncology drugs from 2015 to 2018 was conducted to examine the relationship between drug dose and objective responses. Cancer-specific trials were included if they determined maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D). Data related to the study drug, study design, treatment response, cancer type, dose levels, MTD, and RP2D were all collected. Dose level was categorized into 4 categories (≤40%, 41%–80%, 81%–120%, and >120% of the RP2D) and was further analyzed by class of drug. **Results:** A total of 175 phase I studies were identified, with a total of 7,330 patients showing a median response rate of 5% (range, 0%–83%) across trials. A total of 93 trials with 2,506 participants had response data corresponding to drug dose level. In this subset, the median response rate was 5% (range, 0%–83%) across trials. Across all participants in this subset, the response rate was 12% (57 of 491) among those in the dose range of ≤40% of RP2D, 17% (95 of 562) among those in 41% to 80% of RP2D, 23% (272 of 1,206) among those in 81% to 120% of RP2D, and 29% (71 of 247) among those in >120% of RP2D ($P<.001$). The response rate at ≤40% of RP2D for targeted antibody was 5%, 4% for cellular therapy, 19% for immunotherapy, and 21% for small-molecule targeted inhibitors. **Conclusions:** Whereas our study of published phase I trials continued to show a low response rate consistent with earlier studies, the relationship between response and dose does not always peak at 81% to 120% of RP2D anymore, likely due to the use of novel immunotherapy and targeted agents with distinct efficacy and toxicity patterns.

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Phase I cancer trials are designed to investigate drug safety, tolerability, pharmacodynamics, and pharmacokinetics, and if responses are seen, they may provide reassuring information about drug activity. Prior pooled analyses of published phase I trials testing primarily cytotoxic chemotherapies have shown low overall response rates (ORRs), such as a 1991 study showing a 6% response rate across 228 phase I studies,[1] and more recent analyses confirming a 4% to 6% response rate.[2,3] These studies, which focused on cytotoxic agents,[1–3] also showed that an increasing dose of cytotoxic chemotherapy was associated with improved tumor response and increased toxicity. In one earlier pooled analysis, the maximum response was statistically shown to occur most often at the recommended phase II dose (RP2D), or at approximately 81% to 120% of RP2D.[1]

Recent advances in drug development have allowed for targeted agents, immunotherapy, and other classes of agents, which, in regard to efficacy, may not correlate well with dose level, toxicity, or biologic framework.[4–7] Thus, the RP2D of these newer classes of agents not only incorporates the maximum tolerated dose (MTD) but also must account for delayed and atypical adverse effects that occur after a course of treatment.[8] Although contemporary phase I trial designs have mitigated some inefficiencies related to nonclassic toxicities seen in novel agents,[9] it remains unclear whether the maximum response of these newer classes of agents correlates with the recommended dose used for phase II trials.

For these reasons, we conducted a systematic review of recent early-phase dose-finding clinical trials of novel oncology drugs to examine the dose–efficacy relationship. We aimed to determine whether the RP2D in early-phase trials correlates with their preliminary efficacy endpoints in the modern era, in which noncytotoxic agents dominate oncology drug development.

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Methods

Overview

We conducted a systematic review of contemporary early-phase dose-finding clinical trials of novel oncology drugs to examine the relationship between investigative drug dose and objective response rate.

Literature Search and Selection

We searched MEDLINE/PubMed for the terms *cancer* and *oncology* to identify dose-finding phase I studies from November 15, 2015, through November 15, 2018. The following filters were used: full text, English, humans, clinical trial phase I, and adult aged ≥18 years. The literature search was last accessed on February 2, 2019. Studies were included if they enrolled adult humans aged ≥18 years, investigated cancer treatment (both malignant hematology and oncology), and examined the safety and preliminary efficacy of a proposed drug dose. Data from a minority of dose-expansion cohorts (phase I/II studies) were included for this review. Studies that focused on multidrug combination, radiation, topical, or surgical therapies, or drug delivery were excluded. Studies not accessible by Oregon Health & Science University or with overly incomplete or duplicate data were also excluded (Figure 1).

Data Extracted

For every trial, we collected the treatment response endpoint of every patient at every dose level, if available. Patients were categorized as having achieved complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). We also combined CR and PR over the total number of patients (those with CR, PR, SD, and PD, including patients who were nonevaluable) to assess the ORR. Most response endpoints were classified using RECIST guidelines.[10]

In addition, for every trial, information was collected related to the investigational therapy, treatment regimen, study design, respective dose levels, MTDs, and final RP2D (if available). We also extracted the number of patients comprising the total trial populations and the respective tumor types, the median duration of response, and the median progression-free survival per study.

Data Analysis

The proportions of ORR, SD, disease control rate (ie, ORR + SD), and PD from all dose-finding trials were graphically compared across dose levels. The dose levels were organized by their relationship to the RP2D. For example, if a patient achieved SD at a dose of 10 mg and the final RP2D in the trial was 100 mg, then this trial participant would be assigned to the 10% category. We categorized this assignment into ≤40%, 41% to 80%, 81% to 120%, and >120% of the RP2D.[1] Proportions of ORR were also compared among these categories using the Fisher exact test. Subgroup analyses were conducted in the specific drug class of interest: targeted antibody, immunotherapy, nonantibody targeted inhibitor, and vaccine/cellular therapy. Specific statistical testing was conducted using SAS 9.4 (SAS Institute Inc.); otherwise, all descriptive calculations and figures (including standard error lines) were performed and created using Microsoft Excel.

Results

We retrieved 831 search results that were individually reviewed, of which 175 phase I trials met our eligibility criteria (see Figure 1). These 175 trials (N=7,330) represented >50 tumor types, 7 drug classes, 145 unique drugs, and a median response rate of 5% (supplemental eTables 1–3, available with this article at JNCCN.org). The most common tumor types represented were lung (12%), colorectal (12%), and breast (11%). Among the 175 trials, 1,040 of 7,330 patients (15%) were labeled as having at least PR to therapy despite a median ORR of 5% across

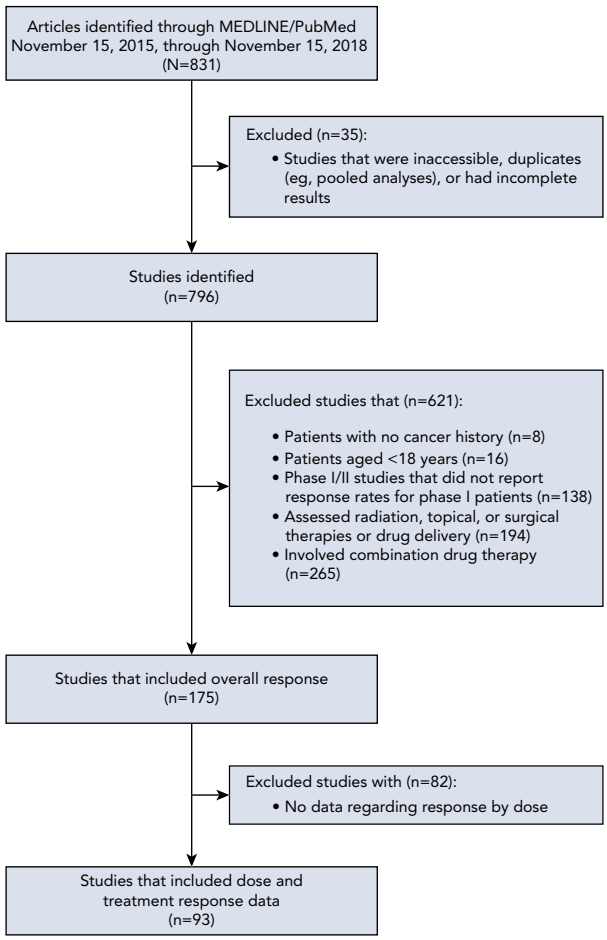

Figure 1. Flow diagram of phase I trial selection.

trials. Nonantibody targeted inhibitors and targeted antibodies were the most common therapies tested (47% and 24%, respectively). Immunotherapy and vaccine/cellular therapy had the greatest median response rate of all drug classes (15%). The median progression-free survival was 4.2 months, as illustrated by 84 studies that provided these data.

