ROADMAPS: An Online Database of Response Data, Dosing Regimens, and Toxicities of Approved Oncology Drugs as Single Agents to Guide Preclinical *In Vivo* Studies

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ABSTRACT

Preclinical studies provide valuable data in the early development of novel drugs for patients with cancer. Many cancer treatment regimens now utilize multiple agents with different targets to delay the emergence of drug-resistant tumor cells, and experimental agents are often evaluated in combination with FDA-approved drugs. The Biological Testing Branch (BTB) of the U.S. NCI has evaluated more than 70 FDA-approved oncology drugs to date in human xenograft models. Here, we report the first release of a publicly available, downloadable spreadsheet, ROADMAPS (Responses to Oncology Agents and Dosing in Models to Aid Preclinical Studies, dtp.cancer.gov/databases_tools/roadmaps. htm), that provides data filterable by agent, dose, dosing schedule, route of administration, tumor models tested, responses, host mouse strain, maximum weight loss, drug-related deaths, and vehicle formulation for preclinical experiments conducted by the BTB. Data from 70 different single targeted and cytotoxic agents and

140 different xenograft models were included. Multiple xenograft models were tested in immunocompromised mice for many cancer histologies, with lung cancer as the most broadly tested (24 models). Many of the dose levels and schedules used in these experiments were comparable with those tolerated in humans. Targeted and cytotoxic single agents were included. The online spreadsheet will be updated periodically as additional agent/dose/model combinations are evaluated. ROADMAPS is intended to serve as a publicly available resource for the research community to inform the design of clinically relevant, tolerable single and combinatorial regimens in preclinical mouse models.

Significance: ROADMAPS includes data that can be used to identify tolerable dosing regimens with activity against a variety of human tumors in different mouse strains, providing a resource for planning preclinical studies.

Introduction

Human tumor xenografts in mice are widely used models for translational studies of experimental anticancer agents (1). Several groups have reported that tumor responses in xenograft models correlate with clinical responses in humans (2–4). Data from patient-derived xenograft (PDX) models have demonstrated consistent results across multiple PDX Development and Trial Centers using varying standard operating procedures (5). Despite the potential predictive value of these experiments for clinical trials in humans, drug-dosing information and vehicle selection from xenograft preclinical studies are not always published. These studies are often the first indicators of reproducible drug activity and/or toxicity *in vivo*; the results can be used to inform further evaluation of the agents in appropriate solid tumor types (6–8). To our knowledge, these data

have never been compiled into a single searchable, publicly available database.

For more than 30 years, the NCI Biological Testing Branch (BTB) has maintained a public repository of human and rodent tumors and cell lines as a research resource for preclinical pharmacologic and pharmacodynamic studies (dtp.cancer.gov/organization/btb/ tumor_repositories.htm). In addition, the BTB actively evaluates the *in vivo* efficacy and the pharmacologic and pharmacodynamic characteristics of potential anticancer compounds (9–11). A critical component of these efforts is the design and conduct of xenograft and allograft studies to define the *in vivo* efficacy of new drugs and drug combinations (12). To facilitate preclinical study design in the research community, data collected by the BTB have been compiled into a spreadsheet named ROADMAPS (Responses to Oncology Agents and Dosing in Models to Aid Preclinical Studies, dtp.cancer.gov/databases_tools/roadmaps.htm). ROADMAPS includes data on drug dose, dosing schedule, route of administration, responsiveness (i.e., sensitive vs. resistant tumor types), maximum weight loss, drug-related deaths, and the drug formulation vehicle.

The NCI-60 cancer cell panel has been used for years as a screening tool for investigational agents (13). The ROADMAPS spreadsheet includes many cell lines from the NCI-60 panel, but those cell lines constitute less than half of the models included in ROADMAPS at the time of this writing (December, 2021). ROADMAPS, which currently includes data for 70 agents and 140 tumor models, can be filtered to highlight tolerable dosing regimens with activity against a variety of human tumors in different immunocompromised mouse strains and will therefore serve as a valuable resource for investigators in planning preclinical studies.

