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REVIEW

Reverse Translation of US Food and Drug Administration Reviews of Oncology New Molecular Entities Approved in 2011–2017: Lessons Learned for Anticancer Drug Development

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INTRODUCTION

We conducted a comprehensive analysis of clinical pharmacology evaluations in initial submissions of 56 oncology new molecular entities approved by the US Food and Drug Administration between January 2011 and April 2017. Results from studies evaluating food effect, QTc prolongation, drug-drug interactions, renal and hepatic impairment effects, and dose optimization, as well as postmarketing requirements/commitments, were reviewed. This reverse translational research highlights the importance of clinical pharmacology and pharmacometrics in benefit-risk characterization, regulatory review, and labeling of anticancer therapeutics.

BACKGROUND

From a clinical pharmacology perspective, oncology drug development is associated with unique challenges compared with other therapeutic areas.[1,2] Clinical pharmacology studies can be more complex because, in many cases, trial participants must be patients with advanced disease rather than healthy volunteers because of the cytotoxic nature and/or mutagenic potential of drugs being evaluated. Additionally, the urgency in delivering effective new therapies to patients with significant unmet medical need drives potentially rapid progression from phase I to registration-enabling studies. This is especially the case when early signs of antitumor activity can lead to a rapid expansion of a phase I clinical program to include pivotal assessment of efficacy and safety in support of accelerated filing strategies. Recent examples include the anaplastic lymphoma kinase (ALK) inhibitor ceritinib engineered for molecularly targeted patient populations[3] and the highly active immunotherapeutic antiprogrammed cell death 1 (PD-1) antibody pembrolizumab.[4,5] Rapid progression of the clinical program can limit the time available to complete all desired clinical pharmacology activities before initial registration. Despite these challenges, characterization of the clinical pharmacology profile of oncology therapies is important to assess the overall benefit:risk ratio, to support dose selection for the general population and subpopulations based on age, ethnicity, genotype, and organ function, and to provide prescribers with dosing guidance with respect to food and concomitant medications.[1,6–16]

In recent years, there has been an increased expectation by the US Food and Drug Administration (FDA) for results of clinical pharmacology studies and analyses to be available in initial new drug application (NDA)/biologic license application (BLA) submissions for oncology therapies.[17] This may reflect the increased availability of targeted therapies, such as tyrosine kinase inhibitors, that can be administered on a continuous dosing schedule and/or for a longer duration than traditional cytotoxic therapies, thus prompting an increased focus on long-term tolerability in the overall benefit:risk assessment. In particular, there has been a greater emphasis on understanding sources of pharmacokinetic (PK) variability and characterizing exposure-response relationships to ensure optimal dose selection.[7,18–20]

We conducted a comprehensive analysis of publicly available documents that summarize clinical pharmacology studies/analyses included in initial NDA/BLA submissions of oncology new molecular entities (NMEs) approved by the FDA during the January 2011 to April 2017 timeframe. The main purpose of this translational research was to distill knowledge from a clinical pharmacology perspective from the FDA reviews of oncology drugs that can be valuable for clinical development of future oncology drugs. Specific objectives were to understand the degree of variation in the extent of clinical pharmacology data submitted to the FDA for different classes of oncology therapeutics, to identify trends and recurring themes among the FDA clinical pharmacology reviews of initial NDA/BLA submissions for oncology drugs, and to assess the frequency and type of postmarketing requirements (PMRs; studies and clinical trials that sponsors are required to conduct under one or more statutes or regulations) and postmarketing commitments (PMCs; studies or clinical trials that a sponsor has agreed to conduct, but that are not required by a statute or regulation)[21] issued by the FDA for clinical pharmacology-related studies and analyses.

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RESEARCH SCOPE AND DATA SOURCES

This review included NDAs/BLAs for all oncology NMEs that were approved by the FDA between January 2011 and April 2017, inclusive. The scope of reviewed documents included those pertaining to the original NDA/BLA submissions for the initially approved indication, but not supplemental applications for the initial indication or original applications for subsequent indications. Relevant publicly available documents at the Drugs@FDA website[22] were reviewed, including Clinical Pharmacology and Biopharmaceutics (including Pharmacometrics) reviews and QT-Interdisciplinary Review Team (IRT) reviews of the FDA Summary Basis of Approvals, United States prescribing information documents, and FDA approval letters. For the majority of NMEs approved in late 2016/early 2017, clinical pharmacology reviews were integrated into multidisciplinary reviews that also included clinical, nonclinical, and statistical reviews. The NDA/BLA approval letters were considered the official source of PMRs/PMCs, as occasionally there were minor differences from those noted in the clinical pharmacology or QT-IRT reviews. Documents were initially accessed between June to August 2014 and August to September 2015 for 37 NMEs, and then again between October 2016 and June 2017 for 19 NMEs. Document reviews focused on evaluations of food effect, corrected QT (QTc) prolongation and drug-drug interaction (DDI) potential, organ impairment, exposure-response analyses, and dose selection. Relevant data from document reviews were extracted into a prespecified Excel spreadsheet by three different authors; a quality control review was performed by one of these authors during manuscript preparation.

A total of 56 oncology NMEs were identified during the period covered by this analysis (January 2011 to April 2017). A summary of key information regarding these NMEs is provided in **Table 1**, and the timeline of their approvals by the FDA is shown in **Figure 1**. Of the 56 oncology NMEs identified, 23 (41%) were small molecule kinase inhibitors, 8 (14%) were small molecule nonkinase targeted agents, 6 (11%) were small molecule cytotoxics, 14 (25%) were monoclonal antibodies, and 2 (4%) were antibody-drug conjugates (**Figure 2a**); the identified set of NMEs also included a radioactive therapeutic, a small molecule immunomodulatory drug, and a fusion protein ($n = 1$ each). Overall, 21 NMEs (37.5%) are administered by the i.v. route and 35 (62.5%) are orally administered. Seventeen (30%) were initially approved for hematologic malignancies and 39 (70%) were initially approved for solid tumor indications, the most common being multiple myeloma ($n = 6$), non-small cell lung cancer ($n = 7$), and melanoma ($n = 7$). Accelerated approval and breakthrough therapy designation were granted for 24 (43%) and 21 (37.5%) of the NMEs, respectively. The majority of NMEs (43; 77%) received orphan drug designations. One or more clinical pharmacology evaluations were performed for 26 NMEs (46%) in healthy subjects; all except one (ziv-aflibercept) of these NMEs were small molecule targeted agents.

FOOD EFFECT EVALUATIONS

Of the 35 NMEs identified that are orally administered, 34 included food effect data in the initial registration package. Vemurafenib was the only NME that did not include these data at the time of initial submission as its food effect study was ongoing. **Figure 2b** summarizes dosing instructions with respect to food intake in the initial labels of all 35 orally administered agents.

Seventeen (49%) orally administered NMEs were initially labeled to be taken without regard to food, nine (26%) on an empty stomach, and seven (20%) with food. The dosing instructions for two NMEs (ibrutinib and olaparib) indicated the dosage form should be swallowed whole but did not provide any instructions with respect to food intake. There was variation among NMEs in the manner in which an empty stomach was described in the dosage and administration sections of the respective labels. For five NMEs (afatanib, dabrafenib, ixazomib, sonidegib, and trametinib), administration instructions were to take the drug at least 1 h before or at least 2 h after a meal. For two NMEs (pomalidomide and ceritinib), the time frame was extended to 2 h before a meal. For the remaining two NMEs (abiraterone and cabozantinib), instructions were to avoid food consumption for at least 2 h before and at least 1 h after dosing. As with empty stomach recommendations, there also was variation in the level of detail provided in the dosing instructions for the seven drugs to be taken with food. Although "take with food" was the most common language used, more granular language was provided for two NMEs, including "take with low-fat breakfast containing less than 30% fat" for regorafenib and "take within 1 hour of completing meal" for trifluridine/tipiracil. Additionally, the dosing and administration section of the label for regorafenib provided examples of low-fat meals that would meet the recommended caloric and percent fat content.

For the majority of NMEs whose clinical pharmacology review specified dosing conditions for the registrational trial(s), initial labeling language with respect to food intake reflected the dosing conditions implemented in those trial(s). Exceptions included axitinib, ibrutinib, olaparib, and palbociclib. Axitinib was taken with food in controlled efficacy and safety trials, but labeled to be taken with or without food; the labeling instructions were supported by the food effect study, which demonstrated no clinically relevant impact of a moderate-fat or high-fat meal on axitinib PK. Ibrutinib and olaparib were administered under modified fasting conditions (fast from 1 h before dosing until 2 h after dosing) in pivotal trials, but, as mentioned above, their labels did not specify dosing conditions with regard to food. Palbociclib also was dosed under modified fasting conditions in pivotal trials but was labeled to be taken with food. Its food effect study demonstrated no clinically relevant effect of food (low-fat, moderate-fat, and high-fat meals) on exposures in the majority of subjects, but increased exposures with food in a subset of subjects with very low exposures. The decision to administer with food was supported by the exposure increase

Table 1 Summary of key information on the 56 oncology NMEs identified during the period covered by this review (January 2011 to April 2017) from initial approved labeling

Drug	Commercial name	Sponsor	Q/year of initial approval	Initial indication(s)	Class	Mechanism of action	Administration	Dosing regimen
Ipilimumab	Yervoy	Bristol-Myers Squibb	Q1 2011	Unresectable or metastatic melanoma	MoAb	CTLA-4 blocking MoAb	i.v.	3 mg/kg i.v. infusion over 90 min period every 3 weeks (total number of doses = 4)
Vandetanib	Caprelsa	AstraZeneca	Q2 2011	Symptomatic or progressive unresectable locally advanced or metastatic medullary thyroid cancer	Small molecule kinase inhibitor	Inhibitor of tyrosine kinases including members of the EGFR family, VEGFRs, RET, BRK, TIE2, members of the EPH receptor kinase family, and members of the Src family of tyrosine kinases	Oral	300 mg q.d. with or without food
Abiraterone	Zytiga	Centocor Ortho Biotech	Q2 2011	mCRPC after prior chemotherapy containing docetaxel, in combination with prednisone	Small molecule targeted drug	CYP17 (17α-hydroxylase/C17,20-lyase) inhibitor	Oral	1,000 mg q.d. (no food 2 h before and 1 h after drug) with 5 mg prednisone b.i.d.
Vemurafenib	Zelboraf	Genentech	Q3 2011	Unresectable or metastatic BRAF V600E mutant melanoma	Small molecule kinase inhibitor	BRAF serine-threonine kinase inhibitor	Oral	960 mg b.i.d. with or without food
Brentuximab vedotin	Adcetris	Seattle Genetics	Q3 2011	Hodgkin lymphoma after failure of ASCT or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, systemic anaplastic large-cell lymphoma after failure of at least 1 prior multi-agent chemotherapy regimen	ADC	CD30-targeted antibody and microtubule disrupting agent (MMAE) conjugate	i.v.	1.8 mg/kg as i.v. infusion over 30 min Q3W
Crizotinib	Xalkori	Pfizer	Q3 2011	Locally advanced or metastatic ALK-positive metastatic NSCLC	Small molecule kinase inhibitor	Inhibitor of receptor tyrosine kinases including ALK, HGFR, and RON	Oral	250 mg b.i.d. with or without food
Ruxolitinib	Jakafi	Incyte	Q4 2011	Intermediate or high-risk myelofibrosis, including primary, post-polycythemia vera, and post-essential thrombocythemia myelofibrosis	Small molecule kinase inhibitor	JAK1 and JAK2 tyrosine kinase inhibitor	Oral	Starting dose of 20 mg b.i.d. for platelet count of $>200 \times 10^9$/L or 15 mg b.i.d. for platelet count of 100–200 $\times$ 10^9/L, with or without food; doses may be titrated based on safety and efficacy (up to maximum dose of 25 mg b.i.d.)