We then identified 93 studies that specifically reported the treatment response endpoint of every patient at every dose level. Among the 3,890 participants, the median response rate was 5% (range, 0%–83%; Table 1). A total of 47 studies involved nonantibody targeted inhibitors, 24 involved targeted antibodies, 7 involved immunotherapy, 6 involved chemotherapy, 5 involved vaccine therapy, 3 involved hormonal therapy, and 1 involved CAR T-cell therapy. The most common cancer types were leukemia (16%), lung (12%), and breast (10%) (Table 1).

Of the 3,890 patients, 2,506 had both response and dose data, among whom the ORR (CR and PR) was 20% (n=495); 1,095 patients (44%) had SD and 916 (37%) had PD (Figure 2). The proportion of patients with response increased with dose (12% in ≤40% of the RP2D, 17% in 41%–80% of the RP2D, 23% in 81%–120% of the RP2D, and 29% in >120% of the RP2D; $P<.001$). The disease control rate (CR+PR+SD) seen in 1,590 patients also increased with dose (58% in ≤40% of the RP2D, 61% in 41%–80% of the RP2D, 65% in 81%–120% of the RP2D, and 71% in >120% of the RP2D; $P<.001$) (Figure 2).

Among the 813 patients treated with targeted antibody medications, 128 (16%) had at least CR or PR, 349 (43%) had SD, and 336 (41%) had PD. The proportion of patients with response was 11 of 209 (5%) in ≤40% of the RP2D, 24 of 189 (13%) in 41% to 80% of the RP2D, 86 of 369 (23%) in 81% to 120% of the RP2D, and 7 of 46 (15%) in >120% of the RP2D ($P<.01$) (Figure 3). The disease control rate was 46% in ≤40% of the RP2D, 59% in 41% to 80% of the RP2D, 64% in 81% to 120% of the RP2D, and 70% in >120% of the RP2D ($P<.01$).

With regard to the 239 patients who received immunotherapy, 52 (22%) had at least CR or PR, 120 (50%) had SD, and 67 (28%) had PD. The proportion of patients with response was 12 of 64 (19%) in ≤40% of the RP2D, 7 of 37 (19%) in 41% to 80% of the RP2D, 31 of 133 (23%) in 81% to 120% of the RP2D, and 2 of 5 (40%) in >120% of the RP2D ($P=.59$) (Figure 4). The disease control rate was 56% in ≤40% of the RP2D, 81% in 41% to 80% of the RP2D, 78% in 81% to 120% of the RP2D, and 40% in >120% of the RP2D ($P<.01$).

Distributions of nonantibody targeted inhibitor (n=1,220) and vaccine/cellular therapy (n=102) are depicted in Figures 5 and 6, respectively. Among the 1,220 patients who were treated with small molecule targeted agents, 32 of 155 (21%) responded at ≤40% of the RP2D, 61 of 170 (23%) responded at 41% to 80% of the RP2D, 148

Table 1. Characteristics of Dose-Escalation Trials

General Characteristic	n (%)
Total pooled studies, N	93
Response rates, %	
Median ORR (range)	5 (0–83)
Median response rate by drug class (range)	
Nonantibody targeted inhibitor/targeted antibody	5
Immunotherapy/Vaccine/CAR T-cell therapy	8
Chemotherapy/Hormonal therapy	5
Representation of therapy class in all studies	
Nonantibody targeted inhibitor	47 (51)
Targeted antibody	24 (26)
Immunotherapy	7 (8)
Chemotherapy	6 (6)
Vaccine therapy	5 (5)
Hormonal therapy	3 (3)
CAR T-cell therapy	1 (1)
Unique therapies, n	85
Patient characteristics	
Patients enrolled, n	3,890
CR	193 (6)
PR	466 (14)
SD	1,389 (40)
PD	1,383 (40)
Median duration of response (range), mo	3.3 (1–19)
Median progression-free survival (range), mo	4.9 (1–30)
Cancer types, n	43
Cancer representation of all patients	
Leukemia	627 (16)
Lung	467 (12)
Breast	369 (10)
Colorectal	358 (9)
Lymphoma	330 (8)
Multiple myeloma	220 (6)
Renal	214 (6)
Ovarian	185 (5)
Not reported or not cancer-specific	156 (4)
Melanoma	95 (2)
Prostate	87 (2)
Pancreatic	83 (2)
Other[a] (all <2%)	699 (18)

Abbreviations: CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Head and neck, pancreatic, mesothelioma, glioblastoma, esophageal, urothelial, gastric, skin, Merkel cell, cervical, neuroendocrine, cancer of unknown primary, myelodysplastic syndromes, bladder, endometrial, cholangiocarcinoma, anal, uterine, thyroid, adrenal, central nervous system, lymphoma, melanoma, gastrointestinal stromal tumor, thymus, ampullary, peritoneal, bile duct, carcinoid, vulvar, testicular, appendiceal, penile, parotid, cardiac, and bone.

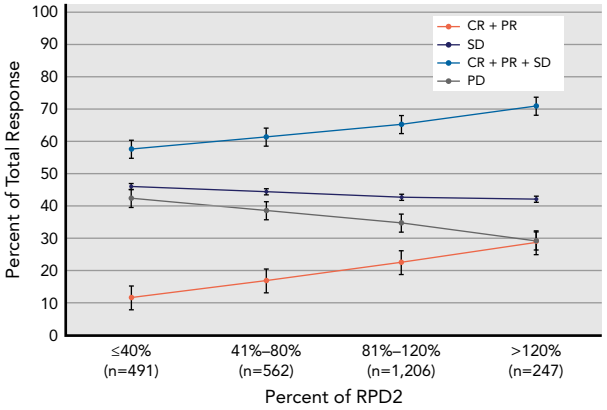

Figure 2. Response rate for all study drugs (n=2,506).
Abbreviations: CR, complete response; PR, partial response; PD, progressive disease, RP2D, recommended phase II dose; SD, stable disease.

of 620 (24%) responded at 81% to 120% of the RP2D, and 60 of 175 (34%) responded at >120% of the RP2D (see Figure 5). Among the 102 patients who were treated with cellular or vaccine therapy, 2 of 49 (4%) responded at ≤40% of the RP2D, 0 of 22 responded at 41% to 80% of the RP2D, 3 of 24 (13%) responded at 81% to 120% of the RP2D, and 0 of 7 responded at >120% of the RP2D (see Figure 6).