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Materials and Methods

Experimental models

NCI-60 cell lines used to generate the xenograft data in this report were obtained from the Division of Cancer Treatment and Diagnosis Tumor Repository (Developmental Therapeutics Program, Frederick National Laboratory for Cancer Research, Frederick, MD). Other cells lines or tumor fragments were provided by NCI investigators, purchased from the ATCC, Jackson Laboratories, or other commercial sources. All tissue procurement trials followed protocols approved by Institutional Review Boards and patients provided written informed consent. The identities of all cell lines used in this study were confirmed using Identifiler short tandem repeat (STR) genotyping (Applied Biosystems) since that technology became available; studies conducted prior to the advent of STR profiling could not be characterized in this manner. Each cell line was tested for *Mycoplasma* when it was accepted into the repository and at each new lot preparation. Routine *Mycoplasma* testing of cells in culture was not performed. All cell lines were screened for rodent and human viral pathogens prior to inoculation into mice using testing methodologies available at the time (e.g., mouse antibody production testing, PCR).

Agents

Agents were selected for testing in consultation with the NCI's Drug Synthesis and Chemistry Branch (DSCB), in response to requests from the NCI's Biological Evaluation Committee within the Developmental Therapeutics Program (DTP), or through other approved methods in the NCI's Division of Cancer Treatment and Diagnosis. Preparation and storage conditions varied by agent. While recommendations from the DSCB informed the handling of each agent, some broad generalizations can be reported. Agents requiring DMSO or ethanol were prepared in stock solutions at $10\times$ the desired concentration and frozen until ready to administer, at which time, stock solutions were thawed and diluted with 9 volumes of the appropriate vehicle. Water-soluble agents were stored as dry powders and resuspended in the appropriate vehicle prior to dosing. Doses were administered on the basis of individual animal body weights rather than group averages. Agents were administered via several routes. For intravenous administration, agents were injected into the lateral tail vein using 27- to 30-gauge needles with mice restrained in commercially available mouse restrainers. For intraperitoneal administration, agents were injected through the abdominal body wall using 23- to 25-gauge needles attached to 1 mL syringes while the mouse was held in the non–syringe-containing hand. For oral administration, agents were administered via 20- to 22-gauge malleable stainless steel feeding needles or flexible oral gavage needles. The standard dosing protocol called for drug solutions to be prepared at concentrations at which 0.1 mL of drug solution was administered per 10 g of body mass (i.e., 0.265 mL of solution would be administered to a 26.5 g mouse). This standardized procedure reduces the risk of dose calculation errors, ensures the dose (mg/kg) is administered accurately, and decreases the time required to perform the injections.

Xenograft studies

Animal experiments were performed at the Frederick National Laboratory for Cancer Research and the Southern Research Institute (SRI); both are accredited by Association for Assessment and Accreditation of Laboratory Animal Care International and follow the Public Health Service Policy for the Care and Use of Laboratory Animals. Animal care was provided in accordance with the procedures outlined in the Guide for Care and Use of Laboratory Animals (14).

Dosing schedules, route of drug administration, tumor models tested, and vehicle used for agent formulation were determined for each individual study following established methods and study designs developed in the BTB (12). For mouse inoculation, tumor cells were used at the fourth to sixth *in vitro* passage from cryopreserved cell stocks. Cells (typically 1×10^7 cells/0.1 mL/injection) were subcutaneously inoculated into female mice (nu/nu NCr mice or SCID/NCr mice) and therapeutic studies were initiated upon reaching a target tumor volume of 100 to 400 mm^3, depending upon the specific study design. Male mice were used for male-specific tumor models (e.g., prostate cancer models) and for other models when availability of female mice was limited. Many of these studies used serially passaged tumors following previously published methods (12). Briefly, donor tumors were harvested, cut into 2 to 3 mm^3 fragments, and implanted subcutaneously using a 9- to 11-gauge tumor implant trocar. Tumors were staged and the mice randomized into groups at the experimentally defined tumor volume ranges (e.g., 125–250 mg, 200–400 mg). More mice were implanted than required for the study so that outlying tumor volumes could be excluded.

Drug-dosing regimens varied and are indicated with each entry in the database. For regimens requiring multiple doses per day, the frequency and number of doses are indicated [e.g., azacitidine was administered twice daily for six doses (BID×6) to mice bearing OVCAR-3 tumors]; other regimens were dosed at multi-day intervals [e.g., methotrexate was dosed against multiple tumor models every 4 days for three doses (Q4D×3)]. Length of drug treatment varied on the basis of the agent and regimen, and mice were followed until tumors reached a calculated mass of 4,000 mg for experiments conducted during or prior to 2000, or 1,500–2,000 mg for experiments conducted from 2001 onward. Control mice were administered drug-free vehicle.

