original report

Prediction of Drug Approval After Phase I Clinical Trials in Oncology: RESOLVED2

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abstract

PURPOSE Drug development in oncology currently is facing a conjunction of an increasing number of antineoplastic agents (ANAs) candidate for phase I clinical trials (P1CTs) and an important attrition rate for final approval. We aimed to develop a machine learning algorithm (RESOLVED2) to predict drug development outcome, which could support early go/no-go decisions after P1CTs by better selection of drugs suitable for further development.

METHODS PubMed abstracts of P1CTs reporting on ANAs were used together with pharmacologic data from the DrugBank5.0 database to model time to US Food and Drug Administration (FDA) approval (FDA approval-free survival) since the first P1CT publication. The RESOLVED2 model was trained with machine learning methods. Its performance was evaluated on an independent test set with weighted concordance index (IPCW).

RESULTS We identified 462 ANAs from PubMed that matched with DrugBank5.0 (P1CT publication dates 1972 to 2017). Among 1,411 variables, 28 were used by RESOLVED2 to model the FDA approval-free survival, with an IPCW of 0.89 on the independent test set. RESOLVED2 outperformed a model that was based on efficacy/toxicity (IPCW, 0.69). In the test set at 6 years of follow-up, 73% (95% CI, 49% to 86%) of drugs predicted to be approved were approved, whereas 92% (95% CI, 87% to 98%) of drugs predicted to be nonapproved were still not approved (log-rank $P < .001$). A predicted approved drug was 16 times more likely to be approved than a predicted nonapproved drug (hazard ratio, 16.4; 95% CI, 8.40 to 32.2).

CONCLUSION As soon as P1CT completion, RESOLVED2 can predict accurately the time to FDA approval. We provide the proof of concept that drug development outcome can be predicted by machine learning strategies.

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INTRODUCTION

Drug development in oncology is a fast-evolving field with numerous challenges.[1] More than 1,000 antineoplastic agents (ANAs) were under investigation in 2018.[2] Oncology had the highest overall attrition rate for US Food and Drug Administration (FDA) approval from phase I (95% between 2006 and 2015), phase II (92%), and phase III (67%) trials.[3,4] The community aims to limit the recruitment of patients to phase II and/or large phase III studies that evaluate treatment that will not be approved for various reasons: It impairs recruitment of patients in other studies, slows down the whole drug development process, and results in substantial financial loss for the pharmaceutical industry and academic institutions.[5] Exposure of patients to ineffective treatments and financial loss has urged the pharmaceutical industry and academic investigators to develop new tools to enhance drug development strategies,[6] such as computer-assisted decisions.

Phase I trials in oncology usually are dedicated to safety analysis and meanwhile can provide early signals of efficacy of the compounds.[7] Classic strategies to improve research and development[5] are the use of surrogate markers of efficacy (overall response rate as a surrogate of overall survival)[8,9] or predictive biomarkers of efficacy (molecular alterations from the tumor or liquid biopsy).[10,11] The biomarker-based strategy used in phase I can significantly increase response rate and the likelihood of FDA approval.[12]

A tool to predict FDA approval for new compounds individually on the basis of early clinical data is still lacking. Pharmacologic data may be a cornerstone to perform such predictions for compounds with original targets or new mechanisms of action. High-volume pharmacologic data are currently available in open-source databases, such as DrugBank5.0.[13] In the current study, we aimed to demonstrate the feasibility and utility of a recommender system that is based on machine learning and that could enhance drug development (RESOLVED2) in oncology by

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

We aimed to evaluate the feasibility and utility of a machine learning recommender system to predict drug development outcome in oncology and, therefore, to support an early go/no-go decision as soon as phase I trial completion.

Knowledge Generated

RESOLVED2 is a lasso penalized Cox regression model. To train RESOLVED2, we developed a new metric, US Food and Drug Administration (FDA) approval-free survival, defined by the time between publication of the first early clinical trial that reports the clinical effect of a drug and FDA approval, censored by date of last news. From pharmacologic data and the early clinical trial's PubMed abstracts, RESOLVED2 can predict accurately the time to FDA approval for an antineoplastic agent.

Relevance

Our work demonstrates that machine learning approaches can enhance drug development in oncology by supporting early go/no-go decisions on the basis of prediction of drug approval.

supporting an early go/no-go decision as soon as phase I trial completion.