Discussion

Multiple studies have sought to characterize the response rates of phase I trials[1–3]; these 3 earlier studies, representing >20,000 patients enrolled in phase I trials from 1970 to 2009, reported an overall objective response of 4% to 7%, despite 1 study showing notable variation from year to year, with a response rate as high as 20% reported.[3] We found that the median response rate in contemporary phase I trials in this study remained approximately 5% of 7,330 patients. However, through aggregating the total number of responding patients and dividing by the total number of treated patients, we found that 1,040 patients (15%) had at least a PR. This

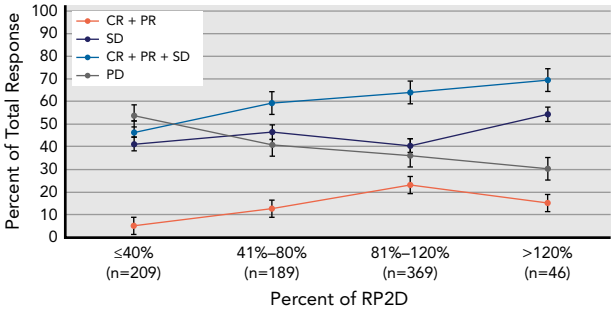

Figure 3. Response rate for targeted antibody (n=813).
Abbreviations: CR, complete response; PR, partial response; PD, progressive disease, RP2D, recommended phase II dose; SD, stable disease.

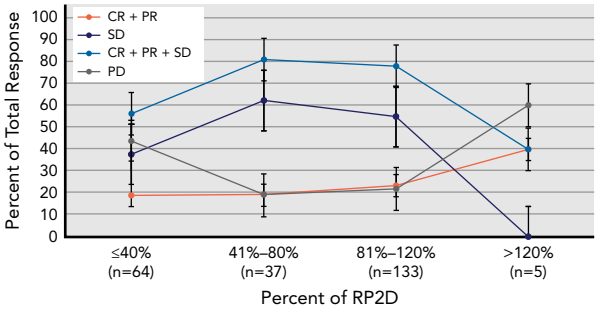

Figure 4. Response rate for immunotherapy (n=239).
Abbreviations: CR, complete response; PR, partial response; PD, progressive disease, RP2D, recommended phase II dose; SD, stable disease.

difference likely occurred because drugs that generate response are more prone to having their trials enlarged with the use of expansion groups and/or increased enrollment. Thus, we found that the probability that a patient would realistically respond to a novel drug in phase I testing was better captured by the ORR reported from each trial rather than the response rate weighted by the sample size of each trial.

There has been variability in earlier reports regarding the relationship between dose–response and outcomes, including some that proposed that low and intermediate doses seem to have the best outcomes.[11–13] In our study, we found that among 2,506 patients in whom response could be correlated with dose, there was a positive relationship between dose level and total response rate (see Figure 2), with the greatest response rate (29%) occurring at a higher dose level (>120%) than the RP2D but still with notable responses (12%) at ≤40% of the RP2D. These findings are in sharp contrast with those for cytotoxic agents, which normally show the greatest response rate at 81% to 120% of the RP2D and the lowest response rates at ≤40% of the RP2D due to insufficient dose and at >120% possibly due to toxicities.[1]

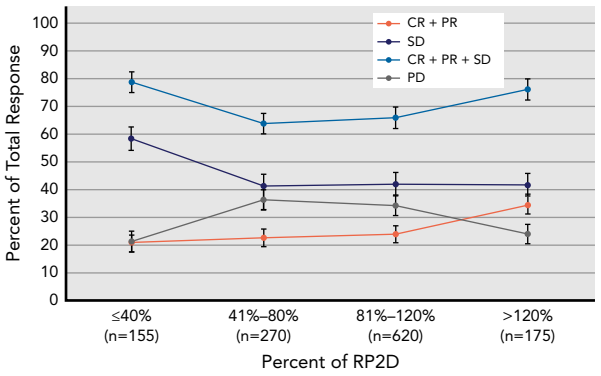

Figure 5. Response rate for nonantibody-targeted inhibitor (n=1,220).
Abbreviations: CR, complete response; PR, partial response; PD, progressive disease, RP2D, recommended phase II dose; SD, stable disease.

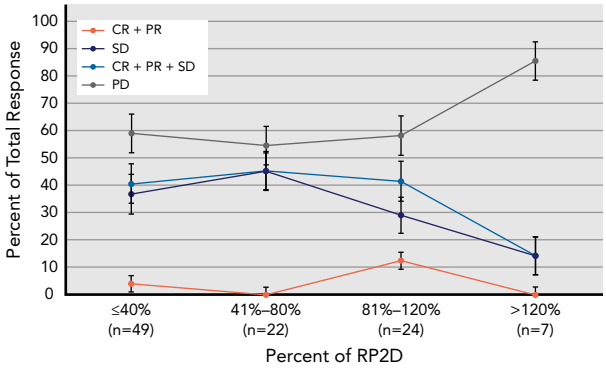

Figure 6. Response rate for vaccine/cellular therapy (n=102).
Abbreviations: CR, complete response; PR, partial response; PD, progressive disease, RP2D, recommended phase II dose; SD, stable disease.

The dose–response curves for each drug class all had varying patterns. Interestingly, the targeted antibody class peaked at 81% to 120% of the RP2D, similar to what is expected with cytotoxic agents, but this class also had high proportions of SD across all levels of RP2D (see Figure 3). The dose–response curves for immunotherapy (Figure 4) and nonantibody targeted agents (Figure 5) both had response rates peaking at >120% of the RP2D but still had response rates of 19% and 21%, respectively, observed at ≤40% of the RP2D. High rates of disease progression for vaccine and cellular therapies across all dose levels are observed due to the fact that these technologies are still premature for most cancers. Given these data, selecting an intermediate dose level of a targeted biologic, small-molecule targeted inhibitor, or immunotherapy agent showing promising efficacy for future trials could still provide reliable disease stability, even if true treatment response is seen at higher doses. In addition, a time-to-event endpoint, such as overall survival or progression-free survival, in phase II/III trials is a better determination of treatment benefit for many cancers, because these endpoints account for durable disease control and are often seen in immunotherapy, targeted biologic, and small-molecule targeted inhibitors. A more conservative dose selection may balance the risk/benefit profile of an investigational drug in subsequent trials, especially when some adverse effects are atypical or occur long after the treatment period. However, these hypotheses should be further explored with other systematic reviews that correlate the relationship between phase I trials and subsequent phase II/III trials.

As oncology drug development focuses more on novel drug classes, an increasing number of studies are using endpoints such as drug levels, drug metabolism, and preliminary efficacy rather than conventional toxicity endpoints.[14] Some studies fail to achieve an MTD or have little rationale for the dose recommended for a phase II trial.[15] These findings likely contributed to the nonclassic patterns of dose–response relationship seen in our analysis. More refined toxicity evaluation, a definition of MTD, and a dose selection with respect to drug class and response are all areas of focus for future investigations. These patterns reflect the observation that contemporary dose-finding designs need to be restructured.

Our study has several limitations. First, our analysis is limited to published dose-finding phase I trials. Earlier research has established that not all phase I trials conducted are represented in the literature, nor do all phase I trials report specific dose levels, RP2D, and efficacy data by dose levels.[16–19] Whether our results would materially change with the addition of unpublished trials remains unknown but warrants exploration.

Second, our study was limited to phase I studies that only tested a single agent. There are phase I studies that include novel therapies in combination with other agents. We also note that some phase I studies have tested different dose schedules rather than dose levels.

Third, our results reflect unique agents studied during our stated time period and may not apply to other highly promising targets or newer agents. Similarly, our analysis tended to favor targeted agents because this class of drug type was more readily studied during our stated time frame, likely because of the decreased focus on cytotoxic chemotherapy. We would expect a shift to occur as more phase I studies further expand on CAR T-cell therapy and immunotherapy.