Analysis

Vehicle control groups typically included 16–20 mice, while drug treatment groups typically included 6–10 mice. If tumors failed to progressively grow in an experimental mouse, that mouse was classified as a "no take." One or two "no takes" were allowed in an experiment, although these mice were excluded from median tumor mass calculations. If more than two "no takes" occurred in the control group, the experiment was considered to have failed quality control and was not included in ROADMAPS. Drug response (i.e., whether a tumor is responsive or nonresponsive to the regimen tested) was determined by calculating the percent test/control (%T/C) of median tumor weights on each day that tumors were measured during the study. Any %T/C less than 40%, regardless of when it occurred during the study, met the DTP threshold for reporting minimal drug activity (i.e., a 60% reduction in median tumor volume in test mice compared with tumors in control mice treated with drug-free vehicle). Tumor masses in milligrams were calculated as (length $\times$ width^2)/2, with length and width in millimeters as measured using bidirectional calipers. Both manually read calipers and electronic calipers were used depending on when the studies were conducted. Manual caliper data were collected by hand with subsequent manual entry into an electronic database for endpoint calculations. When StudyLog software (StudyLog Systems) became available, data collection was accomplished with electronic calipers for automated data upload. Mean weight loss, as a percent of the animals' starting weights, are reported; animals were sacrificed if weight loss exceeded 30% or earlier if there were clinical signs of toxicity in addition to weight loss. Drug-related deaths are also included as a surrogate for toxicity, reported as number of dead animals/total number of animals in a specific dosing cohort.

Results

Overview of dataset

ROADMAPS includes dose(s) tested, dosing schedule, route of administration, mouse strain, maximum weight loss, drug-related mortality, vehicle, and whether the model was responsive or unresponsive (quantified as %T/C, with positive responses indicating that a drug/dose/route combination resulted in median tumor weights in treated mice that were no more than 40% of the median tumor weight in control mice that received drug-free vehicle at one or more timepoints). Data can be filtered to compare responses with specific agents, dosing regimens, or tumor types. Seventy agents were tested against one or more xenograft models (**Table 1**). ROADMAPS currently includes data from 140 xenograft models (**Table 2**). Doxorubicin was tested against more models (76) than any other agent; HCT-116 was tested against more drug/dosing combinations (41) than any other model. A total of 3,161 drug/dosing combinations have been tested at the time of this writing and incorporated into a spreadsheet with 1,212 entries; multiple doses are included in a single entry when other conditions and responses are identical (i.e., methotrexate did not induce responses when dosed Q4D×3 against HOP-92 non–small

cell lung cancer (NSCLC) cells at 18, 27, or 45 mg/kg; all three dose levels are included in one entry).

All nine histologies [lung, melanoma, renal, colon, central nervous system (CNS), leukemia, breast, ovarian, and prostate cancers] represented in the NCI-60 panel are also included in ROADMAPS. In addition, ROADMAPS includes lymphoma and bladder cancer models, as well as a collection of "other" models (e.g., head and neck, gastric, leiomyosarcoma; **Fig. 1**). This initial version of ROADMAPS includes 52 models that are in the NCI-60 panel and an additional 88 models that are not part of the NCI-60. Each model was tested against different agents following differing administration regimens, routes, doses, and vehicles. The number of ROADMAPS entries per model ranges from 13.4 entries per model for renal cancer models to 3.3 entries per model for "other" models; the mean number of entries per model across the entire dataset of xenograft models was 8.4 (1,177 entries for 140 tumor models). An additional 35 entries report results from experiments with five transgenic mouse models (four breast cancer, one prostate cancer) and one canine model (osteosarcoma); these models are included in the downloadable spreadsheet.