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Table 1 Continued

Drug	Commercial name	Sponsor	Q/year of initial approval	Initial indication(s)	Class	Mechanism of action	Administration	Dosing regimen
Axitinib	Inlyta	Pfizer	Q1 2012	Advanced renal cell carcinoma after failure of one prior systemic therapy	Small molecule kinase inhibitor	Inhibitor of receptor tyrosine kinases, including VEGFR-1, 2, and 3	Oral	Starting dose of 5 mg b.i.d. with or without food; dose increase (up to maximum dose of 10 mg b.i.d.) or reduction is recommended based on individual safety and tolerability
Vismodegib	Erivedge	Genentech	Q1 2012	Metastatic BCC, or locally advanced BCC that has recurred following surgery or in patients who are not candidates for surgery and radiation	Small molecule targeted agent	Hedgehog pathway inhibitor	Oral	150 mg q.d. with or without food
Pertuzumab	Perjeta	Genentech	Q2 2012	HER2-positive metastatic breast cancer, in combination with trastuzumab and docetaxel	MoAb	HER2 receptor antagonist	i.v.	Initial dose of 840 mg by 60 min i.v. infusion, followed Q3W thereafter by 420 mg by 30–60 min i.v. infusion
Carfilzomib	Kyprolis	Onyx	Q3 2012	Multiple myeloma following at least two prior therapies, including bortezomib and an immunomodulatory agent	Small molecule cytotoxic	Proteasome inhibitor	i.v.	Cycle 1: 20 mg/m^2 by 2–10-min i.v. infusion on 2 consecutive days, each week for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (days 17–28). If tolerated in cycle 1, the dose should be escalated to 27 mg/m^2 beginning in cycle 2 and continued at 27 mg/m^2 in subsequent cycles
Enzalutamide	Xtandi	Medivation	Q3 2012	Patients with mCRPC who have previously received docetaxel	Small molecule targeted drug	Androgen receptor inhibitor	Oral	160 mg q.d. with or without food
Bosutinib	Bosulif	Pfizer/Wyeth	Q3 2012	Chronic, accelerated, or blast phase Ph+ CML in patients with resistance or intolerance to prior therapy	Small molecule kinase inhibitor	Bcr-Abl tyrosine kinase inhibitor; also inhibits Src-family kinases including Src, Lyn, and Hck	Oral	500 mg q.d. with food; consider dose escalation to 600 mg q.d. in patients who do not reach complete hematological response by week 8 or a complete cytogenetic response by week 12, who did not have grade ≥3 adverse reactions, and who are currently taking 500 mg q.d.

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Table 1 Continued

Drug	Commercial name	Sponsor	Q/year of initial approval	Initial indication(s)	Class	Mechanism of action	Administration	Dosing regimen
Regorafenib	Stivarga	Bayer Healthcare Pharmaceuticals	Q3 2012	Metastatic colorectal cancer following previous treatment with fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapy, an anti-VEGF therapy, and if KRAS wild-type, an anti-EGFR therapy	Small molecule kinase inhibitor	Inhibitor of multiple membrane-bound and intracellular kinases, including but not limited to, VEGFR1/2/3, RET, KIT, PDGFRα/β, BRAF, and TIE2	Oral	160 mg q.d. for first 21 days of 28-day cycles; take with low-fat breakfast that contains <30% fat
Ziv-aflibercept	Zaltrap	Sanofi-Aventis	Q3 2012	Metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen, in combination with 5-fluorouracil, leucovorin, and irinotecan	Fusion protein	Binds to VEGF-A, VEGF-B, and PlGF ligands to inhibit the binding and activation of their cognate receptors	i.v.	4 mg/kg by 1-h i.v. infusion Q2W
Cabozantinib	Cometriq	Exelixis	Q4 2012	Progressive, metastatic medullary thyroid cancer	Small molecule kinase inhibitor	Inhibitor of tyrosine kinase activity of RET, MET, VEGFR1/2/3, KIT, TRKB, FLT3, AXL, and TIE2	Oral	140 mg q.d.; no food for at least 2 h before and at least 1 h after drug
Ponatinib	Iclusig	ARIAD	Q4 2012	Chronic phase, accelerated phase, or blast phase CML, or Ph+ ALL, that is resistant or intolerant to prior tyrosine kinase inhibitor therapy	Small molecule kinase inhibitor	Bcr-Abl tyrosine kinase inhibitor; also inhibits activity of additional kinases, including members of the VEGFR, PDGFR, FGFR, EPH receptors, and SRC families of kinases, and KIT, RET, TIE2, and FLT3	Oral	45 mg q.d. with or without food
Ado-trastuzumab emtansine	Kadcyla	Genentech	Q1 2013	HER2-positive metastatic breast cancer following previous treatment with trastuzumab and a taxane, separately or in combination	ADC	HER2-targeted antibody and microtubule inhibitor conjugate	i.v.	3.6 mg/kg by 90-min i.v. infusion (for first infusion) or by 30-min i.v. infusion (for subsequent infusions if prior infusions well-tolerated) Q3W
Pomalidomide	Pomalyst	Celgene	Q1 2013	Multiple myeloma after at least 2 prior therapies, including lenalidomide and bortezomib, with disease progression on or within 60 days of completion of last therapy	Small molecule immuno-modulator	Immunomodulatory drug	Oral	4 mg q.d. on days 1–21 of 28-day cycles; avoid for at least 2 h before and 2 h after meal; may be given in combination with dexamethasone
Trametinib	Mekinist	Novartis	Q2 2013	Unresectable or metastatic melanoma with BRAF V600E or V600K mutation	Small molecule kinase inhibitor	MEK1/MEK2 inhibitor	Oral	2 mg q.d., at least 1 h before or 2 h after meal

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Table 1 Continued

Drug	Commercial name	Sponsor	Q/year of initial approval	Initial indication(s)	Class	Mechanism of action	Administration	Dosing regimen
Dabrafenib	Tafinlar	Novartis	Q2 2013	Unresectable or metastatic melanoma with BRAF V600E mutation	Small molecule kinase inhibitor	BRAF kinase inhibitor	Oral	150 mg b.i.d., at least 1 h before or 2 h after meal
Radium-223 dichloride	Xofigo	Bayer	Q2 2013	Castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease	Radiopharmaceutical	Alpha particle-emitting radiopharmaceutical	i.v.	50 kBq per kg body weight by slow i.v. injection over 1 min Q4W for 6 injections
Afatinib	Gilotrif	Boehringer Ingelheim	Q3 2013	First-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 substitution mutations	Small molecule kinase inhibitor	HER2/HER4/EGFR tyrosine kinase inhibitor	Oral	40 mg q.d., at least 1 h before or 2 h after meal
Obinutuzumab	Gazyva	Genentech	Q4 2013	Previously treated CLL in combination with chlorambucil	MoAb	CD20-directed cytolytic MoAb	i.v.	100 mg i.v. infusion on day 1 and 900 mg on day 2 of cycle 1, 1,000 mg on days 8 and 15 of cycle 1, and 1,000 mg on day 1 of cycles 2–6 (28-day cycles)
Ibrutinib	Imbruvica	Pharmacyclics	Q4 2013	Mantle cell lymphoma following at least 1 prior therapy	Small molecule kinase inhibitor	Bruton's tyrosine kinase inhibitor	Oral	560 mg q.d. with water
Ramucirumab	Cyramza	Eli Lilly	Q2 2014	Advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine or platinum-containing chemotherapy	MoAb	VEGFR2 antagonist	i.v.	8 mg/kg i.v. infusion over 60 min Q2W
Ceritinib	Zykadia	Novartis	Q2 2014	Patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib	Small molecule kinase inhibitor	ALK, IGF-1R, InsR, and ROS1 inhibitor	Oral	750 mg q.d. on empty stomach (i.e., do not administer within 2 h of meal)
Idelalisib	Zydelig	Gilead Sciences	Q3 2014	Relapsed follicular B-cell NHL following at least 2 prior systemic therapies; relapsed CLL in combination with rituximab, relapsed SLL following at least 2 prior systemic therapies	Small molecule kinase inhibitor	PI3Kδ inhibitor	Oral	150 mg b.i.d. with or without food

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Table 1 Continued

Drug	Commercial name	Sponsor	Q/year of initial approval	Initial indication(s)	Class	Mechanism of action	Administration	Dosing regimen
Belinostat	Beleodaq	Spectrum	Q3 2014	Relapsed or refractory peripheral T-cell lymphoma	Small molecule cytotoxic	HDAC inhibitor	i.v.	1,000 mg/m^2 by 30-min i.v. infusion on days 1–5 of 21-day cycles
Pembrolizumab	Keytruda	Merck & Co	Q3 2014	Unresectable or metastatic melanoma with disease progression following ipilimumab, and if BRAF V600 mutation positive, a BRAF inhibitor	MoAb	PD-1 blocking MoAb	i.v.	2 mg/kg by 30-min i.v. infusion Q3W
Nivolumab	Opdivo	Bristol-Myers Squibb	Q4 2014	Unresectable or metastatic melanoma with disease progression following ipilimumab, and if BRAF V600 mutation positive, a BRAF inhibitor	MoAb	PD-1 blocking MoAb	i.v.	3 mg/kg by 60-min i.v. infusion Q2W
Olaparib	Lynparza	AstraZeneca	Q4 2014	Deleterious or suspected deleterious germline *BRCA* mutated advanced ovarian cancer after 3 or more prior lines of chemotherapy	Small molecule targeted agent	PARP-1/PARP-2/PARP-3 inhibitor	Oral	400 mg b.i.d.
Blinatumomab	Blincyto	Amgen	Q4 2014	Ph- relapsed or refractory B-cell precursor ALL	Bispecific MoAb	Bispecific CD19-directed CD3 T-cell engager	i.v.	For patients ≥45 kg: 9 mcg/day on days 1–7 of cycle 1 and 28 mcg/day on days 8–28 of cycle 1, and then 28 mcg/day on days 1–28 of subsequent cycles; each cycle consists of 4 weeks of continuous infusion followed by a 2-week treatment-free interval; up to 2 cycles for induction followed by 3 additional cycles for consolidation
Dinutuximab	Unituxin	United Therapeutics	Q1 2015	Pediatric high-risk neuroblastoma after achieving at least a partial response to prior first-line multi-agent, multimodality therapy, in combination with GM-CSF, IL-2, and RA	MoAb	GD2-binding MoAb	i.v.	17.5 mg/m^2/day i.v. infusion over 10–20 h for 4 consecutive days for a maximum of 5 cycles; cycles 1, 3, and 5: days 4, 5, 6, and 7 of a 24-day cycle; cycles 2 and 4: days 8, 9, 10, and 11 of a 32-day cycle
Lenvatinib	Lenvima	Eisai	Q1 2015	Locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC; RCC	Small molecule kinase inhibitor	VEGFR1/2/3, FGFR1/2/3/4, PDGFRα, KIT, and RET tyrosine kinase inhibitor	Oral	24 mg q.d. with or without food