Fourth, most studies did not provide toxicity data for individual patient results. Although these data were not the main focus of our study, it would be interesting to know how dose–response levels correlated, if at all, with toxicity. Future studies could also systematically measure how well toxicities are captured in a phase I study compared with later-phase trials, and how the RP2D in phase I trials translates into actual doses used in phase II and III trials.

Fifth, we did not have access to all patient data for each phase I study. Our hope is that future phase I studies will make patient data readily available for systematic analyses.

Finally, our search strategy was broad, limited to one search engine, and involved individual analysis of >800 articles. We may have missed some phase I trials during our search time frame. For these reasons, we again encourage future investigators to add to our analyses as new phase I trials become available.

Conclusions

This study of published phase I oncology trials shows a modest response rate among all tested agents (~5%), in line with results of earlier studies, and the relationship between

response and dose may vary by class of agent, with novel nonantibody targeted inhibitors and immunotherapies especially deviating from a classic, positive relationship between dose level and treatment response. These results should be confirmed and further studied with a determination of the risk/benefit balance to better inform optimal dose selection for subsequent trials.

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eTable 1. Characteristics of Initially Pooled Phase I Trials (N=175)

General Characteristic	n (%)
Study design	
Total pooled studies, N	175
Dose escalation study	128 (73)
Dose expansion study	3 (2)
Dose expansion + escalation study	23 (13)
1- or 2-dose-level study	21 (12)
Identified as phase I or II study	9 (7)
Median dose level (range)	4 (1–14)
Response rates	
Median ORR (range), %	5 (0–83)
Studies with response rate >0%	113 (65)
Median response rate per drug class, %	
Nonantibody targeted inhibitor/targeted antibody	4
Immunotherapy/Vaccine/CAR T-cell therapy	15
Chemotherapy/Hormonal therapy	0
Representation of therapy class in all studies	
Nonantibody targeted inhibitor	83 (47)
Targeted antibody	42 (24)
Immunotherapy	23 (13)
Chemotherapy	8 (5)
Vaccine therapy	9 (5)
CAR T-cell therapy	7 (4)
Hormonal therapy	3 (2)
Unique therapies, n	145
Patient characteristics	
Patients enrolled, n	7,330
CR	273 (4)
PR	767 (11)
SD	2,531 (35)
PD	2,929 (40)
Median duration of response (range), mo	5.6 (1–23)
Median progression-free survival (range), mo	4.2 (1–30)
Cancer types, n	50
Cancer representation of all patients	
Lung	889 (12)
Colorectal	859 (12)
Breast	792 (11)
Leukemia	668 (9)
Lymphoma	401 (5)
Ovarian	359 (5)
Multiple myeloma	279 (4)
Not reported or not cancer-specific	278 (4)
Renal	254 (3)
Sarcoma	251 (3)
Prostate	232 (3)
Melanoma	215 (3)
Liver	187 (3)
Other[a] (<3%)	1,666 (23)

Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response; PD, progressive disease; SD, stable disease.
[a]Head and neck, pancreatic, mesothelioma, glioblastoma, esophageal, urothelial, gastric, skin, Merkel cell, cervical, neuroendocrine, cancer of unknown primary, myelodysplastic syndromes, bladder, endometrial, cholangiocarcinoma, anal, uterine, thyroid, adrenal, central nervous system, lymphoma, melanoma, gastrointestinal stromal tumor, thymus, ampullary, peritoneal, bile duct, carcinoid, vulvar, testicular, appendiceal, penile, parotid, cardiac, and bone.

eTable 2. List of All Studies

PMID	Authors	Article Title	Journal
30040168	Iwasa S, et al	Dose-finding study of the checkpoint kinase 1 inhibitor, prexasertib, in Japanese patients with advanced solid tumors	Cancer Sci
30014244	Gargett T, et al	Phase I trial of Lipovaxin-MM, a novel dendritic cell-targeted liposomal vaccine for malignant melanoma	Cancer Immunol Immunother
30039554	Usuki K, et al	Clinical profile of gilteritinib in Japanese patients with relapsed/refractory acute myeloid leukemia: an open-label phase 1 study	Cancer Sci
29972716	Murakami, H et al	Clinical activity of ASP8273 in Asian patients with non-small-cell lung cancer with EGFR activating and T790M mutations	Cancer Sci
29863979	Migden MR, et al	PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma	N Engl J Med
29860938	DiNardo CD, et al	Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML	N Engl J Med
29567081	Beatty GL, et al	Activity of mesothelin-specific chimeric antigen receptor T cells against pancreatic carcinoma metastases in a phase 1 trial	Gastroenterology
29434192	Kater AP, et al	Final results of a phase 1b study of the safety and efficacy of the PI3Kδ inhibitor acalisib (GS-9820) in relapsed/refractory lymphoid malignancies	Blood Cancer J
29423683	Tanaka H, et al	A phase I study of afatinib for patients aged 75 or older with advanced non–small cell lung cancer harboring EGFR mutations	Med Oncol
29385376	Park JH, et al	Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia	N Engl J Med
29363250	Kiura K, et al	Osimertinib in patients with epidermal growth factor receptor T790M advanced non–small cell lung cancer selected using cytology samples	Cancer Sci
29284010	O'Neil BH, et al	Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma	PLoS One
29225263	Ri M, et al	A phase I/II study for dose-finding, and to investigate the safety, pharmacokinetics and preliminary efficacy of NK012, an SN-38-incorporating macromolecular polymeric micelle, in patients with multiple myeloma	Intern Med
29145039	Angevin E, et al	A first-in-human phase I study of SAR125844, a selective MET tyrosine kinase inhibitor, in patients with advanced solid tumors with MET amplification	Eur J Cancer
29144985	Navada SC, et al	A phase 1/2 study of rigosertib in patients with myelodysplastic syndromes (MDS) and MDS progressed to acute myeloid leukemia	Leuk Res
29095678	Frenel JS, et al	Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: results from the phase Ib KEYNOTE-028 trial	J Clin Oncol
29075855	van den Bent M, et al	Efficacy of depatuxizumab mafodotin (ABT-414) monotherapy in patients with EGFR-amplified, recurrent glioblastoma: results from a multicenter, international study	Cancer Chemother Pharmacol
29074098	Shaw AT, et al	Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial	Lancet Oncol
29063313	Dirix LY, et al	Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study	Breast Cancer Res Treat
29059492	Doi T, et al	Phase I study of single-agent ribociclib in Japanese patients with advanced solid tumors	Cancer Sci
29055839	Schöffski P, et al	First-in-man phase I study assessing the safety and pharmacokinetics of a 1-hour intravenous infusion of the doxorubicin prodrug DTS-201 every 3 weeks in patients with advanced or metastatic solid tumors	Eur J Cancer
29018077	Kumar S, et al	Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma	Blood
28972963	Papadopoulos KP, et al	A phase 1 study of ARQ 087, an oral pan-FGFR inhibitor in patients with advanced solid tumors	Br J Cancer
28954786	Yu HA, et al	A phase I, dose escalation study of oral ASP8273 in patients with nonsmall cell lung cancers with epidermal growth factor receptor mutations	Clin Cancer Res
28954784	Jimeno A, et al	A first-in-human phase I study of the anticancer stem cell agent ipafricept (OMP-54F28), a decoy receptor for Wnt ligands, in patients with advanced solid tumors	Clin Cancer Res
28949050	Ueda Y, et al	Phase 1/2 study of the WT1 peptide cancer vaccine WT4869 in patients with myelodysplastic syndrome	Cancer Sci

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eTable 2. List of All Studies (cont.)