Filtering by agent

Paclitaxel is presented as an example of how ROADMAPS can be filtered. At present, there are 69 unique entries for paclitaxel administered on different schedules, via different routes, in different vehicles, and in different models. To facilitate comparison, these entries were filtered to include combinations involving only intravenous administration of paclitaxel in vehicle containing ethanol and Cremaphor, with 58 entries matching these criteria. Of those 58 entries, tumor responses were observed in 39 entries, while 19 did not yield tumor response (67.2% positive responses). Pharmacokinetic factors associated with paclitaxel monotherapy influence clinical outcomes in patients (15). Paclitaxel was administered daily in 33 entries with 84.8% yielding positive tumor responses (28/33); positive responses were observed in 44.0% (11/25) of entries that utilized other dosing schedules. MDA-MB-231 tumor was responsive when paclitaxel was administered daily for 5 days at doses from 6.7 to 22.5 mg/kg; this model was not responsive to 10 mg/kg paclitaxel administered every 4 days for three doses. These data are consistent with the clinical observation that similar tumors respond differently to an agent based on the administration schedule.

Filtering by tumor model

A broad spectrum of tumor histologies are included in the dataset (**Fig. 1**; **Table 2**). Colon cancer models are the most abundant group in the current iteration of ROADMAPS, with 173 different entries in the spreadsheet. Included within this group is the single most tested model, HCT-116, with 41 distinct entries (13 responsive entries and 28 unresponsive entries). Nine agents led to tumor responses (dactinomycin, mitomycin C, vincristine, bleomycin, decitabine, sirolimus, clofarabine, topotecan, and irinotecan) via differing routes of administration and dosing schedules, while 24 agents failed to induce tumor response (**Table 3**). Several agents (mitomycin C, vincristine, bleomycin, and topotecan) led to drug toxicity at higher doses, but all these agents induced tumor response without mortality at lower doses. For example, 2 of 10 mice died after receiving mitomycin C at 4.5 mg/kg, while no deaths occurred in mice receiving mitomycin C at 2 or 3 mg/kg. An additional six entries include data from five cell lines derived from HCT-116 [HCT-116-luc2, HCT-116 (Pommier), HCT-116/Mre11Ch, HCT-116H1, and HCT-116B]; these cell lines are not included in the above description of HCT-116 results. These data indicate ROADMAPS may be used to guide preclinical studies with regard to toxic dose levels in addition to responsiveness.

Table 1. List of agents.

NSC	Agent (# models tested)	NSC	Agent (# models tested)
740	Methotrexate (64)	246131	Valrubicin (4)
750	Busulfan (2)	279836	Mitoxantrone (4)
752	Thioguanine (2)	312887	Fludarabine phosphate (2)
755	Mercaptopurine (5)	362856	Temozolomide (30)
762	Mechlorethamine (2)	409962	Carmustine (56)
1390	Allopurinol (3)	606869	Clofarabine (13)
3053	Dactinomycin (63)	608210	Vinorelbine (1)
3088	Chlorambucil (12)	609699	Topotecan (56)
6396	Thiotepa (1)	616348	Irinotecan (14)
8806	Melphalan (52)	628503	Docetaxel (5)
19893	Fluorouracil (65)	673596	SN-38 (1)
26271	Cyclophosphamide (71)	683864	Temsirolimus (13)
26980	Mitomycin C (54)	701852	Vorinostat (3)
27640	Floxuridine (7)	702294	Estramustine phosphate (3)
45388	Dacarbazine (63)	707389	Eribulin mesylate (3)
49842	Vinblastine (59)	715055	Gefitinib (7)
63878	Cytarabine (6)	718781	Erlotinib (12)
67574	Vincristine (12)	732517	Dasatinib (15)
71423	Megestrol acetate (12)	733504	Everolimus (5)
79037	Lomustine (CCNU) (3)	737754	Pazopanib (2)
82151	Daunorubicin (5)	743414	Imatinib (6)
91485	Metformin (3)	744009	Sildenafil (1)
102816	Azacitidine (6)	745750	Lapatinib (11)
105014	Cladribine (1)	747599	Nilotinib (7)
109724	Ifosfamide (2)	747971	Sorafenib (12)
119875	Cisplatin (72)	749226	Abiraterone (2)
122758	Tretinoin (6)	754143	Romidepsin (2)
123127	Doxorubicin (76)	755986	Vismodegib (1)
125066	Bleomycin (60)	756645	Crizotinib (1)
125973	Paclitaxel (69)	758246	Trametinib (6)
127716	Decitabine (8)	759224	Idelalisib (1)
141540	Etoposide (8)	760766	Vandetanib (1)
180973	Tamoxifen citrate (12)	761190	Panobinostat (1)
226080	Sirolimus (Rapamycin) (12)	761431	Vemurafenib (1)
241240	Carboplatin (11)	763932	Regorafenib (1)

Table 2. ROADMAPS models to date.