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Table 1 Continued

Drug	Commercial name	Sponsor	Q/year of initial approval	Initial indication(s)	Class	Mechanism of action	Administration	Dosing regimen
Palbociclib	Ibrance	Pfizer	Q1 2015	Treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer, in combination with letrozole, as initial endocrine-based therapy for metastatic disease	Small molecule kinase inhibitor	CDK4/6 inhibitor	Oral	125 mg q.d. with food for 21 consecutive days followed by 7 days off in 28-day cycles, in combination with letrozole 2.5 mg q.d. given continuously throughout the 28-day cycles
Panobinostat	Farydak	Novartis	Q1 2015	In combination with bortezomib and dexamethasone for multiple myeloma after at least 2 prior regimens, including bortezomib and an immunomodulatory agent	Small molecule cytotoxic	HDAC inhibitor	Oral	20 mg on days 1, 3, 5, 8, 10, and 12 of 21-day cycles, for 8 cycles; consider treatment for an additional 8 cycles for patients with clinical benefit who do not experience unresolved severe or medically significant toxicity
Sonidegib	Odomzo	Novartis	Q3 2015	Locally advanced BCC that has recurred after surgery or radiation, or for those who are not candidates for surgery or radiation	Small molecule targeted agent	Hedgehog pathway inhibitor	Oral	200 mg q.d. on empty stomach, at least 1 h before or 2 h after meal
Trifluridine and tipiracil	Lonsurf	Taiho Oncology	Q3 2015	Metastatic colorectal cancer following previous treatment with fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy	Small molecule cytotoxic	Trifluridine: nucleoside metabolic inhibitor, tipiracil: thymidine phosphorylase inhibitor	Oral	35 mg/m^2 (max 80 mg) b.i.d. on days 1–5 and 8–12 of 28-day cycles, within 1 h of completion of morning and evening meals
Alectinib	Alecensa	Genentech	Q4 2015	ALK-positive metastatic NSCLC patients who have progressed on or are intolerant to crizotinib	Small molecule kinase inhibitor	ALK and RET tyrosine kinase inhibitor	Oral	600 mg b.i.d. with food
Cobimetinib	Cotellic	Genentech	Q4 2015	Unresectable or metastatic melanoma with BRAF V600E or V600K mutation, in combination with vemurafenib	Small molecule kinase inhibitor	MEK1/MEK2 inhibitor	Oral	60 mg q.d. for first 21 days of 28-day cycles, with or without food

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Table 1 Continued

Drug	Commercial name	Sponsor	Q/year of initial approval	Initial indication(s)	Class	Mechanism of action	Administration	Dosing regimen
Daratumumab	Darzalex	Janssen Biotech	Q4 2015	Multiple myeloma following at least 3 prior lines of therapy, including a PI and an immunomodulatory drug, or double-refractory to a PI and immunomodulatory drug	MoAb	CD38-targeting MoAb	i.v.	16 mg/kg i.v. infusion Q1W for weeks 1–8, then Q2W for week 9 through 24, and Q4W thereafter
Elotuzumab	Empliciti	Bristol-Myers Squibb	Q4 2015	Multiple myeloma in combination with lenalidomide and dexamethasone following 1–3 prior treatments	MoAb	SLAMF7-directed immunostimulatory antibody	i.v.	10 mg/kg i.v. infusion Q1W for cycles 1 and 2, then Q2W thereafter for cycles 3 and beyond (28-day cycles)
Ixazomib	Ninlaro	Takeda	Q4 2015	Multiple myeloma in combination with lenalidomide and dexamethasone following at least 1 prior treatment	Small molecule cytotoxic	Proteasome inhibitor	Oral	4 mg on days 1, 8, and 15 of 28-day cycles, at least 1 h before or at least 2 h after food
Necitumumab	Portrazza	Eli Lilly	Q4 2015	First-line treatment of metastatic squamous NSCLC in combination with gemcitabine and cisplatin	MoAb	EGFR-targeting MoAb	i.v.	800 mg by 60-min i.v. infusion on days 1 and 8 of 21-day (3-week) cycles
Osimertinib	Tagrisso	AstraZeneca	Q4 2015	Metastatic EGFR T790M mutation-positive NSCLC following progression on/after EGFR TKI therapy	Small molecule kinase inhibitor	EGFR inhibitor	Oral	80 mg q.d. with or without food
Trabectedin	Yondelis	Janssen Biotech	Q4 2015	Unresectable or metastatic liposarcoma or leiomyosarcoma following a prior anthracycline-containing regimen	Small molecule cytotoxic	DNA guanine residue binder	i.v.	1.5 mg/m^2 i.v. infusion over 24 h Q3W
Atezolizumab	Tecentriq	Genentech	Q2 2016	Locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	MoAb	PD-L1 blocking MoAb	i.v.	1200 mg by i.v. infusion over 60-min Q3W
Venetoclax	Venclexta	AbbVie	Q2 2016	CLL with 17p deletion after at least 1 prior therapy	Small molecule targeted agent	BCL-2 inhibitor	Oral	Weekly ramp-up over 5 weeks from 20 mg q.d. to 400 mg q.d., with a meal and water

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Table 1 Continued

Drug	Commercial name	Sponsor	Q/year of initial approval	Initial indication(s)	Class	Mechanism of action	Administration	Dosing regimen
Rucaparib	Rubraca	Clovis	Q4 2016	Deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer following treatment with 2 or more chemotherapies	Small molecule targeted agent	PARP-1/PARP-2/ PARP-3 inhibitor	Oral	600 mg b.i.d. with or without food
Olaratumab	Lartruvo	Eli Lilly	Q4 2016	Soft-tissue sarcoma with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery, in combination with doxorubicin	MoAb	PDGFR-α blocking MoAb	i.v.	15 mg/kg by i.v. infusion over 60-min on days 1 and 8 of each 21-day cycle; administered with doxorubicin for the first 8 cycles
Avelumab	Bavencio	EMD Serono	Q1 2017	Metastatic Merkel cell carcinoma (adults and pediatric patients 12 years and older)	MoAb	PD-L1 blocking MoAb	i.v.	10 mg/kg by i.v. infusion over 60-min Q2W
Niraparib	Zejula	Tesaro	Q1 2017	Maintenance treatment of adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum- based chemotherapy	Small molecule targeted agent	PARP-1/PARP-2 inhibitor	Oral	300 mg q.d. with or without food
Ribociclib	Kisqali	Novartis	Q1 2017	Initial endocrine-based therapy for treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, in combination with an aromatase inhibitor	Small molecule kinase inhibitor	CDK4/6 inhibitor	Oral	600 mg q.d. with or without food for 21 consecutive days followed by 7 days off in 28-day cycles, in combination with letrozole 2.5 mg q.d. throughout 28 day cycles. For dosing and administration with other aromatase inhibitors refer to the applicable full prescribing information.
Brigatinib	Alunbrig	ARIAD	Q2 2017	ALK-positive metastatic NSCLC patients who have progressed on or are intolerant to crizotinib	Small molecule kinase inhibitor	Inhibitor of multiple tyrosine kinases including ALK, ROS1, IGF-1R, and FLT3, as well as EGFR deletions and point mutations	Oral	90 mg q.d. for first 7 days, then increase to 180 mg q.d. if 90 mg is tolerated for first 7 days, with or without food

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Table 1 Continued

Drug	Commercial name	Sponsor	Q/year of initial approval	Initial indication(s)	Class	Mechanism of action	Administration	Dosing regimen
Midostaurin	Rydapt	Novartis	Q2 2017	FLT3 mutation-positive newly diagnosed AML, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy; ASM, SM-AHN, or MCL	Small molecule kinase inhibitor	Inhibitor of multiple tyrosine kinases, including wild-type and mutant (ITD and TKD) FLT3, KIT (wild-type and D816V mutant), PDGFRα/β, VEGFR2, as well as members of the serine/threonine kinase protein C kinase family	Oral	AML: 50 mg b.i.d. with food on days 8–21 of each cycle of induction with cytarabine and daunorubicin and on days 8–21 of each cycle of consolidation with high-dose cytarabine; ASM, SM-AHN, MCL: 100 mg b.i.d. with food

ADC, antibody-drug conjugate; ALK, anaplastic lymphoma kinase; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; ASCT, autologous stem cell transplant; ASM, aggressive systemic mastocytosis; BCC, basal cell carcinoma; b.i.d., twice daily; BRCA, breast cancer gene; BRK, protein tyrosine kinase 6; CDK, cyclin-dependent kinase; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; ER, estrogen receptor; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase-3; GM-CSF, granulocyte-macrophage colony-stimulating factor; HDAC, histone deacetylase; HER, human epidermal growth factor receptor; HGFR, hepatocyte growth factor receptor; HR, hormone receptor; IGF-1R, insulin-like growth factor 1 receptor; IL-2, interleukin-2; InsR, insulin receptor; ITD, internal tandem duplication; i.v., intravenous; JAK1/2, Janus Associated Kinases; MCL, mast cell leukemia; mCRPC, metastatic castrate-resistant prostate cancer, MEK, mitogen-activated protein kinase kinase; MoAb, monoclonal antibody; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; PARP, poly (ADP-ribose) polymerase; PDGFR, platelet-derived growth factor receptor; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; Ph+/Ph-, Philadelphia chromosome positive/negative; PI, proteasome inhibitor; PI3Kδ, phosphatidylinositol-4,5-bisphosphate 3-kinase delta; Q(2/3/4)W, once every 2/3/4 weeks; q.d., once-daily; RA, 13-cis-retinoic acid; RON, Recepteur d'Origine Nantais; SLAMF7, signaling lymphocyte activation molecule; SLL, small lymphocytic lymphoma; SM-AHN, systemic mastocytosis with associated hematological neoplasm; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
Note that subsequent indication expansions or updates to dosing regimens are not captured and as such, this table is not intended to reflect current prescribing information of these therapeutics.

in this small subset and the decrease in intersubject PK variability under fed conditions relative to fasting conditions.

Food effect evaluations for the majority of NMEs compared single-dose PK following administration in the fasting state (generally an overnight fast) vs. administration with a high-fat, high-calorie meal. However, other types of meals were evaluated in addition to high-fat meals for some NMEs. Food effect studies for abiraterone, ceritinib, palbociclib, ponatinib, regorafenib, venetoclax, and vismodegib evaluated low-fat meals, those for axitinib and palbociclib evaluated moderate-fat meals, and those for midostaurin, olaparib, and panobinostat evaluated standard or normal meals in addition to high-fat meals. The food effect studies for ibrutinib and palbociclib also evaluated PK under modified fasting conditions (dosing at least 30 min before and 2 h after a meal) in addition to overnight fasting conditions. These observations suggest a shift from only evaluating the high-fat, high-calorie meal and overnight fasting conditions described in the current FDA guidance on food effect bioavailability studies to also evaluating alternative meals and alternative timing of food relative to dosing.

PMRs related to food effect were issued for two NMEs (pomalidomide and ceritinib). For pomalidomide, the FDA clinical pharmacology reviewer concluded that results of the food effect evaluation in healthy subjects were unreliable due to suboptimal design features. First, the food effect evaluation was conducted with the test formulation instead of the reference or final commercial formulation. Second, the test formulation failed to meet the FDA's bioequivalence criteria (equivalence limits of 80–125%) compared with the reference formulation utilized in registrational trials. In light of these issues, a PMR was issued to conduct a food effect study with the commercial formulation in accordance with FDA guidance (Food Effect Bioavailability and Fed Bioequivalence Studies) and recommended that pomalidomide be taken under fasting conditions until the food effect was evaluated in a properly designed study.

A food-related PMR also was issued for ceritinib for different reasons than pomalidomide. The registrational trial, consisting of dose-escalation and expansion phases, was conducted with dosing on an empty stomach. A single-dose food effect study in healthy subjects with the to-be-marketed formulation demonstrated that low-fat and high-fat meals increased peak plasma concentration (C_{max}) and area under the curve (AUC) relative to fasting conditions. Consequently, the sponsor proposed a dosing regimen of 750 mg q.d. on an empty stomach at least 2 h before and 2 h after food. However, a high rate of gastrointestinal adverse events (AEs) was observed at the proposed dose when administered under these conditions. The clinical pharmacology reviewer noted that administration with food may improve gastrointestinal tolerability but also increase the rates of other AEs, such as liver enzyme abnormalities and QTc prolongation, due to increased exposure. Accordingly, the reviewer recommended a PMR for further evaluation of a lower dose administered with food that would provide similar exposures to the dose (750 mg) administered on an empty stomach but that would potentially improve gastrointestinal tolerability without compromising efficacy.