PMID	Authors	Article Title	Journal
28859471	Kim TM, et al	Phase 1 studies of poziotinib, an irreversible pan-HER tyrosine kinase inhibitor in patients with advanced solid tumors	Cancer Res Treat
28597723	Goyal S, et al	Minimal activity of nanoparticle albumin-bound (nab) paclitaxel in relapsed or refractory lymphomas: results of a phase-I study	Leuk Lymphoma
28841236	Abaza YM, et al	Phase 1 dose escalation multicenter trial of pracinostat alone and in combination with azacitidine in patients with advanced hematologic malignancies	Cancer
28817190	Shah JJ, et al	A Phase 1 and 2 study of Filanesib alone and in combination with low-dose dexamethasone in relapsed/refractory multiple myeloma	Cancer
28801852	Matsubara N, et al	Phase 1 study of darolutamide (ODM-201): a new-generation androgen receptor antagonist, in Japanese patients with metastatic castration-resistant prostate cancer	Cancer Chemother Pharmacol
28391576	Lee SJ, et al	Phase I trial and pharmacokinetic study of tanibirumab, a fully human monoclonal antibody to vascular endothelial growth factor receptor 2, in patients with refractory solid tumors	Invest New Drugs
28813164	Ott PA, et al	Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study	J Clin Oncol
28855356	Heery CR, et al	Phase I study of a poxviral TRICOM-based vaccine directed against the transcription factor brachyury	Clin Cancer Res
28765328	Aftimos P, et al	Phase I dose-escalation study of the anti-CD70 antibody ARGX-110 in advanced malignancies	Clin Cancer Res
28763368	Steffensen KD, et al	Veliparib monotherapy to patients with BRCA germ line mutation and platinum-resistant or partially platinum-sensitive relapse of epithelial ovarian cancer: a phase I/II study	Int J Gynecol Cancer
28973403	Doi T, et al	A Phase 1/1b tolerability study of rilotumumab alone or in combination with cisplatin and capecitabine in Japanese patients with gastric cancer	Jpn J Clin Oncol
29037983	Doi T, et al	Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-esophageal tumors: a phase 1 dose-escalation study	Lancet Oncol
28854070	Goetz MP, et al	First-in-human phase I study of the tamoxifen metabolite Z-endoxifen in women with endocrine-refractory metastatic breast cancer	J Clin Oncol
28817371	Dotan E, et al	Phase I/II trial of labetuzumab govitecan (anti-CEACAM5/SN-38 antibody-drug conjugate) in patients with refractory or relapsing metastatic colorectal cancer	J Clin Oncol
28558150	Ocean AJ, et al	Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate for the treatment of diverse epithelial cancers: safety and pharmacokinetics	Cancer
28608115	Sonpavde G, et al	Phase I trial of antigen-targeted autologous dendritic cell-based vaccine with in vivo activation of inducible CD40 for advanced prostate cancer	Cancer Immunol Immunother
28655795	Papadopoulos KP, et al	First-in-human study of AMG 820, a monoclonal anti-colony-stimulating factor 1 receptor antibody, in patients with advanced solid tumors	Clin Cancer Res
28645941	Mateo J, et al	A first-time-in-human study of GSK2636771, a phosphoinositide 3 kinase beta-selective inhibitor, in patients with advanced solid tumors	Clin Cancer Res
28864289	Boyiadzis M, et al	Phase 1 clinical trial of adoptive immunotherapy using "off-the-shelf" activated natural killer cells in patients with refractory and relapsed acute myeloid leukemia	Cytotherapy
28498781	Ma F, et al	Phase I study and biomarker analysis of pyrotinib, a novel irreversible pan-ErbB receptor tyrosine kinase inhibitor, in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer	J Clin Oncol
28615371	Paik PK, et al	A phase Ib open-label multicenter study of AZD4547 in patients with advanced squamous cell lung cancers	Clin Cancer Res
28899363	Reynolds KL, et al	A phase I open-label dose-escalation study of the anti-HER3 monoclonal antibody LJM716 in patients with advanced squamous cell carcinoma of the esophagus or head and neck and HER2-overexpressing breast or gastric cancer	BMC Cancer
28619981	Grommes C, et al	Ibrutinib unmasks critical role of Bruton tyrosine kinase in primary CNS lymphoma	Cancer Discov

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eTable 2. List of All Studies (cont.)

PMID	Authors	Article Title	Journal
28665051	Nishikawa T, et al	Phase 1 dose-escalation study of single-agent veliparib in Japanese patients with advanced solid tumors	Cancer Sci
28490463	Juric D, et al	A first-in-human, phase I, dose-escalation study of TAK-117, a selective PI3Kα isoform inhibitor, in patients with advanced solid malignancies	Clin Cancer Res
28805662	Ramos CA, et al	Clinical and immunologic responses after CD30-specific chimeric antigen receptor-redirected lymphocytes	J Clin Invest
28440955	Moore KN, et al	Phase 1 dose-escalation study of mirvetuximab soravtansine (IMGN853), a folate receptor α-targeting antibody-drug conjugate, in patients with solid tumors	Cancer
28468947	Lee JM, et al	Phase I trial of intratumoral injection of CCL21 gene-modified dendritic cells in lung cancer elicits tumor-specific immune responses and CD8+ T-cell infiltration	Clin Cancer Res
28420720	Britten CD, et al	A phase I study of ABC294640, a first-in-class sphingosine kinase-2 inhibitor, in patients with advanced solid tumors	Clin Cancer Res
28719152	Izar B, et al	A first-in-human phase I, multicenter, open-label, dose-escalation study of the oral RAF/VEGFR-2 inhibitor (RAF265) in locally advanced or metastatic melanoma independent from BRAF mutation status	Cancer Med
28331050	Stein MN, et al	First-in-human clinical trial of oral ONC201 in patients with refractory solid tumors	Clin Cancer Res
28161886	LoRusso PM, et al	Phase 1 study of narnatumab, an anti-RON receptor monoclonal antibody, in patients with advanced solid tumors	Invest New Drugs
28426845	Ahmed N, et al	HER2-specific chimeric antigen receptor-modified virus-specific T cells for progressive glioblastoma: a phase 1 dose-escalation trial	JAMA Oncol
28582510	Yasui H, et al	A phase 1 study evaluating AMG 337 in Asian patients with advanced solid tumors	Jpn J Clin Oncol
27911138	Vey N, et al	Phase 1 dose-escalation study of oral abexinostat for the treatment of patients with relapsed/refractory higher-risk myelodysplastic syndromes, acute myeloid leukemia, or acute lymphoblastic leukemia	Leuk Lymphoma
28490569	Zinzani PL, et al	Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma	Blood
28053022	Moulder SL, et al	Phase I study of ONT-380, a HER2 inhibitor, in patients with HER2+-advanced solid tumors, with an expansion cohort in HER2+ metastatic breast cancer (MBC)	Clin Cancer Res
28498618	Obara W, et al	Phase I clinical trial of cell division associated 1 (CDCA1) peptide vaccination for castration resistant prostate cancer	Cancer Sci
28053021	Beatty GL, et al	first-in-human phase I study of the oral inhibitor of indoleamine 2,3-dioxygenase-1 epacadostat (incb024360) in patients with advanced solid malignancies	Clin Cancer Res
28531881	Keilholz U, et al	First-in-man dose escalation and pharmacokinetic study of CAP7.1, a novel prodrug of etoposide, in adults with refractory solid tumors	Eur J Cancer
28375787	Apolo AB, et al	Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study	J Clin Oncol
28159938	Xu JM, et al	Sulfatinib, a novel kinase inhibitor, in patients with advanced solid tumors: results from a phase I study	Oncotarget
28434648	El-Khoueiry AB, et al	Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, noncomparative, phase 1/2 dose escalation and expansion trial	Lancet
28336527	Garzon R, et al	A phase 1 clinical trial of single-agent selinexor in acute myeloid leukemia	Blood
28463960	Bahleda R, et al	Phase I dose-escalation studies of roniciclib, a pan-cyclin-dependent kinase inhibitor, in advanced malignancies	Br J Cancer
28242752	de Bono J, et al	Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline BRCA1/2 mutations and selected sporadic cancers	Cancer Discov
28150073	Fu S, et al	First-in-human phase I study of SOR-C13, a TRPV6 calcium channel inhibitor, in patients with advanced solid tumors	Invest New Drugs