Histology	Model (# agents tested)	Histology	Model (# agents tested)	Histology	Model (# agents tested)
Bladder	BL0293F563[a] (2) BL0382F1232[a] (1) BL0479F1894[a] (1) ECV-304 (2) JCA-1 (15)	**Leukemia**	CCRF-CEM (15) HL-60 (2) HL-60(TB) (3) K-562 (14) MOLT-4 (16) NB4 (3)	**Lung (SCLC)**	DMS 114 (12) DMS 273 (10) H510A (1) NCI-H69 (3) NCI-H82 (1) NCI-H209 (1) NCI-H345 (2)
Breast	MAXF 401 (2) MCF7 (19) MCF7-LUC-F5 (3) MDA-MB-231 (16) MDA-MB-231T (12) MDA-MB-361 (3) MDA-MB-435 (23) MDA-MB-468 (10) MDA-N (13) MX-1 (14) SUM 52 PE (3) SUMI49PT (3) UISO-BCA (1) UISO-BCA-1 (9) ZR-75–1 (14)	**Lymphoma**	AS283 (22) BJAB Human (1) CA 46 HUMAN B (3) KD488 (12) PA682 (12) RL (12) SR (12) SU-DHL-6 (12) SU-DHL-7 (12)	**Ovarian**	A2780 (11) BG-1 (2) IGROV1 (21) NCI/ADR-RES (1) OVCAR-3 (12) OVCAR-4 (8) OVCAR-5 (8) OVCAR-8 (12) SK-OV-3 (19)
Colon	172845–121B[a] (1) 172845–121T[a] (1) 172845–288R[a] (3) CN0375F725[a] (1) CN0428F1126[a] (1) CN0446F447[a] (3) COLO 205 (18) COLO 320DM (9) DLD-1 (1) HCC-2998 (15) HCT-15 (17) HCT-116 (41) HCT-116B (2) HCT-116H1 (1) HCT-116-luc2 (1) HCT-116/Mre11Ch (1) HCT-116 (Pommier) (1) HT29 (21) KM12 (8) KM20L2 (12) SW-620 (15)	**Melanoma**	A375 (11) COLO 829 MEL (8) LOX IMVI (17) M14 (23) M19-MEL (3) MALME-3M (12) SK-MEL-1 (1) SK-MEL-2 (14) SK-MEL-28 (13) SK-MEL-31 (9) SK-MEL-5 (3) UACC-62 (19) UACC-257 (12) UISO-MEL-2 (1)	**Prostate**	DU-145 (22) DU-145 (TR) (2) LNCAP-FGC (1) PC-3 (33) PC-3/luciferase (1)
				Renal	786–0 (5) A498 (25) CAKI-1 (18) RXF 393 (19) RXF 631 (4) SN12C (11) SN12K1 (12)
		Lung (NSCLC)	A549(ASC)[1] (14)[b] A549/ATCC (7) A549-lucC8 (1) EKVX (13) HOP-62 (8) HOP-92 (12) LG0520F434[a] (1) LG0567F671[a] (1) LG1189F1952[a] (1) LXFL 529 (2) NCI-H23 (18) NCI-H157 (1) NCI-H226 (2) NCI-H322M (13) NCI-H460 (20) NCI-H522 (14) SK-MES-1 (2)	**Other**	
CNS	SF-295 (22) SNB-19 (8) SNB-75 (3) U-87 MG (3) U251 (28) U251-HRE (5) U251/Pgl3 transf (2) U373 (1) XF 498 (12)			ASPS Cervical Gastric Gastric GIST Head and neck Head and neck Head and neck Hepatocellular Hurthle cell Leiomyosarcoma Leiomyosarcoma Mesothelioma Myeloma Pancreatic Sarcoma	ASPS 4C[a] (2) HeLa-Luc (2) MKN-45 (1) SNU-5 (1) ST0110F1568[a] (1) 114551–80T[a] (2) KB-8–5-11 (1) WSU-HN-31 (4) HEP-G2 (1) 248138–237R[a] (3) 692163–330T[a] (1) SA0426F1136[a] (2) 941425–263T[a] (4) RPMI-8226 (23) PSN-1 (1) MHM-8 (3)

[a]Indicates PDX models. Other models are derived from cell lines.
[b]The superscript numeral is part of the model name.