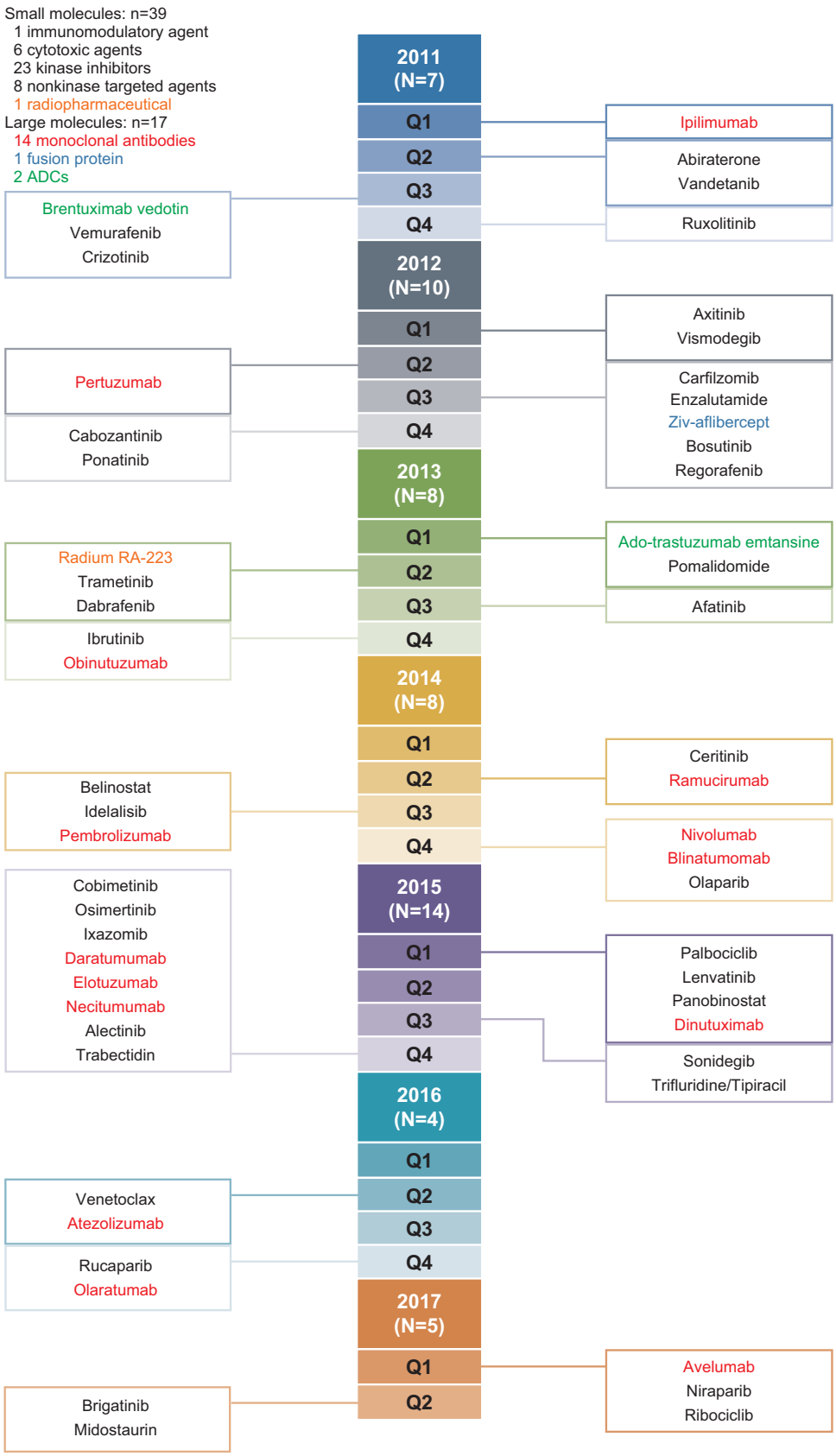

Figure 1 Timeline showing approvals of all NMEs included in the present analysis. ADC, antibody-drug conjugate.

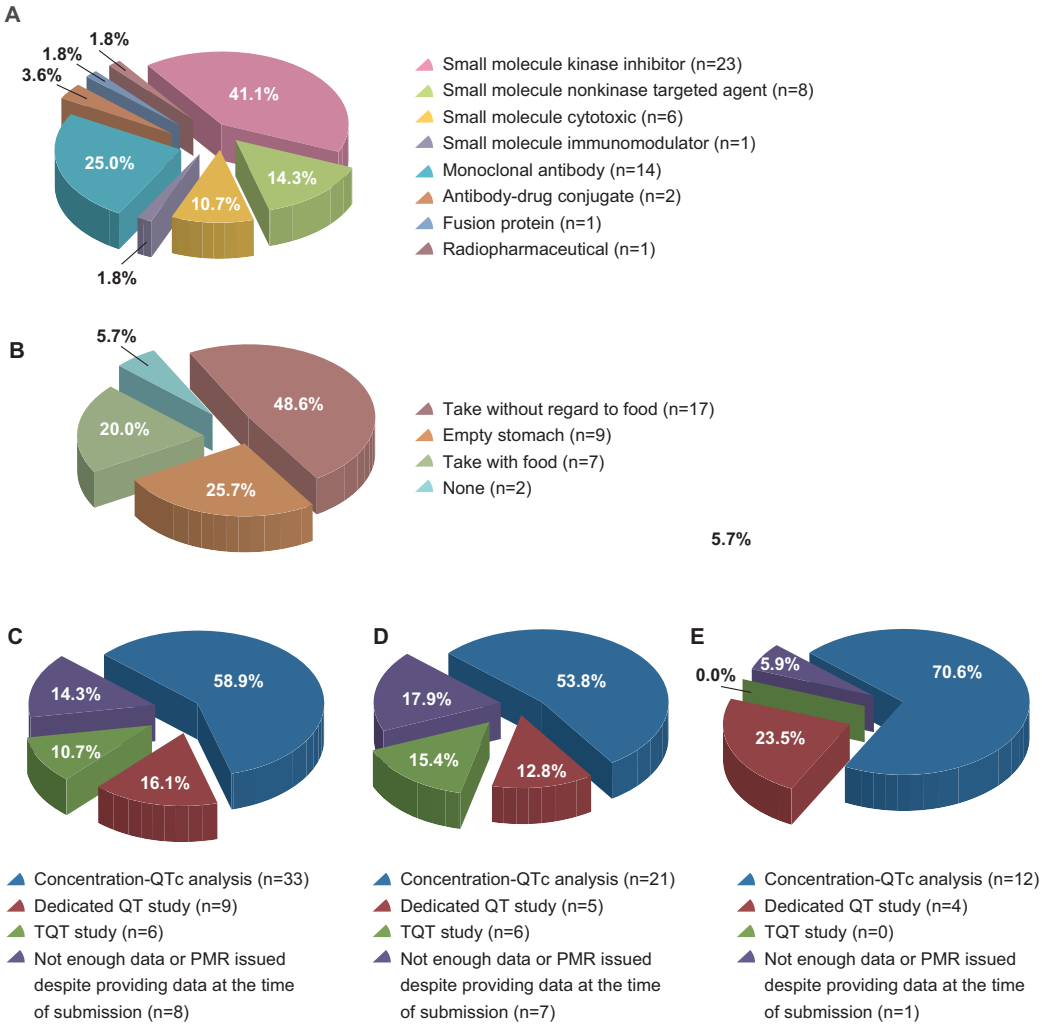

Figure 2 **(a)** Classification of the 56 oncology NMEs. **(b)** Initial labeling language for dosing instructions with respect to food intake for orally administered agents ($n = 35$). **(c–e)** Types of studies/analyses conducted to evaluate the potential for the NME to prolong the QTc interval in relation to the number of (c) total NMEs ($n = 56$), (d) small molecule ($n = 39$), and (e) large molecule ($n = 17$) agents. PMR, postmarketing requirement; TQT, thorough QT.

QTc PROLONGATION EVALUATIONS

Three different approaches for evaluating QTc prolongation potential were identified among the 56 NDA/BLA submissions. As summarized in **Figure 2c**, NMEs were classified into the following four categories: concentration-QTc analysis, dedicated QT study, thorough QT (TQT) study, and not enough data or PMR issued despite providing data at the time of submission. It is important to note that the full QT-IRT review could not be located within the Summary Basis of Approvals for all 56 drugs. For such drugs, assignment to one of the categories above was based on information shared in the clinical pharmacology reviews.

Concentration-QTc analyses were performed for 33 (59%) of the total NMEs using pooled PK/QTc data, specifically for 21 of 39 (54%) small molecules (**Figure 2d**; alectinib, belinostat, brigatinib, cabozantinib, carfilzomib, ceritinib, cobimetinib, enzalutamide, ixazomib, niraparib, olaparib, osimertinib, palbociclib, panobinostat, radium Ra-223, ribociclib, rucaparib, sonidegib, vandetanib, vemurafenib, and venetoclax) and 12 of 17 (71%) biologics (**Figure 2e**; atezolizumab, avelumab, blinatumomab, daratumumab, dinutuximab, elotuzumab, ipilimumab, necitumumab, nivolumab, olaratumab, pembrolizumab, and pertuzumab). Common features of most NMEs that successfully utilized this approach included a collection of PK time-matched electrocardiograms (ECGs; either triplicate ECGs or Holter monitoring with triplicate extractions) at multiple time points over the dosing interval, collection over a sufficiently wide dose/concentration range, and adequate baseline characterization in close proximity to initiation of dosing. In addition, ECGs were usually of high quality, centrally read, and interpreted by a blinded reviewer.

Dedicated QT studies were conducted for 9 (16%) of the total NMEs, including 5 of 39 (13%) small molecules (abiraterone, afatinib, axitinib, trabectedin, and trifluridine/tipiracil) and 4 of 17 (23.5%) large molecules (adotrastuzumab emtansine, brentuximab vedotin, ramucirumab, and ziv-aflibercept). TQT studies, including placebo as a

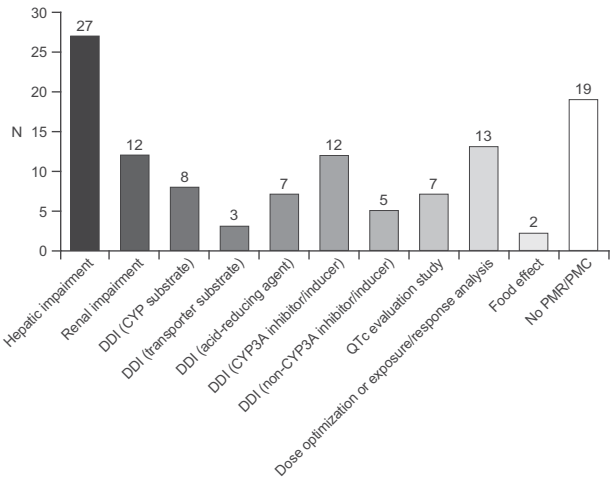

Figure 3 Summary of PMR/PMC studies requested for the 56 identified oncology NMEs across different types of clinical pharmacology evaluations. (Some NMEs had more than one PMR/PMC issued and so one NME may be counted in more than one bar.) CYP, cytochrome P450; DDI, drug-drug interaction; QTc, corrected QT.

negative control and moxifloxacin as a positive control, were conducted for 6 (11%) of the total NMEs, all of which were small molecules that could be evaluated in healthy subjects – bosutinib, idelalisib, lenvatinib, midostaurin, ruxolitinib, and vismodegib). Large increases (i.e., >20 ms) in the QTc interval were excluded for all the NMEs that conducted dedicated QT studies or TQT studies, although for several of these, small increases in QTc (i.e., <10 ms) could not be excluded due to study design limitations, such as lack of positive control (e.g., moxifloxacin).

For 4 of the total 56 NMEs (dabrafenib, obinutuzumab, pomalidomide, and regorafenib), QTc prolongation assessment had not been performed or fully completed at the time of initial submission. However, PMRs were only issued for dabrafenib and regorafenib to complete ongoing dedicated studies, and for pomalidomide to conduct a proposed TQT study. An additional four NMEs (crizotinib, ibrutinib, ponatinib, and trametinib) that implemented concentration-QTc analyses were issued PMRs to conduct dedicated QT studies. For these NMEs, results from concentration-QTc analyses were considered inconclusive because of ECG collection or interpretation issues (crizotinib and ibrutinib), uncertainty about whether the worst-case exposure scenario was evaluated (ponatinib), or for unspecified reasons (trametinib). Overall, 7 (12.5%) of the total NMEs were issued PMRs related to the need for additional QTc evaluation (**Figure 3**).