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PMID	Authors	Article Title	Journal
28070718	Shapiro G, et al	First-in-human trial of an anti-5T4 antibody-monomethylauristatin conjugate, PF-06263507, in patients with advanced solid tumors	Invest New Drugs
28465370	Cao J, et al	Phase I dose-escalation study of ramucirumab in Chinese patients with advanced solid tumors	Oncologist
27902470	Zhang T, et al	Phase I study of QLNC120, a novel EGFR and HER2 kinase inhibitor, in pretreated patients with HER2-overexpressing advanced breast cancer	Oncotarget
28366766	Zhang C, et al	Phase I escalating-dose trial of CAR-T therapy targeting CEA+ metastatic colorectal cancers	Mol Ther
28453692	Ott PA, et al	Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal	Ann Oncol
28266765	Taniguchi H, et al	Phase 1 study of OCV-C02, a peptide vaccine consisting of two peptide epitopes for refractory metastatic colorectal cancer	Cancer Sci
28324749	de Jonge M, et al	A phase I study of SAR405838, a novel human double minute 2 (HDM2) antagonist, in patients with solid tumors	Eur J Cancer
28373007	Heery CR, et al	Avelumab for metastatic or locally advanced previously treated solid tumors (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial	Lancet Oncol
28373005	Gulley JL, et al	Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial	Lancet Oncol
28291584	Alley EW, et al	Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a nonrandomized, open-label, phase 1b trial	Lancet Oncol
28291776	Angevin E, et al	First-in-human phase 1 of YS110, a monoclonal antibody directed against CD26 in advanced CD26-expressing cancers	Br J Cancer
28240971	Wagner AJ, et al	Phase I trial of the human double minute 2 inhibitor MK-8242 in patients with advanced solid tumors.	J Clin Oncol
27803065	Rosen LS, et al	A first-in-human phase I study of a bivalent MET antibody, emibetuzumab (LY2875358), as monotherapy and in combination with erlotinib in advanced cancer	Clin Cancer Res
28168303	Hui R, et al	Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced nonsmall cell lung cancer: a phase 1 trial	Ann Oncol
28119295	Bang YJ, et al	First-in-human phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors	Ann Oncol
28283736	Yamazaki N, et al	Phase 1b study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in Japanese patients with advanced melanoma (KEYNOTE-041)	Cancer Chemother Pharmacol
28280971	Tolcher AW, et al	A phase 1 study of anti-TGFβ receptor type-II monoclonal antibody LY3022859 in patients with advanced solid tumors	Cancer Chemother Pharmacol
27928714	Yamamoto N, et al	Phase I study of nivolumab, an anti-PD-1 antibody, in patients with malignant solid tumors	Invest New Drugs
28029313	Moore KN, et al	Safety and activity of mirvetuximab soravtansine (IMGN853), a folate receptor alpha-targeting antibody-drug conjugate, in platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a phase I expansion study	J Clin Oncol
28158463	Nokihara H, et al	A phase 1 study of ramucirumab in Japanese patients with advanced solid tumors	Jpn J Clin Oncol
28344808	Hege KM, et al	Safety, tumor trafficking and immunogenicity of chimeric antigen receptor (CAR)-T cells specific for TAG-72 in colorectal cancer	J Immunother Cancer
27601593	Advani RH, et al	Phase I study of the anti-CD22 antibody-drug conjugate pinatuzumab vedotin with/without rituximab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma	Clin Cancer Res
27582488	Wang CM, et al	Autologous T cells expressing CD30 chimeric antigen receptors for relapsed or refractory Hodgkin lymphoma: an open-label phase I trial	Clin Cancer Res
28073786	Yu HA, et al	Phase 1 study of twice weekly pulse dose and daily low-dose erlotinib as initial treatment of patients with EGFR-mutant lung cancers	Ann Oncol
27826831	Rampurwala M, et al	Phase 1b study of orteronel in postmenopausal women with hormone-receptor positive (HR+) metastatic breast cancer	Invest New Drugs

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eTable 2. List of All Studies (cont.)

PMID	Authors	Article Title	Journal
27650277	Adjei AA, et al	A phase I dose-escalation study of TAK-733, an investigational oral MEK inhibitor, in patients with advanced solid tumors	Invest New Drugs
28081914	Plimack ER, et al	Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a nonrandomized, open-label, phase 1b study	Lancet Oncol
28143428	Miyamoto S, et al	BK-UM in patients with recurrent ovarian cancer or peritoneal cancer: a first-in-human phase-I study	BMC Cancer
27673440	Ragon BK, et al	Buparlisib, a PI3K inhibitor, demonstrates acceptable tolerability and preliminary activity in a phase I trial of patients with advanced leukemias	Am J Hematol
27915408	Doi T, et al	A phase I study of intravenous PI3K inhibitor copanlisib in Japanese patients with advanced or refractory solid tumors	Cancer Chemother Pharmacol
28122892	Ishizawa K, et al	Safety, efficacy and pharmacokinetics of humanized anti-CD52 monoclonal antibody alemtuzumab in Japanese patients with relapsed or refractory B-cell chronic lymphocytic leukemia	Jpn J Clin Oncol
27932068	Rudin CM, et al	Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study	Lancet Oncol
27733373	Soria JC, et al	A phase I, pharmacokinetic and pharmacodynamic study of GSK2256098, a focal adhesion kinase inhibitor, in patients with advanced solid tumors	Ann Oncol
27627050	Okusaka T, et al	Phase I study of nintedanib in Japanese patients with advanced hepatocellular carcinoma and liver impairment	Cancer Sci
27542767	Infante JR, et al	A phase I study of the cyclin-dependent kinase 4/6 inhibitor ribociclib (LEE011) in patients with advanced solid tumors and lymphomas	Cancer Sci
27595901	Mukai H, et al	Phase I study of NK105, a nanomicellar paclitaxel formulation, administered on a weekly schedule in patients with solid tumors	Invest New Drugs
26926685	Abdul Razak AR, et al	First-in-class, first-in-human phase I study of selinexor, a selective inhibitor of nuclear export, in patients with advanced solid tumors	J Clin Oncol
27920527	Coriat R, et al	Pharmacokinetics and safety of DTS-108, a human oligopeptide bound to SN-38 with an esterase-sensitive cross-linker in patients with advanced malignancies: a phase I study	Int J Nanomedicine
27169994	Choueiri TK, et al	Immunomodulatory activity of nivolumab in metastatic renal cell carcinoma	Clin Cancer Res
27793850	Liu JF, et al	Phase I study of safety and pharmacokinetics of the anti-MUC16 antibody-drug conjugate DMUC5754A in patients with platinum-resistant ovarian cancer or unresectable pancreatic cancer	Ann Oncol
27793950	Wu YL, et al	Phase I study of the pan-PI3K inhibitor buparlisib in adult Chinese patients with advanced solid tumors	Anticancer Res
27628194	Tamura Y, et al	Phase I study of the second-generation, recombinant, human EGFR antibody necitumumab in Japanese patients with advanced solid tumors	Tamura Y
27734609	Reed GA, et al	A phase 1 study of intravenous infusions of tigecycline in patients with acute myeloid leukemia	Cancer Med
27797971	Khalil DN, et al	An open-label, dose-escalation phase I study of anti-TYRP1 monoclonal antibody IMC-20D7S for patients with relapsed or refractory melanoma	Clin Cancer Res
27693888	Jamieson D, et al	A phase I pharmacokinetic and pharmacodynamic study of the oral mitogen-activated protein kinase (MEK) inhibitor, WX-554, in patients with advanced solid tumors	Eur J Cancer
27789778	Liu J, et al	A phase I study of the safety and pharmacokinetics of higher-dose icotinib in patients with advanced non-small cell lung cancer	Oncologist
27178743	Almhanna K, et al	Phase I study of the investigational anti-guanylyl cyclase antibody-drug conjugate TAK-264 (MLN0264) in adult patients with advanced gastrointestinal malignancies	Clin Cancer Res
27528724	Naing A, et al	Safety, antitumor activity, and immune activation of pegylated recombinant human interleukin-10 (AM0010) in patients with advanced solid tumors	J Clin Oncol
27672108	Patnaik A, et al	First-in-human phase I study of copanlisib (BAY 80-6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas	Ann Oncol
27467121	Minami H, et al	Phase I, multicenter, open-label, dose-escalation study of sonidegib in Asian patients with advanced solid tumors	Cancer Sci