Discussion

Use of preclinical xenograft models to evaluate the effects of cancer drugs on human tumor growth *in vivo* is a well-established component of the drug development pathway (4, 5, 9, 16). As such, the data and methods used to generate data from preclinical studies are not always published. The database of preclinical data outlined in this article addresses an unmet need for such information. Although the results of preclinical drug evaluation studies are not always predictive of human clinical activity and antitumor immune responses cannot be evaluated in immunocompromised mice, evaluating agents against xenograft
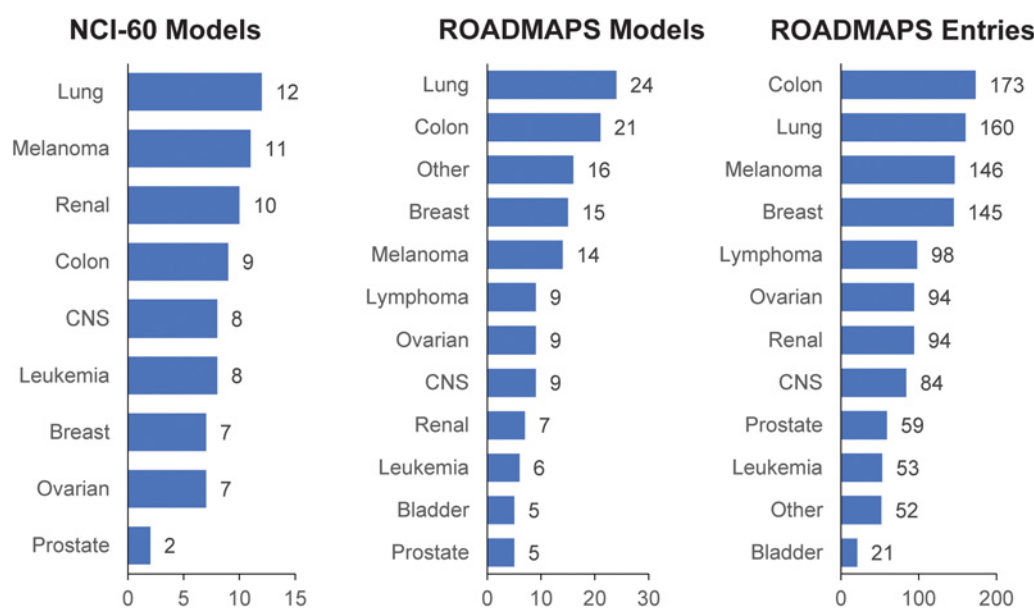
Figure 1.
Left, composition of the NCI-60 panel and associated BTB models in terms of tumor histologies. This includes the 60 cell lines in the *in vitro* screen plus additional cell lines available from the NCI for testing and distribution (https://dtp.cancer.gov/discovery_development/nci-60/cell_list.htm). Middle, composition of ROADMAPS models included in the initial spreadsheet. Right, entries in the ROADMAPS spreadsheet by tumor type. "Other" tumors include ASPS, cervical, gastric, gastrointestinal stromal tumor, head and neck, hepatocellular, Hurthle cell, leiomyosarcoma, mesothelioma, myeloma, pancreatic, and unspecified sarcoma models.

models can facilitate the identification and optimization of *in vivo* dosing regimens appropriate for further testing (16). Further studies could assess whether toxicities are comparable in additional mouse strains, as SCID mice have known DNA repair defects (17), making them more sensitive to DNA-damaging agents than athymic nude mice. In addition, the role of metastasis in disease progression must be considered when reviewing data in ROAD-MAPS, as orthotopic implantation may result in more clinically relevant tumor spread (18) as well as differences in drug exposure at various body sites due to the drug's absorption, distribution, metabolism, and excretion characteristics.

It is anticipated that the data shared in ROADMAPS will help investigators to select tolerable and active dosing regimens for single- and combination-drug studies, as well as to identify suitable, sensitive tumor types. To this end, an optimal 40% T/C threshold was selected for sorting tumor growth into a qualitative yes/no response filter in ROADMAPS; multiple studies over time have used this threshold and statistical analysis has demonstrated sufficient statistical power to evaluate tumor responsiveness (19). One such analysis calculated that groups of 6 mice with a "moderate" coefficient of variation (defined as $CV = 0.6$) would have 80% power to detect a 60% reduction in mean relative tumor volume (i.e., a T/C of 40%) using a one-sided *t* test with $\alpha = 0.05$ and assuming equal numbers of mice in test and control groups (20). Drug-treated groups in ROADMAPS included 6–10 mice, while control groups included 16–20 mice, suggesting that these studies would have at least 80% power to detect 40% T/C ratios given similar CV values.