Among the 56 total NMEs, 9 NMEs (16%) were associated with the potential for QTc prolongation based on QT-IRT assessment and/or clinical safety observations; all were small molecules (ceritinib, crizotinib, lenvatinib, osimertinib, panobinostat, ribociclib, rucaparib, vandetanib, and vemurafenib). **Table 2** provides the ratios of human ether-a-go-go related gene (hERG) concentration associated with 50% inhibition (IC_{50}) to unbound steady-state maximum concentration ($C_{max,ss}$), as well as the point estimates and 90% confidence intervals (CIs) for the model-predicted QTc change from baseline at the C_{max} achieved following single-dose administration or the $C_{max,ss}$ achieved following multiple-dose administration, at the approved and/or maximum evaluated dose of these NMEs. A significant positive relationship between concentration and change in QTc from baseline was noted for all but two of these NMEs (lenvatinib and panobinostat). Cautionary language about the potential for QTc prolongation was included in the warnings and precautions section of the labels of all but one of the above NMEs (rucaparib). For vandetanib, the concerns about QTc prolongation were included as a boxed warning in the label and a risk evaluation and mitigation strategy was developed to ensure restricted access. Ribociclib received a PMR to conduct a clinical trial to evaluate the efficacy and safety of an alternative dose regimen to decrease QTc prolongation risk without compromising efficacy.

DRUG-DRUG INTERACTION EVALUATIONS

Of the 56 NMEs identified, clinical pharmacology reviews indicated that results from physiologically based pharmacokinetic (PBPK) modeling and simulation were used successfully to support clinical DDI risk evaluations for 10 agents (18%), all small molecules (alectinib, ceritinib, cobimetinib, ibrutinib, lenvatinib, olaparib, panobinostat, ponatinib, ribociclib, and sonidegib). For all but one of these agents (alectinib), use of PBPK modeling and simulation was specifically noted in the clinical pharmacology section of their respective labels.

The initial submission for ponatinib included clinical DDI data regarding the effect of a strong cytochrome P450 (CYP)3A inhibitor (ketoconazole), but not a strong CYP3A inducer, on ponatinib PK. Although the sponsor proposed conducting a postapproval study with a strong CYP3A inducer, the reviewer developed a PBPK model to simulate the effect of rifampin, a strong CYP3A inducer, on ponatinib PK in order to provide labeling recommendations on concomitant dosing with strong CYP3A inducers in the absence of actual clinical data. After confirming the model was accurate in predicting actual results from the completed ketoconazole DDI study, it was used to simulate concomitant dosing of ponatinib and rifampin, resulting in the labeling recommendation to avoid concomitant dosing of ponatinib with strong CYP3A inducers unless the benefit of coadministration outweighed the risk of reduced exposures.

For ibrutinib, the sponsor developed a PBPK model and verified its predictive ability by demonstrating that the predicted effects of a strong CYP3A inhibitor (ketoconazole) or inducer (rifampin) were similar to observed effects from dedicated DDI studies. Subsequently, the sponsor used the model to predict the effects of weak (fluvoxamine) or moderate CYP3A inhibitors (diltiazem and erythromycin) and a moderate CYP3A inducer (efavirenz) on ibrutinib PK. Additional simulations were conducted by the reviewer to predict the effect of dose staggering or ibrutinib dose reduction on ibrutinib exposures following concurrent use of strong or moderate CYP3A inhibitors, as well as the effect of ibrutinib dose increases or no dose adjustment on ibrutinib exposures following concurrent use with strong or moderate CYP3A inducers. The additional simulations, in the context

Table 2 NMEs with potential for QTc prolongation: ratios of hERG IC_{50} to unbound $C_{max,ss}$ and point estimates (90% CI) of the QTc change from baseline at C_{max} or $C_{max,ss}$ at approved and/or maximum evaluated doses

Drug	hERG IC_{50}	$C_{max,ss}$ (μg/mL)[a]	fu[b]	Ratio of hERG IC_{50} to unbound $C_{max,ss}$	QT evaluation approach	Point estimate (90% CI) for ΔQTc[c] (ms)	Concentration-dependent QTc prolongation	Label sections with QTc-related information
Ceritinib	0.4 μM (MW = 558)	1.10 (750 mg b.i.d.)	0.028	7.2	Conc-QT modeling	18.8 (17.1, 20.6) (at mean $C_{max,ss}$ of 1.10 μg/mL at 750 mg b.i.d.)	Yes	Dosage and administration, warnings and precautions, adverse reactions, clinical pharmacology
Crizotinib	1.1 μM (MW = 450)	0.478 (250 mg b.i.d.)	0.093	11.1	Conc-QT modeling	7.5 (2.3, 12.8) (at mean $C_{max,ss}$ of 0.380 μg/mL at 250 mg b.i.d.)	Yes	Dosage and administration, warnings and precautions, clinical pharmacology
Lenvatinib	11.9 μM (MW = 427)	0.562 (32 mg q.d.)	0.018	502	TQT study	-4.62 (-5.86, -3.38) (at geometric mean C_{max} of 0.370 μg/mL at 32 mg single dose)	No	Dosage and administration, warnings and precautions, adverse reactions, clinical pharmacology
Osimertinib	0.69 μM (MW = 500)	0.267 (80 mg q.d.)	0.01	129	Conc-QT modeling	14.2 (NR, 15.8) (at geometric mean $C_{max,ss}$ of 0.263 μg/mL at 80 mg q.d.)	Yes	Dosage and administration, warnings and precautions, adverse reactions, clinical pharmacology
Panobinostat	3.5 μM (MW = 349)	0.0081 (20 mg TIW)	0.102	1478	Conc-QT modeling	NR (full QT-IRT review not available)	No (dose but not concentration-dependent)	Dosage and administration, warnings and precautions, drug interactions, clinical pharmacology
Ribociclib	5.5 μM (MW = 435)	2.24 (600 mg q.d.)	0.30	3.6	Conc-QT modeling	22.6 (20.2, 25.1) (at mean $C_{max,ss}$ of 2.24 μg/mL at 600 mg q.d.)	Yes	Dosage and administration, warnings and precautions, drug interactions, clinical pharmacology
Rucaparib	22.6 μM (MW = 323)	2.42 (600 mg b.i.d.)	0.30	10.1	Conc-QT modeling	12.3 (7.6, 17) (at mean $C_{max,ss}$ of 2.42 μg/mL at 600 mg b.i.d.)	Yes	Clinical pharmacology
Vandetanib	0.4 μM (MW = 475)	0.973 (300 mg q.d.)	0.06	3.3	Conc-QT modeling	35 (33-36) (at mean $C_{max,ss}$ of 0.973 μg/mL at 300 mg q.d.)	Yes	Boxed warning, dosage and administration, contraindications, warnings and precautions (including REMS), adverse reactions, drug interactions, clinical pharmacology
Vemurafenib	1.24 μM (MW = 490)	56.7	0.0014	7.7	Conc-QT modeling	15.1 (NR, 17.7) (at 960 mg b.i.d.)	Yes	Dosage and administration, warnings and precautions, clinical pharmacology

b.i.d., twice daily; CI, confidence interval; C_{max}, maximum plasma concentration achieved after single-dose administration; $C_{max,ss}$, maximum plasma concentration achieved at steady-state after multiple-dose administration; Conc, concentration; fu, unbound fraction in plasma; hERG, human ether-a-go-go related gene; IC_{50}, concentration associated with 50% inhibition; ms, millisecond; MW, molecular weight; NR, not reported; q.d., once daily; ΔQTc, change from baseline in heart rate-corrected QT interval; REMS, risk evaluation and mitigation strategy; TIW, three times per week

[a]Mean or geometric mean values for $C_{max,ss}$ were taken from QT-IRT reviews and correspond to the maximum evaluated dose for lenvatinib or to the approved dose for all other drugs. The highest (most conservative) value is shown if different values were reported in the review. For panobinostat, the $C_{max,ss}$ value was obtained from the clinical pharmacology review.

[b]For unbound fraction in plasma, the average value is shown if a range of values was provided in the clinical pharmacology or QT-IRT reviews. The reported value for osimertinib represents a predicted rather than an experimentally determined value.

[c]Except for panobinostat and vemurafenib, the values are based on model predictions at the C_{max} at the maximum evaluated single dose (lenvatinib) or at the $C_{max,ss}$ at the approved dose (all others). In some cases, the $C_{max,ss}$ value associated with model predictions was different from the $C_{max,ss}$ value indicated in column 3. For vemurafenib, the indicated values are based on observed changes from baseline at the approved dose at the time point with the largest upper bound of the 90% CI. The highest (most conservative) values are shown if the sponsor's and reviewer's analyses yielded different values.

of exposure-response relationships, supported the recommendations to avoid concomitant dosing with strong CYP3A inhibitors requiring chronic administration, to reduce the dose by 75% in the presence of moderate CYP3A inhibitors, to avoid concomitant use of strong CYP3A inducers, and to maintain the dose in the presence of moderate CYP3A inducers.

For ceritinib, a PBPK model was verified using data from DDI studies evaluating the effect of repeated doses of ketoconazole or rifampin on the single-dose PK of ceritinib. Because ceritinib demonstrated nonlinear, time-dependent PK, the sponsor conducted simulations with repeated doses of ceritinib and ketoconazole or rifampin, which demonstrated a lower magnitude of effect of strong CYP3A inhibitors or inducers on steady-state ceritinib exposures compared with single-dose exposures. Other simulations were performed by the sponsor and/or reviewer to predict steady-state exposures of ceritinib when co-administered with a moderate CYP3A inhibitor (fluconazole) or inducer (efavirenz) at the approved dose, or when administered with a strong CYP3A inhibitor at reduced doses, and to predict the effects of repeated doses of ceritinib on the single-dose PK of a sensitive CYP3A substrate (midazolam). Overall, the simulation results were used to support labeling recommendations to reduce the ceritinib dose by approximately one-third if concomitant use with strong CYP3A inhibitors could not be avoided, to avoid the use of strong CYP3A inducers, and to avoid concurrent use of CYP3A substrates with narrow therapeutic indices or metabolized predominantly by CYP3A.

Following PBPK model verification with observed clinical DDI data, simulations were also performed instead of dedicated clinical studies to evaluate olaparib with a moderate CYP3A inhibitor (fluconazole) and inducer (efavirenz), to evaluate panobinostat with a strong CYP3A inducer (rifampin), a sensitive CYP3A substrate (midazolam), and elevated gastric pH (to mimic potential effects of gastric acid-reducing agents), and to predict the effect of lenvatinib on sensitive substrates of CYP3A (midazolam) and CYP2C8 (repaglinide). In addition, PBPK modeling and simulation was used to evaluate alectinib with a sensitive CYP2C8 substrate (repaglinide), sonidegib with a moderate CYP3A inhibitor (erythromycin) or inducer (efavirenz), and cobimetinib with a strong CYP3A inducer (rifampin), a moderate CYP3A inducer (efavirenz), and moderate CYP3A inhibitors (erythromycin and diltiazem). Additionally, PBPK modeling and simulation was used to predict the effects of acid-reducing agents, a moderate CYP3A inhibitor (erythromycin), and a moderate CYP3A inducer (efavirenz) on ribociclib exposure, as well as to predict the effect of therapeutic doses of ribociclib on a CYP3A (midazolam) and CYP1A2 substrate (caffeine), to supplement results of a dedicated study conducted with a lower dose of ribociclib.