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eTable 2. List of All Studies (cont.)

PMID	Authors	Article Title	Journal
27422720	Yoh K, et al	A phase I dose-escalation study of LY2875358, a bivalent MET antibody, given as monotherapy or in combination with erlotinib or gefitinib in Japanese patients with advanced malignancies	Invest New Drugs
27363843	Mizugaki H, et al	Phase I dose-finding study of monotherapy with atezolizumab, an engineered immunoglobulin monoclonal antibody targeting PD-L1, in Japanese patients with advanced solid tumors	Invest New Drugs
27117181	Harrison SJ, et al	Phase I clinical trial of marizomib (NPI-0052) in patients with advanced malignancies including multiple myeloma: study NPI-0052-102 final results	Clin Cancer Res
27076631	Dowlati A, et al	A phase I, first-in-human study of AMG 780, an angiopoietin-1 and -2 inhibitor, in patients with advanced solid tumors	Clin Cancer Res
27458288	Gounder MM, et al	Phase IB study of selinexor, a first-in-class inhibitor of nuclear export, in patients with advanced refractory bone or soft tissue sarcoma	J Clin Oncol
27329247	Simonelli M	Phase I study of PF-03446962, a fully human monoclonal antibody against activin receptor-like kinase-1, in patients with hepatocellular carcinoma	Ann Oncol
27449137	Beg MS, et al	A phase 1 dose-escalation study of NEO-102 in patients with refractory colon and pancreatic cancer	Cancer Chemother Pharmacol
27422301	Yonemori K, et al	Safety and tolerability of the olaparib tablet formulation in Japanese patients with advanced solid tumors	Cancer Chemother Pharmacol
27169385	Badar T, et al	Phase I study of evofosfamide, an investigational hypoxia-activated prodrug, in patients with advanced leukemia	Am J Hematol
27349901	Mross K, et al	A phase I study of BI 811283, an Aurora B kinase inhibitor, in patients with advanced solid tumors	Cancer Chemother Pharmacol
27299749	Cao J, et al	A phase I study of safety and pharmacokinetics of fruquintinib, a novel selective inhibitor of vascular endothelial growth factor receptor-1, -2, and -3 tyrosine kinases in Chinese patients with advanced solid tumors	Cancer Chemother Pharmacol
27285281	Fiedler W, et al	A phase I study of PankoMab-GEX, a humanized glyco-optimized monoclonal antibody to a novel tumor-specific MUC1 glycopeptide epitope in patients with advanced carcinomas	Eur J Cancer
27056178	Bhatia S, et al	A phase I study of the investigational NEDD8-activating enzyme inhibitor pevonedistat (TAK-924/MLN4924) in patients with metastatic melanoma	Invest New Drugs
27480598	Siefker-Radtke A, et al	A phase I study of a tumor-targeted systemic nanodelivery system, SGT-94, in genitourinary cancers	Mol Ther
27138582	Nanda R, et al	Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study	J Clin Oncol
27169794	Bechter OE, et al	Phase I safety and pharmacokinetic dose-escalation study of pilaralisib polymorph E, a phosphoinositide 3-kinase inhibitor in tablet formulation, in patients with solid tumors or lymphoma	Cancer Chemother Pharmacol
27151992	Brown JR, et al	Phase I study of single-agent CC-292, a highly selective Bruton's tyrosine kinase inhibitor, in relapsed/refractory chronic lymphocytic leukemia	Haematologica
27100354	Schäfer N, et al	Phase I trial of dovitinib (TKI258) in recurrent glioblastoma	J Cancer Res Clin Oncol
27247226	Seiwert TY, et al	Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial	Lancet Oncol
26787751	Dolly SO, et al	Phase I study of apitolisib (GDC-0980), dual phosphatidylinositol-3-kinase and mammalian target of rapamycin kinase inhibitor, in patients with advanced solid tumors	Clin Cancer Res
27009059	Richardson PG, et al	Phase 1 study of marizomib in relapsed or relapsed and refractory multiple myeloma: NPI-0052-101 part 1	Blood
27022067	Chi KN, et al	A phase I dose-escalation study of apatorsen (OGX-427), an antisense inhibitor targeting heat shock protein 27 (Hsp27), in patients with castration-resistant prostate cancer and other advanced cancers	Ann Oncol
27071922	Watanabe K, et al	A phase I study of binimetinib (MEK162) in Japanese patients with advanced solid tumors	Cancer Chemother Pharmacol
26991823	Tamura K, et al	Phase I study of palbociclib, a cyclin-dependent kinase 4/6 inhibitor, in Japanese patients	Cancer Sci

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eTable 2. List of All Studies (cont.)