ROADMAPS includes drugs with a wide variety of mechanisms of action, including cytotoxic agents (e.g., methotrexate, doxorubicin, cyclophosphamide, cisplatin), targeted agents (e.g., imatinib, everolimus, pazopanib, dasatinib), and drugs used in the adjuvant setting (e.g., tamoxifen, abiraterone). Several agents have been tested against multiple models with similar tumor histologies and demonstrated differing responses. As has been reported previously, topotecan has antitumor activity against A375 melanoma xenograft tumors as a single agent, whereas human Colo829 melanoma xenografts are unresponsive to topotecan at the same doses (9). Given the number of agents and models tested in ROADMAPS, no simple nomogram exists for converting mouse dosing regimens to human equivalents. This goal was also hindered by the fact that mouse model experiments are often conducted before human doses are known. Mouse doses presented here may not have had equivalent doses tested in humans due to lack of efficacy or to toxicity. However, an extensive comparison of mouse and human dosing has been published (21).

Relationships derived from these data can be applied to study designs where it may be more efficient to use a sensitive model during early evaluation of a new anticancer agent or agents before committing resources to optimizing the dosing regimen in more resistant models. The four tumor types with the most entries in this dataset (colon, lung, melanoma, and breast; **Fig. 1**) are all among the five most common cancer types in the United States (breast, prostate, lung, colorectal, and melanoma; https://www.cancer.gov/types/common-cancers). Several models within each tumor type have been tested against many agents (**Table 2**). Furthermore, the BTB has previously reported details on growth rates and gene expression profiles of a panel including 49 human tumor xenografts (22). Of those 49 cell lines, 42 are included in ROADMAPS and account for 629 of the 1,212 (51.9%) total entries in the database. The growth characteristics of many NCI-60 cell line xenografts were reported by Plowman and colleagues along with their sensitivities to a panel of 12 agents (12). In addition, growth curves for a selection of human tumor xenografts are available at http://dtp.cancer.gov/organization/btb/growth_assay_data.htm. The ROADMAPS database substantially expands on

Table 3. Agents and responses with HCT-116.