Overall, PMRs/PMCs related to DDI evaluation were issued for 20 NMEs (36%), all of which were small molecules. **Table 3** summarizes these PMRs/PMCs, as well as additional comments provided to the sponsor that were not formal PMRs/PMCs. The most commonly requested postmarketing DDI studies involved strong CYP3A inhibitors and/or inducers for nine NMEs (abiraterone, crizotinib, dabrafenib, enzalutamide, ibrutinib, osimertinib, pomalidomide, ponatinib, and vemurafenib); one or more gastric acid-reducing agents for seven NMEs (cabozantinib, ceritinib, crizotinib, dabrafenib, ponatinib, sonidegib, and vismodegib); and one or more sensitive CYP substrates for eight NMEs (brigatinib, ceritinib, dabrafenib, enzalutamide, osimertinib, regorafenib, rucaparib, and vismodegib; **Figure 3**). Other PMRs/PMCs for DDI studies or PBPK modeling and simulation included a moderate CYP3A inhibitor (bosutinib and brigatinib) or inducer (brigatinib and palbociclib), a breast cancer resistance protein (BCRP) substrate (osimertinib), a P-glycoprotein (P-gp) substrate (rucaparib and venetoclax), a uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) inhibitor (belinostat), a CYP2C8 inhibitor (dabrafenib), a CYP1A2 inducer (pomalidomide), and oral contraceptives (vismodegib). In addition, three NMEs were issued PMRs/PMCs for completing *in vitro* studies to evaluate CYP2B6 and CYP2C induction potential (crizotinib), to evaluate CYP2B6 and CYP2C8 inhibition potential (vemurafenib), and to identify CYPs responsible for the biotransformation of an active metabolite (enzalutamide).

ORGAN IMPAIRMENT EVALUATIONS

The approaches taken for renal and hepatic impairment evaluations for the 56 identified oncology NME submissions are summarized in **Table 4**. For 30 NMEs (54%), population PK analysis in lieu of a dedicated study was deemed sufficient to evaluate one or more categories of renal impairment, whereas this was the case for 13 NMEs (23%) in the setting of hepatic impairment. In the majority of the above cases, population PK analysis was used to assess the effect of mild impairment or both mild and moderate impairment on exposure of the NME, with insufficient data to assess the effect in the remaining categories of impairment. However, for these NMEs, a PMR/PMC was not issued for the category (severe) or categories (moderate and severe) with insufficient data for population PK analysis, most likely because the particular route of clearance (renal or hepatic) was demonstrated to be minor in a human mass balance study or not expected to be relevant (e.g., monoclonal antibodies). It should be noted that as monoclonal antibodies are not expected to be cleared via renal or hepatic routes, all except dinutuximab and ramucirumab used population PK analysis to evaluate the effect of one or more categories of renal and hepatic impairment on NME exposure.

As demonstrated in **Figure 3**, requests for renal and hepatic impairment studies were among the most common reasons for which PMRs were issued among the 56 oncology NMEs. PMRs were issued to submit results from dedicated studies for one or more categories of renal impairment for 12 NMEs (21%), all of which were small molecules (**Table 4**). Although a dedicated study of mild, moderate, and severe renal impairment was completed for carfilzomib prior to submission, the evaluated dose regimen differed from the one shown to be efficacious; as such, a PMR was issued to conduct an additional dedicated study with the approved dose regimen. Brigatinib, dabrafenib, olaparib, ribociclib, and trifluridine/tipiracil were issued PMRs to complete dedicated studies that were ongoing at the time of submission (in all

Table 3 NMEs with PMRs/PMCs or comments related to evaluation of DDI potential

Drug	PMR/PMC or comment	Summary of PMR/PMC or comment
Abiraterone	PMRs	• *In vitro* evaluation of CYP2C8 inhibition potential; potential clinical DDI trial with CYP2C8 substrate depending on *in vitro* results • Clinical DDI trial to determine the effect of a strong CYP3A inhibitor (e.g., ketoconazole) on abiraterone PK • Clinical DDI trial to determine the effect of a strong CYP3A inducer (e.g., rifampin) on abiraterone PK
Alectinib	Comments	• Clinical DDI trial to determine the effect of alectinib on the PK of a sensitive P-gp substrate • Clinical DDI trial to determine the effect of alectinib on the PK of a sensitive BCRP substrate
Belinostat	PMRs	• *In vitro* assessment to determine exact contributions of UGT1A1, CYP2A6, CYP2C9, and CYP3A4 to biotransformation • Clinical DDI trial to determine the effect of strong UGT1A1 inhibitors on belinostat PK • Evaluate safety and PK in patients with wild-type, heterozygous, and homozygous UGT1A1*28 genotypes. The evaluations should be conducted for sufficient duration and in a sufficient number of subjects in order to evaluate safety following multiple dose administration.
Bosutinib	PMR	• Clinical DDI trial to evaluate the effect of a moderate CYP3A inhibitor (e.g., erythromycin) on bosutinib PK
Brigatinib	PMR	• Conduct a PBPK modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose PK of brigatinib, to assess the potential for excessive drug toxicity
	PMCs	• Conduct a PBPK modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single-dose PK of brigatinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations • Conduct a clinical PK trial to evaluate the effect of repeat doses of brigatinib on the single dose PK of midazolam (a sensitive CYP3A4 substrate) to assess the magnitude of decreased exposures of a sensitive CYP3A4 substrate and to determine appropriate dosing recommendations
	Comment	• *In vitro* evaluation of CYP2C induction potential
Cabozantinib	PMR	• Clinical DDI trial to evaluate if gastric pH elevating agents alter the bioavailability of cabozantinib (PPI first, then H2A and antacid if large effect of PPI on exposure). Results should allow for determination on how to dose cabozantinib with concomitant gastric pH elevating agents.
	Comment	• Clinical DDI trial with oral P-gp probe substrate
Ceritinib	PMRs	• Clinical DDI trial to evaluate the effect of repeat doses of ceritinib on the single-dose PK of midazolam (a sensitive CYP3A4 substrate) • Clinical DDI trial to evaluate the effect of repeat doses of ceritinib on the single-dose PK of warfarin (a sensitive CYP2C9 substrate) • Clinical DDI trial to determine if PPIs, H2As, and antacids alter the bioavailability of ceritinib, and how to dose ceritinib with concomitant gastric acid reducing agents
Crizotinib	PMRs	• Submit final report on the ongoing *in vitro* evaluations of CYP2B and CYP2C induction potential • Conduct multiple-dose trial in patients to determine how to adjust the crizotinib dose when it is co-administered with a strong CYP3A inhibitor (e.g., ketoconazole) • Conduct multiple-dose trial in patients to determine how to adjust the crizotinib dose when it is co-administered with a strong CYP3A inducer (e.g., rifampin) • Conduct trial to determine how to dose crizotinib with gastric pH elevating agents (i.e., a PPI, a H2A, and an antacid)
Dabrafenib	PMRs	• Clinical DDI trial to evaluate the effect of repeat doses of oral ketoconazole on the repeat-dose PK of dabrafenib. Results should allow determination of how to dose dabrafenib with concomitant strong CYP3A4 inhibitors • Clinical DDI trial to evaluate the effect of rifampin (a strong CYP2C8 and CYP3A4 inducer) on the repeat-dose PK of dabrafenib. Results should allow determination of how to dose dabrafenib with concomitant strong CYP2C8 and CYP3A4 inducers. • Clinical DDI trial to evaluate the effects of repeat doses of oral gemfibrozil on the repeat-dose PK of dabrafenib. Results should allow determination of how to dose dabrafenib with concomitant strong CYP2C8 inhibitors. • Clinical DDI trial to evaluate the effects of repeat doses of dabrafenib on the single-dose PK of warfarin (CYP2C9 substrate). Results should allow determination of how to dose dabrafenib with sensitive CYP2C9 substrates or CYP2C9 substrates with narrow therapeutic windows.

(*Continued*)

Table 3 Continued

Drug	PMR/PMC or comment	Summary of PMR/PMC or comment
	PMC	• Clinical DDI trial to evaluate if PPIs, H2As, and antacids alter the bioavailability of dabrafenib. The worst-case scenario can be assessed first to determine if further trials of other gastric pH elevating agents are necessary. Results should allow determination of how to dose dabrafenib with concomitant gastric pH elevating agents.
Enzalutamide	PMRs	• Perform *in vitro* screen to determine if N-desmethyl enzalutamide is metabolized by the major CYP enzymes. Clinical DDI trials may be needed based on results from the *in vitro* screen. • Clinical DDI trial to evaluate the effect of rifampin (a strong CYP3A inducer and moderate CYP2C8 inducer) on enzalutamide and N-desmethyl enzalutamide PK • Clinical DDI trial to evaluate the effect of enzalutamide at steady-state on the PK of CYP2D6 substrates • Clinical DDI trial to evaluate the effect of enzalutamide at steady-state on the PK of CYP1A2 substrates
Ibrutinib	PMR	• Clinical DDI trial to determine the effect of a strong CYP3A inducer on ibrutinib PK
	Comment	• *In vitro* evaluation of the potential for ibrutinib to inhibit transporters such as BCRP, OATP1B1, OATP1B3, OCT2, OAT1, and OAT3
Osimertinib	PMR	• Complete clinical DDI trial to evaluate the effect of strong CYP3A4 inhibitor on osimertinib PK
	PMCs	• Complete clinical DDI trial to evaluate the effect of strong CYP3A4 inducer on osimertinib PK • Complete clinical DDI trial to evaluate the effect of repeated doses of osimertinib on the PK of a CYP3A4 probe substrate • Complete clinical DDI trial to evaluate the effect of repeated doses of osimertinib on the PK of a BCRP probe substrate
Palbociclib	PMC	• Submit final report for ongoing clinical DDI trial investigating the effect of modafinil (moderate CYP3A inducer) given as multiple doses on the single-dose PK of palbociclib
Pomalidomide	PMRs	• Clinical DDI trial to determine the effect of CYP3A induction on pomalidomide PK • Clinical DDI trial to determine the effect of CYP3A inhibition on pomalidomide PK
	PMC	• Clinical DDI trial to determine the effect of a CYP1A2 inducer (such as montelukast) on pomalidomide PK
Ponatinib	PMRs	• Clinical DDI trial to determine the effect of strong CYP3A4 inducer, rifampin, on ponatinib PK • Clinical DDI trial to determine the effect of multiple doses of lansoprazole on ponatinib PK
Regorafenib	PMR	• Complete clinical trial and submit final report to evaluate the effect of repeated doses of 160 mg regorafenib on the PK of probe substrates of CYP2C8, CYP2C9, CYP2C19, and CYP3A4
	Comments	• Clinical DDI trial in subjects administered an oral P-gp probe substrate with and without regorafenib • Clinical DDI trial in subjects administered a CYP2D6 probe substrate with and without regorafenib if a DDI is demonstrated between regorafenib and a CYP2C8, 2C9, 2C19, or 3A4 probe substrate in the ongoing study • Conduct *in vitro* studies to determine if regorafenib and active metabolites M-2 and M-5 induce CYP1A2, CYP2B6, or CYP3A4 mRNA expression levels • Clinical DDI trial to determine the PK of a sensitive substrate or a substrate with a narrow therapeutic index of CYP1A2 or CYP2B6, depending on *in vitro* induction results • Clinical DDI trial in subjects administered regorafenib with and without rifaximin
Rucaparib	PMR	• Complete the ongoing DDI trial (evaluating the effect of rucaparib on the PK of CYP1A2, 2C9, 2C19, 3A4, and P-gp probe substrates) and submit the final study report
Sonidegib	PMR	• Submit final report for the clinical DDI trial to determine how to dose a gastric acid reducing agent with sonidegib
Vemurafenib	PMRs	• *In vitro* evaluation of CYP2B6 and CYP2C8 inhibition potential; potential clinical DDI trial with CYP2B6 or CYP2C8 substrate depending on *in vitro* results • Clinical DDI trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on vemurafenib PK • Clinical DDI trial to evaluate the effect of a strong CYP3A4 inducer (e.g., rifampin) on vemurafenib PK
Venetoclax	PMR	• Clinical DDI trial to determine the effect of venetoclax on the PK of an oral P-gp probe substrate

(*Continued*)

Table 3 Continued

Drug	PMR/PMC or comment	Summary of PMR/PMC or comment
Vismodegib	PMRs	• Submit final report for the ongoing clinical DDI trial to evaluate the effect of vismodegib on the PK of a sensitive CYP2C8 substrate (rosiglitazone) and of oral contraceptive components (ethinyl estradiol and norethindrone) • Clinical DDI trial to evaluate if gastric pH elevating agents alter the bioavailability and impact the steady-state exposure of vismodegib (PPI first, then H2A and antacid if large effect of PPI on exposure). Results should allow for determination on how to dose vismodegib with concomitant gastric pH elevating agents.
	Comments (applicable for future development in other indications)	• Clinical DDI study with strong P-gp inhibitor • Clinical DDI study with BCRP substrate • Conduct *in vitro* studies to assess whether vismodegib is a substrate and/or inhibitor of OATP1B1 and OATP1B3; results will determine need for clinical investigations

BCRP, breast cancer resistance protein; CYP, cytochrome P450; DDI, drug-drug interaction; H2A, H2-receptor antagonist; NME, new molecular entity; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; PBPK, physiologically based pharmacokinetic; P-gp, p-glycoprotein; PK, pharmacokinetic; PMC, postmarketing commitment; PMR, postmarketing requirement; PPI, proton pump inhibitor; UGT, uridine 5'-diphospho-glucuronosyltransferase.