PMID	Authors	Article Title	Journal
26961907	Shah MH, et al	Phase I study of IMGN901, a CD56-targeting antibody-drug conjugate, in patients with CD56-positive solid tumors	Invest New Drugs
27081038	Vey N, et al	Phase I clinical study of RG7356, an anti-CD44 humanized antibody, in patients with acute myeloid leukemia	Oncotarget
27044938	Johnson FM, et al	Phase I study of LY2606368, a checkpoint kinase 1 inhibitor, in patients with advanced cancer	J Clin Oncol
27025608	Shimizu T, et al	A first-in-Asian phase 1 study to evaluate safety, pharmacokinetics and clinical activity of VS-6063, a focal adhesion kinase (FAK) inhibitor in Japanese patients with advanced solid tumors	Cancer Chemother Pharmacol
26920496	Iwasa S, et al	Phase I study of a new cancer vaccine of ten mixed peptides for advanced cancer patients	Cancer Sci
26655846	Goff LW, et al	A phase I study of the anti-activin receptor-like kinase 1 (ALK-1) monoclonal antibody PF-03446962 in patients with advanced solid tumors	Clin Cancer Res
27049457	Younes A, et al	Safety, tolerability, and preliminary activity of CUDC-907, a first-in-class, oral, dual inhibitor of HDAC and PI3K, in patients with relapsed or refractory lymphoma or multiple myeloma: an open-label, dose-escalation, phase 1 trial	Lancet Oncol
27091421	Agarwal N, et al	Phase I study of the prolactin receptor antagonist LFA102 in metastatic breast and castration-resistant prostate cancer	Oncologist
27115568	Mahalingam D, et al	Mipsagargin, a novel thapsigargin-based PSMA-activated prodrug: results of a first-in-man phase I clinical trial in patients with refractory, advanced or metastatic solid tumors	Br J Cancer
27008709	Soliman HH, et al	A phase I study of indoximod in patients with advanced malignancies	Oncotarget
26603258	Munster P, et al	First-in-human phase I study of GSK2126458, an oral pan-class I phosphatidylinositol-3-kinase inhibitor, in patients with advanced solid tumor malignancies	Clin Cancer Res
26931343	Tamura K, et al	Safety and tolerability of AZD5363 in Japanese patients with advanced solid tumors	Cancer Chemother Pharmacol
26792581	Cirkel GA, et al	A dose escalating phase I study of GLPG0187, a broad spectrum integrin receptor antagonist, in adult patients with progressive high-grade glioma and other advanced solid malignancies	Invest New Drugs
26884582	Goebeler ME, et al	Bispecific T-cell engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: final results from a phase I study	J Clin Oncol
26490310	Papadopoulos KP, et al	A phase I first-in-human study of nesvacumab (REGN910), a fully human anti-angiopoietin-2 (Ang2) monoclonal antibody, in patients with advanced solid tumors	Clin Cancer Res
26755520	McDermott DF, et al	Atezolizumab, an anti-programmed death-ligand 1 antibody, in metastatic renal cell carcinoma: long-term safety, clinical activity, and immune correlates from a phase Ia study	J Clin Oncol
26966027	Li T, et al	First-in-human, open-label dose-escalation and dose-expansion study of the safety, pharmacokinetics, and antitumor effects of an oral ALK inhibitor ASP3026 in patients with advanced solid tumors	J Hematol Oncol
26732066	Watanabe T, et al	A phase 1/2 study of carfilzomib in Japanese patients with relapsed and/or refractory multiple myeloma	Br J Haematol
26791870	Bruce JY, et al	A pharmacodynamically guided dose selection of PF-00337210 in a phase I study in patients with advanced solid tumors	Cancer Chemother Pharmacol
26823490	Weekes CD, et al	Phase I study of DMOT4039A, an antibody-drug conjugate targeting mesothelin, in patients with unresectable pancreatic or platinum-resistant ovarian cancer	Mol Cancer Ther
26463709	Meulendijks, D et al	First-in-human phase I study of lumretuzumab, a glycoengineered humanized anti-HER3 monoclonal antibody, in patients with metastatic or advanced HER3-positive solid tumors	Clin Cancer Res

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eTable 2. List of All Studies (cont.)

PMID	Authors	Article Title	Journal
26446947	Patnaik A, et al	Safety, pharmacokinetics, and pharmacodynamics of a humanized anti-semaphorin 4D antibody, in a first-in-human study of patients with advanced solid tumors	Clin Cancer Res
26542378	Walter HS, et al	A phase 1 clinical trial of the selective BTK inhibitor ONO/GS-4059 in relapsed and refractory mature B-cell malignancies	Blood
26639348	Roberts AW, et al	Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia	N Engl J Med
26695442	Yong K, et al	Phase I study of KW-2478, a novel Hsp90 inhibitor, in patients with B-cell malignancies	Br J Cancer
25715767	Oh DY, et al	Phase I study of CKD-516, a novel vascular disrupting agent, in patients with advanced solid tumors	Cancer Res Treat
26561559	Shah JJ, et al	Phase I study of the novel investigational NEDD8-activating enzyme inhibitor pevonedistat (MLN4924) in patients with relapsed/refractory multiple myeloma or lymphoma	Clin Cancer Res
26530955	Nakamichi S, et al	A phase 1 study of lenvatinib, multiple receptor tyrosine kinase inhibitor, in Japanese patients with advanced solid tumors	Cancer Chemother Pharmacol

eTable 3. List of Drug Therapies
ABC294640
Abexinostat
Acalisib
Activated natural killer cells
Afatinib
Alemtuzumab
AM0010
AMG 337
AMG 780
AMG 820
Apatorsen
Apitolisib
ARGX-110
ARQ 087
ASP3026
ASP8273
Atezolizumab
Autologous HER2-chimeric antigen receptor (CAR) virus-specific T cells
Avelumab
AZD4547
AZD5363
BI811283
Binimetinib (MEK 162)
BK-UM (CRM197)
Blinatumomab
BPX-101
Buparlisib
CAP7.1
CAR T-cell-autologous (mesothelin-specific)
CAR T-cell—19-28z
CAR-T-cell—AG-72
CAR T-cell—CD30
CAR T-cell—CEA
Carfilzomib
CC-292
CCL21 gene vaccine
CDCA1 peptide vaccination
Cemiplimab
CKD-516
Copanlisib (BAY 80-6946)
CUDC-907
Darolutamide (ODM-201)
Depatuxizumab mafodotin
DMOT4039A
DMUC5754A

(continued)

eTable 3. List of Drug Therapies (cont.)
Dovitinib (TKI258)
DTS-108
DTS-201
Emibetuzumab
Epacadostat
Erlotinib
Evofosfamide
Filanesib (ARRY-520)
Fruquintinib (HMPL-013)
Gilteritinib
GLPG0187
GSK2126458
GSK2256098
GSK2636771
Ibrutinib
Icotinib
IMC-20D7S
IMGN901
Indoximod
Ipafricept (OMP-54F28)
Ivosidenib
KRM-10
KW-2478
Labetuzumab govitecan
Lenvatinib mesylate
LFA102
Lipovaxin-MM
LJM716
Lorlatinib
Lumretuzumab
LY2606368
LY2875358
LY3022859
Margetuximab (MGAH22)
Marizomib (NPI-0052)
Mipsagargin
Mirvetuximab soravtansine (IMGN853)
MK-8242
Modified vaccinia virus Ankara (MVA) vector-based vaccine
Nanoparticle albumin-bound (nab) paclitaxel
Narnatumab
Necitumumab
NEO-102 (ensituximab)
Nesvacumab (REGN910)
Nintedanib

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eTable 3. List of Drug Therapies (cont.)
Nivolumab
NK012
NK105
OCV-C02 (peptide vaccine)
Olaparib
ONC201
ONO/GS-4059
ONT-380 (ARRY-380)
Orteronel
Osimertinib mesylate
Palbociclib
PankoMab-GEX
Pembrolizumab
Pevonedistat (TAK-924/MLN4924)
PF-00337210
PF-03446962
PF-06263507
Pilaralisib
Pinatuzumab vedotin
Poziotinib
Pracinostat
Prexasertib
Pyrotinib
QLNC120
RAF265
Ramucirumab
RG7356
Ribociclib
Rigosertib sodium
Rilotumumab
Roniciclib
Rovalpituzumab tesirine
Sacituzumab govitecan
SAR125844
SAR405838
Selinexor (KPT-330)
SGT-94
Sonidegib
SOR-C13
Sulfatinib
TAK-117
TAK-264 (MLN0264)
TAK-733
Talazoparib tosylate
Tanibirumab

(continued)

eTable 3. List of Drug Therapies (cont.)
Tigecycline
Trastuzumab deruxtecan (DS-8201)
Veliparib
Venetoclax
VS-6063
VX15/2503
WT4869 (peptide vaccine)
WX-554
YS110
Z-endoxifen