NSC	Agent	Doses (mg/kg)	Mouse strain	Route	Schedule	Response?	Maximum weight loss
740	Methotrexate	45, 27, 18	NUDE	IP	Q4DX3	N	0%
3053	Dactinomycin	0.3, 0.2, 0.13	NUDE	IP	Q4DX3	Y	16%
3088	Chlorambucil	27, 18, 12	NUDE	IP	Q4DX3	N	19%
19893	Fluorouracil	25, 18	NUDE	IP	QDX5	N	0%
26271	Cyclophosphamide	100, 50	NUDE	IP	Q4DX3	N	7%
26980	Mitomycin C	4.5, 3, 2	NUDE	IP	Q4DX3	Y	5%
45388	Dacarbazine	225, 150, 100	NUDE	IP	Q4DX3	N	19%
49842	Vinblastine	1.5, 1.0	NUDE	IP	QDX4	N	7%
63878	Cytarabine	37.5, 25.0, 16.8	NUDE	IP	Q4HX6	N	29%
67574	Vincristine	2.0, 1.0, 0.5	NUDE	IV	Q7DX3	Y	23%
71423	Megestrol acetate	10.0, 7.5	NUDE	IP	QDX16	N	6%
105014	Cladribine	30, 20	NUDE	IP	QDX5	N	6%
119875	Cisplatin	3.5, 2.0	NUDE	IP	Q3DX3	N	9%
122758	Tretinoin	5	NUDE	IV	QDX5	N	0%
122758	Tretinoin	5	NUDE	IV	Q2DX5	N	1%
122758	Tretinoin	22.5, 15.0	NUDE	PO	BIDX20	N	8%
123127	Doxorubicin	8.0, 5.4, 3.6	NUDE	IV	Q4DX3	N	5%
125066	Bleomycin	36, 24, 16	NUDE	IP	Q4DX3	Y	12%
125973	Paclitaxel	12	NUDE	IV	Q7DX3	N	13%
127716	Decitabine	0.75	NUDE	IP	QDX5	Y	11%
141540	Etoposide	40, 27, 18	Athymic	IP	Q4DX3	N	12%
226080	Sirolimus	200, 100	Athymic	IP	Q4DX3	Y	8%
226080	Sirolimus	120, 60	Athymic	IP	QDX5	Y	4%
241240	Carboplatin	80, 54, 36	Athymic	IV	QDX1	N	5%
362856	Temozolomide	120, 80, 54	Athymic	PO	QDX5	N	20%
409962	Carmustine	27, 18	NUDE	IP	Q4DX3	N	3%
606869	Clofarabine	100	NUDE	PO	QDX5	Y	15%
606869	Clofarabine	100	NUDE	PO	Q2DX5	Y	13%
606869	Clofarabine	200	NUDE	PO	Q4DX5	Y	11%
609699	Topotecan	15	NUDE	IP	Q4DX3	Y	13%
609699	Topotecan	15.0, 10.0, 6.7	NUDE	IP	Q4DX3	Y	11%
616348	Irinotecan	100, 75	NUDE	IV	Q4DX4	Y	13%
673596	SN-38	0.3, 0.25	NUDE	IP	Q4DX3	N	4%
715055	Gefitinib	200, 100, 67	NUDE	PO	QDX14	N	12%
718781	Erlotinib	100, 67, 45	NUDE	PO	QDX14	N	16%
732517	Dasatinib	100, 50	NUDE	PO	QDX14	N	8%
745750	Lapatinib	150, 100, 67	NUDE	PO	BIDX28	N	2%
747971	Sorafenib	100	NUDE	PO	QDX12	N	0%
747971	Sorafenib	100	NUDE	PO	Q2DX6	N	1%
747971	Sorafenib	50	NUDE	PO	BIDX28	N	6%
759224	Idelalisib	30	NUDE	PO	TIDX42	N	6%

these prior publications in terms of both the number of models and agents tested, and organizes the data into a searchable database. Such a breadth of data on the most common tumor types will streamline the search for appropriate models in which to test novel agents and should facilitate the translation of these agents from preclinical to clinical studies. The data will also help identify doses and tumor types to avoid, whether from lack of activity or association with morbidity.

Complementary pharmacokinetic data to aid determination of desired exposures in nonclinical studies have been published (21). Data presented here demonstrate the relative antitumor efficacies when an agent is administered at differing intervals or via different routes. For example, the Colo829 melanoma model was responsive to intravenous paclitaxel administered daily for 5 days. This model was not responsive to paclitaxel administered weekly at the same doses via the same route. The MDA-MB-231T breast cancer model was responsive to paclitaxel administered

intravenously on both daily (QD×5) and weekly (Q7D×3) schedules. However, while weekly dosing was well tolerated (i.e., no mortality or weight loss at any dose tested), daily dosing at the highest dose (15 mg/kg) resulted in drug toxicity for 3 of 8 mice. These examples demonstrate the utility of these data in identifying suitable models and dosing regimens.

ROADMAPS is the first publicly available resource with data compiled over many years available in a filterable format. The NCI's BTB will continue its work testing anticancer agents against various tumor models in mice. Targeted agents tend to be newer and therefore have been tested against fewer models than older agents; multiple ongoing studies are evaluating the efficacy of targeted agents against an array of tumor models. As the BTB expands its repertoire of drug studies in PDX as well as xenograft models, the spreadsheet will be updated periodically, with the most recent version available for download by members of the research community.

Authors' Contributions

M.G. Hollingshead: Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, validation, investigation, methodology, writing–original draft, project administration, writing–review and editing. **N. Greenberg:** Data curation, validation, investigation, methodology, writing–review and editing. **M. Gottholm-Ahalt:** Data curation, formal analysis, validation, writing–review and editing. **R. Camalier:** Supervision, funding acquisition, investigation, methodology, writing–review and editing. **B.C. Johnson:** Formal analysis, writing–original draft, writing–review and editing. **J.M. Collins:** Writing–original draft, writing–review and editing. **J.H. Doroshow:** Funding acquisition, project administration, writing–review and editing.

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