Table 4 Approaches to evaluating different categories of renal impairment and hepatic impairment among the 56 oncology NMEs

	PMRs/PMCs	Approach to renal impairment evaluation, no. (%)	Approach to hepatic impairment evaluation, no. (%)
Dedicated study ongoing or completed at filing	No	10 (18)	12 (21)
	Issued	6 (11)	17 (30)
No dedicated study, population PK analysis only	No	30 (54)	13 (23)
	Issued	3 (5)	7 (13)
Neither dedicated study nor population PK analysis	No	4 (7)	4 (7)
	Issued	3 (5)	3 (5)

NME, new molecular entity; PK, pharmacokinetic; PMC, postmarketing commitment; PMR, postmarketing requirement.

categories of impairment for olaparib and in severe impairment for brigatinib, dabrafenib, ribociclib, and trifluridine/tipiracil). Of the agents that utilized population PK analysis only to evaluate the impact of one or more categories of renal impairment on exposure, PMRs for dedicated studies were issued to belinostat for varying degrees of impairment, to afatanib for moderate and severe impairment, and to vismodegib for severe impairment. Additionally, among the drugs that did not seem to conduct population PK analysis or that did not have dedicated renal impairment studies ongoing or completed at filing, a PMR was issued to crizotinib and regorafenib in the setting of severe renal impairment, and to pomalidomide for varying degrees of renal impairment.

PMRs were issued to submit results from dedicated studies for one or more categories of hepatic impairment for 27 NMEs (48%); all were small molecule entities except for ado-trastuzumab (**Table 4**). Although dedicated studies to evaluate the impact of mild and moderate hepatic impairment were completed for abiraterone and enzalutamide prior to their submissions, both received PMRs to conduct additional evaluation in severe impairment. An additional 15 NMEs were issued PMRs to complete dedicated studies that were ongoing at the time of submission: belinostat, ceritinib, ibrutinib, ponatinib, and venetoclax for varying degrees of impairment; ado-trastuzumab emtansine, olaparib, and osimertinib for mild and moderate impairment; and brigatinib, cobimetinib, dabrafenib, palbociclib, sonidegib, trabectedin, and trifluridine/tipiracil for moderate and severe impairment. Of the agents that utilized population PK analyses only to evaluate the impact of or one or more categories of hepatic impairment on exposure, PMRs for dedicated studies were issued to cabozantinib, crizotinib, and trametinib for varying degrees of impairment, to niraparib and rucaparib for moderate impairment, to alectinib for moderate and severe impairment, and to vemurafenib for severe impairment. In addition, among the drugs that did not seem to conduct population PK analysis or that did not have dedicated hepatic impairment studies ongoing or completed at filing, carfilzomib, pomalidomide, and vismodegib received PMRs to conduct dedicated studies in patients with hepatic impairment.

EXPOSURE-RESPONSE ANALYSES AND DOSE SELECTION

Table 5 indicates the approved dose relative to the maximum tolerated dose (MTD) for all reviewed NMEs. Overall, 37 NMEs (66%) were approved with starting doses less than the MTD, including NMEs for which the MTD was not reached and those with the potential for upward dose titration, whereas 19 NMEs (34%) were approved with starting doses at the MTD, including NMEs with the potential for upward dose titration beyond the MTD. Individualized dosing approaches (intrapatient upward dose titration from the MTD or a dose less than the MTD based on response and/or tolerability) were approved for six NMEs (11%; axitinib, blinatumomab, bosutinib, brigatinib, carfilzomib, and ruxolitinib). The dosage regimens (dose or schedule) of other NMEs changed over time, but the changes were meant to be applicable to all patients and not according to individual response and/or tolerability as with the previous six

Table 5 Relationship of approved dose to MTD for the 56 oncology NMEs

Approved dose relative to MTD	No. of NMEs (%)	NMEs
Less than MTD, MTD not reached or determined with approved dosing schedule	24 (43)	Abiraterone, alectinib, atezolizumab, avelumab, dabrafenib, daratumumab, elotuzumab*, ibrutinib, idelalisib, ipilimumab*, midostaurin, necitumumab, nivolumab, obinutuzumab, olaratumab, osimertinib, pembrolizumab, pertuzumab, radium-223 dichloride*, rucaparib, trifluridine/tipiracil, venetoclax, vismodegib, ziv-aflibercept
Less than MTD, MTD determined[a]	9 (16)	Afatanib, enzalutamide, ixazomib, panobinostat*, ramucirumab, ribociclib*, sonidegib, trabectedin, trametinib
Equal to MTD	17 (30)	Ado-trastuzumab* emtansine, belinostat, brentuximab vedotin, cabozantinib*, ceritinib*, crizotinib*, cobimetinib, dinutuximab, lenvatinib*, niraparib, olaparib, palbociclib, pomalidomide, ponatinib*, regorafenib*, vandetanib*, vemurafenib
Equal to MTD with potential for intrapatient dose titration	2 (4)	axitinib, bosutinib
Less than MTD with potential for intrapatient dose titration	4 (7)	Blinatumomab, brigatinib, carfilzomib, ruxolitinib

MTD, maximum tolerated dose; NME, new molecular entity; PMC, postmarketing commitment; PMR, postmarketing requirement.
Asterisks indicate NMEs with a PMR or PMC related to exposure-response analysis or additional dose evaluation.
[a]Includes NMEs for which the approved dose regimen has lower dose intensity than the maximally determined dose intensity (panobinostat, ramucirumab).

NMEs. Examples of drugs whose dose intensity (dose or schedule) changed during the treatment period include daratumumab, elotuzumab, obinutuzumab, pertuzumab, and venetoclax (**Table 1**). Notably, venetoclax was approved with a unique ramp-up dosing regimen (starting dose of 20 mg q.d. followed by weekly ramp-up to 400 mg q.d.) to manage tumor lysis syndrome.

Clinical pharmacology reviews indicated that insufficient or limited PK data were collected during pivotal trials to enable the conduct of exposure-efficacy and/or exposure-safety analyses for 16 NMEs (29%). PMRs/PMCs related to conducting exposure-response analyses or additional clinical trials for dose evaluation were issued for 5 of these 16 NMEs: panobinostat, ponatinib, radium-223 dichloride, regorafenib, and ribociclib. In total, 13 NMEs (23%) were issued a PMR or PMC to conduct exposure-response analyses using data from ongoing or future studies to determine whether the approved dose required dose optimization ($n = 5$; ado-trastuzumab emtansine, crizotinib, elotuzumab, ponatinib, and regorafenib), or to conduct additional clinical trials for definitive evaluation of alternative dose regimens ($n = 8$; cabozantinib, ceritinib, ipilimumab, lenvatinib, panobinostat, radium-223 dichloride, ribociclib, and vandetanib). Of these 13 NMEs, 10 were small molecules, of which 8 were kinase inhibitors, and 8 were approved at the MTD (**Table 5**). Among the eight NMEs with a PMR or PMC to conduct additional studies to evaluate alternative dose regimens, two (ipilimumab and radium-223 dichloride) were requested to evaluate a higher dose relative to the approved dose. Five drugs (cabozantinib, ceritinib, lenvatinib, panobinostat, and vandetanib) were requested to evaluate a lower dose, and one (ribociclib) was requested to evaluate an alternative dosing regimen that would decrease maximum plasma concentrations to decrease the magnitude of QTc prolongation. For four NMEs, although the FDA did not issue a PMR or PMC, the Agency issued comments relating to the exploration of dose optimization. Specifically, the FDA recommended additional dose exploration when more data became available from ongoing clinical studies of blinatumomab, daratumumab, and ibrutinib, and evaluation of weight-based dosing of obinutuzumab in future studies.

Although it is common in oncology drug development to evaluate a single dose regimen in registration-enabling studies based on the PK, pharmacodynamic, safety, and preliminary efficacy data observed in phase I trials, particularly when there is rapid progression from the first-in-human study to registrational trials, some NMEs evaluated more than one dose regimen within phase II studies conducted prior to pivotal studies, or within phase II or phase III pivotal studies. Ten drugs (18%) evaluated at least two dose regimens (within the same study) in phase II supportive studies: afatinib, elotuzumab, ipilimumab, midostaurin, olaparib, pertuzumab, radium-223 dichloride, ramucirumab, trabectedin, and ziv-aflibercept. For most of these drugs, the dose selected for the pivotal trial was less than the maximum dose evaluated in supportive phase II studies. In addition, four drugs evaluated two dose regimens within their pivotal trials: brigatinib, daratumumab, pembrolizumab, and sonidegib. Although two different doses were tested for ruxolitinib, these were based on baseline platelet counts and were not tested in the overall patient population. Of the 14 drugs that evaluated more than one dose regimen within the same phase II supportive study or within the same registrational study, only one (elotuzumab) received a PMC related to dose optimization.

LESSONS LEARNED FOR ANTICANCER DRUG DEVELOPMENT

This reverse translational regulatory science research focused on clinical pharmacology components of the original NDA or BLA submissions to the FDA of 56 oncology NMEs approved between January 2011 and April 2017. The purpose of this effort was to extract lessons learned from clinical pharmacology and QT-IRT reviews of recently approved oncology drugs that can be applied during the development of investigational oncology drugs. Based on the knowledge distilled from this review, a general framework can be recommended to maximize the robustness and

efficiency of the clinical pharmacology aspects of the clinical development plan of new oncology agents.

Although all NMEs included one or more clinical pharmacology studies and/or analyses in the initial NDA/BLA filings, there was considerable variation in the extent of studies and/or analyses that were completed by sponsors and included in the initial submissions of these NMEs. There were notable differences between submissions for small molecules and large molecules, specifically monoclonal antibodies, in the number and type of dedicated clinical pharmacology studies conducted. Relative to submissions for small molecules, submissions for monoclonal antibodies were more likely to rely on model-based approaches in place of dedicated clinical studies for evaluation of QTc prolongation potential and effects of organ impairment. Of the 14 monoclonal antibodies included in this review, a dedicated QTc study was conducted for only ramucirumab. This observation is not surprising because it is unlikely that these large molecules can cross cell membranes to inhibit hERG or other ion channels directly to result in delayed ventricular repolarization. Submissions for monoclonal antibodies also were more likely to utilize population PK analysis only to assess the effects of renal and hepatic impairment on PK; a dedicated renal impairment study was conducted for only elotuzumab. Again, this observation is not surprising because monoclonal antibodies undergo proteolytic degradation to amino acids and are not expected to undergo renal elimination or hepatic metabolism like small molecule drugs.

In general, clinical pharmacology packages for initial approvals were most extensive for oncology NMEs that could be evaluated in healthy subjects; however, the option to conduct clinical pharmacology studies in healthy subjects did not ensure availability of results from all required clinical pharmacology evaluations at initial filing. In fact, for agents that could be studied in healthy subjects, only four small molecules (axitinib, idelalisib, midostaurin, and ruxolitinib) obtained FDA approval without receiving any clinical pharmacology-related PMRs or PMCs. Overall, only five small molecule NMEs (the four listed above plus ixazomib) obtained FDA approval without receiving any clinical pharmacology-related PMRs or PMCs. Excluding PMRs/PMCs related to immunogenicity evaluation, which was beyond the scope of this review, the majority of large molecules (14 of 17) did not receive clinical pharmacology-related PMRs or PMCs, with the exception of ado-trastuzumab, elotuzumab, and ipilimumab, which were issued PMRs or PMCs related to dose optimization. Of note, in all three cases, the concern was regarding the proposed dose being lower than what may maximize efficacy (ipilimumab) or related to uncertainty in sufficiency of the dose and achieved exposure in patients within the low end of the population exposure range (ado-trastuzumab and elotuzumab) due to complexities in characterizing the true exposure-efficacy relationships in the setting of disease-drug interactions that can impact monoclonal antibody PK.[23–25] This is in contrast to the dose optimization-related PMRs/PMCs for small molecule drugs (e.g., cabozantinib, ponatinib, ceritinib, and ribociclib), in which the concerns more commonly stemmed from a less than desirable safety and/or tolerability profile suggesting the need to study a lower dose, an alternate regimen, or different dosing conditions, rather than a recommendation to increase exposure/dose to maximize efficacy. Overall, 19 NMEs (34%) did not receive PMRs/PMCs related to food effect, QTc, or DDI evaluation, renal and hepatic impairment, exposure-response analyses, or dose optimization (**Figure 3**).

There were a number of trends and recurring themes identified after reviewing FDA clinical pharmacology reviews and QT-IRT reviews of oncology NMEs. The first involved variability in the approach used to evaluate food effect. Although almost all orally administered NMEs examined fed conditions as a high-fat, high-calorie meal only (administered 30 min prior to dosing), there was an emerging trend toward also evaluating alternative meals (low-fat and moderate-fat) at different times relative to dosing. As previously described by Parsad *et al.*,[26] there was variation in how "empty stomach" and "take with food" were expressed in the dosage and administration sections of the labels for applicable NMEs, as well as variation in the level of detail provided about meals in the clinical pharmacology section of the labels. Finally, there were a few examples that illustrated potential consequences of not evaluating food effect during early development (vemurafenib), or not conducting the formal food effect study with the final to-be-marketed formulation or one that is not bioequivalent to the final formulation (pomalidomide). Of note, the current FDA guidance for food effect bioavailability studies and publications by key opinion leaders already recommend evaluation of food effect during early clinical development.[26–29] Understanding the impact of food can help define optimal dosing conditions or formulations for pivotal evaluations of efficacy and safety. For example, if an early food effect evaluation demonstrates a lack of substantial food effect, the drug could be administered without regard to food in pivotal evaluations, which could later support labeling without regard to food. At this point in development, the assessment of food effect would not necessarily have to rely on the 80-125% bioequivalence limits that are used for a formal food effect study. The flexibility to take the drug with or without food has the potential to decrease patient burden and increase medication compliance, which may be particularly relevant for drugs that are administered more frequently than once daily and/or on continuous dosing schedules without treatment-free periods. In addition, knowing that the drug demonstrates a positive food effect before initiation of pivotal trials can influence dose selection for pivotal trials and how the drug is administered with respect to food in these trials. Traditionally, oncology drugs with positive food effects have been administered on an empty stomach; however, there may be advantages to the administration of a lower dose with food, such as decreased PK variability for drugs with low bioavailability and improved tolerability for drugs with gastrointestinal-related AEs.[26,29] Overall, the findings from our analysis of the FDA reviews of oncology NME NDA submissions indicate that consideration should be given to evaluating food effect prior to pivotal studies, as well as alternatives to high-fat meals, which may be more reflective of actual patient diets.

Another trend observed from this review is the increasing use of concentration-QTc analysis to evaluate QTc

prolongation potential. The findings showed that concentration-QTc analysis is an acceptable, alternative approach for assessing the QTc prolongation risk instead of a dedicated or TQT study, even for drugs with clinical safety observations related to QTc prolongation. Although a TQT study in healthy volunteers has been the standard regulatory paradigm for evaluating drug-related effects on the QT/QTc interval for nononcology agents, this type of study may not be ethically or practically possible for many oncologic agents, particularly those that are cytotoxic and/or mutagenic. Thus, pooling of time-matched PK and ECG collections across studies followed by model-based analysis can provide appropriate risk assessment for QTc prolongation at initial filing. Indeed, this is in line with published guidance from the International Council for Harmonisation[30] and several recent publications on the evolving approach to assessing QTc prolongation and proarrhythmic risk of new drugs.[31–34] The concentration-QTc modeling approach also has been applied to early-phase single-ascending-dose and multiple-ascending-dose studies for nononcology agents that can be evaluated in healthy volunteers,[35,36] and results from a recent study suggest that robust QT assessment in early-phase clinical studies can replace a TQT study in healthy volunteers.[37] The current analyses highlight that certain data elements are ideal for successful use of concentration-QTc analysis. First, triplicate ECGs or triplicate extractions from Holter monitoring should be obtained over a sufficiently wide dose/concentration range (including the highest expected exposure scenario) in an adequate number of patients. The ECG collections should be standardized to the best extent possible (e.g., the same type of ECG machines should be used across different study sites). Digital readings of ECGs should be transferred to a central laboratory for blinded review by an independent cardiologist. Ideally, baseline ECGs should be collected at more than one time point and matched to the timing of post-treatment ECGs. In addition, baseline ECGs should be collected in close proximity to the first dose of the study drug instead of at any time during the screening period. If one of more these elements are missing, there is a risk that concentration-QTc modeling will not be accepted by the FDA, leading to a PMR/PMC for a dedicated QT study.

Another trend evident from our survey and also consistent with findings in another recent survey[38] is that PBPK modeling and simulation is increasingly accepted by the FDA to inform clinical DDI risk in product labeling, provided that PBPK models are first qualified with PK data from one or more clinical studies designed to evaluate the worst-case scenario with respect to DDIs or drug-genotype interactions (e.g., DDI study with a strong CYP inhibitor or inducer, or study assessing genotype-PK relationships in extensive vs. poor metabolizers).[39–41] In this context, PBPK modeling and simulation can subsequently be used to predict lower-risk scenarios (e.g., the effect of moderate inhibitors or inducers or intermediate metabolizers) and support labeling statements related to DDI risk. This approach was utilized successfully for small molecule drugs, such as cobimetinib and ibrutinib, the details of which have been previously published.[42,43] However, at the current time, a PBPK modeling approach cannot be relied upon exclusively to assess clinical DDI risk. To enable PBPK modeling, there should be a detailed characterization of the physicochemical properties of the drug as well as the determination of *in vitro* parameters of metabolism and transport processes that may contribute to *in vivo* disposition. Additionally, clinical PK data are required to assess and gain confidence in the predictive ability of the model.

This review also indicated that organ impairment evaluations represent one of the most common reasons for clinical pharmacology-related PMRs/PMCs, particularly in the setting of hepatic impairment.[8,44] This may reflect the fact that enrollment in organ impairment studies in oncology patients is challenging and may take several years to complete, particularly when enrolling patients with severe impairment. Population PK modeling was used commonly in lieu of dedicated studies to evaluate the effect of at least one category of renal or hepatic impairment, most frequently for monoclonal antibodies. Results from population PK analysis can support labeling statements regarding the effect of renal and hepatic impairment and other intrinsic factors on PK, thus reducing the number of patients required for clinical pharmacology assessment.

To ensure development of a robust population PK model that will allow evaluation of covariate effects (e.g., age, race, and renal and hepatic function) on PK and evaluation of exposure-response analyses, both intensive and informative sparse PK data should be collected throughout development, and informative sparse PK should be collected in all of the patients enrolled in registration-enabling studies. The present analyses showed that PK data collection among a sufficient number of patients in pivotal trials to enable exposure-response analyses is a key component of dose justification. Approximately one-third of the drugs that did not collect sparse PK data were issued PMRs/PMCs to conduct exposure-response analyses using data from ongoing or future trials or to conduct clinical studies to evaluate additional doses.

Issues of dose optimization are becoming increasingly important in the era of targeted therapies. This was identified as a key review issue for several oncology NMEs, as 23% of the oncology NMEs in this survey were issued a PMR or PMC related to dose optimization (i.e., to conduct exposure-response analyses and/or clinical trials to further evaluate dose). Lu *et al.*[45] reported similar results in a survey of new oncology drug approvals by the FDA from 2010–2015 that focused on PMRs/PMCs relating to outcomes associated with initial dose selection; in this survey, 27% of drugs were approved with PMRs/PMCs issued related to dose justification/optimization. In a broader review of NDAs across multiple therapeutic areas, Sacks *et al.*[46] indicated that dose concerns were the primary reason for first-cycle review failure for 16% of drugs. Although the establishment of an MTD for cytotoxic drugs may often be appropriate, it may not be necessary for some biologics or targeted small molecule drugs to provide optimal therapeutic benefit.[6,7,47,48] The findings of this review demonstrated that 66% of the 56 oncology NMEs were approved at starting doses less than the MTD, compared with 34% approved at starting doses equal to the MTD. Of the drugs approved at the MTD, 42% received

a PMR/PMC related to exposure-response analyses or additional dose evaluation compared with 14% of drugs with an approved dose less than the MTD. These results suggest that sub-MTD doses may confer optimal benefit:risk for some drugs by providing similar efficacy as MTDs but improved long-term tolerability and patient adherence over time, which may be particularly relevant for drugs to be administered continuously for a longer duration compared with traditional cytotoxic agents. In addition, the results suggest that additional opportunities exist for dose optimization of oncology drugs. Sachs *et al.*[48] reviewed strategies to achieve optimal dosing, including the integration of pharmacodynamic biomarkers into phase I studies to identify the biologically active dose range, the conduct of phase II dose-ranging studies prior to registration-enabling studies, and the use of individualized dose-titration based on clinical efficacy and safety parameters. However, these strategies are not consistently applied for oncologic agents. Although pharmacodynamic measurements can inform the bioactive dose/exposure range, dose selection based on pharmacodynamic biomarker studies is not straightforward and requires careful consideration of many factors, including mechanistic linkage of the measured pharmacodynamic effect to antitumor activity, informative study design and analysis, and quantitative understanding of the required extent and duration of effect.[49] Sacks *et al.*[46] noted that phase III studies are rarely used for dose-optimization for maximizing efficacy while minimizing toxicity, and suggested that alternative trial designs may be helpful in this context, instead of having the registrational trial dose determined early in clinical development among relatively small numbers of patients.

Overall, our analyses reported here highlight the importance of rigorous clinical pharmacology evaluations in supporting the assessment of the benefit:risk profile of oncologic agents, providing dose justification for the general population and for selected subpopulations based on age, race, organ function, genotype, and concomitant medication use, and exploring the potential for therapeutic individualization. These evaluations represent a vital component of clinical development and regulatory submissions of new oncology agents, for ensuring dose optimization and timely dosing guidelines in prescribing information across different contexts of clinical use. Regulatory review of clinical pharmacology evaluations may identify gaps in the knowledge of the clinical pharmacology profile that results in suboptimal therapeutic use in the overall patient population or in a subset of the population, and provide guidance for addressing those gaps in a timely fashion through the issuance of PMRs/PMCs.[17] Therefore, identifying issues that commonly prompt PMRs and PMCs may aid in enhancing the quality of clinical pharmacology development plans for investigational oncology drugs, ultimately enabling scientifically rigorous assessment of benefit:risk and expediting approval of oncology NMEs with robust prescribing guidance across different contexts of clinical use.

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