METHODS

ANAs: Identification and Selection

We extracted all PubMed abstracts in English and related to phase I trials in oncology that evaluated ANAs for adult patients (package RISMed in R version 3.3.3), without limitation for date of publication (Data Supplement). Drug names were extracted from the titles of PubMed articles by regular expressions (package stringr). Drug names were identified by their suffix; for example, all monoclonal antibody names were queried from the mab suffix (see Data Supplement for suffix list). For encoded drug names, we extracted drug codes using the following regular expression: get any word with two to four numerical characters, optionally followed by one to eight digital characters ("\\b[:alpha:]{2,4}-?[:digit:]{1,8}\\b").

All article titles where no drug or code was identified were manually checked. The PubChem database[14] and Chemical Identifier Resolver[15] were downloaded to annotate all identified drugs with all available aliases. Individual drug names/codes were manually confirmed by a search of the National Cancer Institute Drug Dictionary,[16] PubChem,[14] and Google (Mountain View, CA) and to obtain an alias for a drug code, when available.

ANA Annotations: Pharmacologic Data

To use pharmacologic characteristics in modeling, we matched drugs identified from the PubMed abstract corpus to DrugBank5.0 database identifiers.[13] From DrugBank5.0, we extracted the drug pharmacologic category and drug molecular target.[17] Briefly, the *.xml database file was downloaded and processed using a Python-based program (ElementTree module; Python Software Foundation, Wilmington, DE). Each drug was annotated with feature lists of various lengths; each feature was transformed as binary variables (Data Supplement). Scripts are available at https://github.com/DITEP/RESOLVED2.

Results of Early Clinical Trial Data

For each ANA, the earliest phase I trial (without ANA combination) was selected as follows: the first clinical study reporting observations of tolerability in human, or the first phase I trial, or the first-in-human trial, regardless of the inclusion criteria. Drugs for which the earliest phase I trial abstract was not available were excluded. We selected only drugs initially developed as ANAs (ie, antibiotics or anti-rheumatoid agents subsequently developed as ANAs were not retained). In addition, when only phase II trial publications were available in PubMed, conference abstracts that reported dose escalation results from phase I were considered (see the Data Supplement for the abstract identifier list).

The following variables were manually extracted from abstracts: primary tumor sites; study enrichment with a specific tumor site; and mention of drug target, dose expansion cohort, molecular biomarkers, pathologic biomarkers, circulating biomarkers, dose-limiting toxicity (DLT) or maximum tolerated dose (MTD), antitumor clinical activity, complete tumor response, objective response rate, occurrence of Common Terminology Criteria for Adverse Events (version 4.0) grade V treatment-related adverse event, and treatment-related cardiac or neuropsychological adverse events (see the Data Supplement for variable definitions).

Primary Outcome of Interest: FDA Approval-Free Survival

We considered time to FDA approval as a right-censored variable to consider the unknown probability of future approval for drugs under follow-up. The FDA approval database (Drugs@FDA) was extracted from the FDA portal on July 30, 2018, and thus considered as the date point for the nonapproved drugs.[18] FDA approval was considered an event, whereas drugs without FDA approval were censored at the time of date point. We defined FDA approval-free survival (FDA-aFS) as the time between the first publication date of the earliest phase I trial to the date of first FDA approval, censored by date of last news.

Statistical Analysis: Machine Learning Model and Performance Evaluation

Descriptive statistics were used to describe the earliest phase I trial data (absolute value and percent for binary variables; median and interquartile range [Q1-Q3] for continuous variables). FDA-aFS follow-up was described using the Kaplan-Meier method, with median, range, and Q1-Q3.

Statistical analyses were performed with R version 3.3.3 (see https://github.com/DITEP/RESOLVED2 for scripts). The data set was randomly split using the package caret in a training set (70% for model training) and a test set (30% for model performance evaluation) with similar time distribution. The test set remained unused during all training. All DrugBank5.0 categorical features were encoded as binary variables. Finally, all features were binary variables. To maximize the number of drugs with complete annotation, variables were rejected rather than drugs when missing data were more than 2.5%.

A multivariable Cox model with lasso penalization was trained to predict the FDA-aFS for each ANA.[19] To avoid overfitting and to allow feature selection, inverse performance of the lasso (L1 normalization) penalization parameter (λ-value) was minimized on a 100-fold cross-validation set derived from the training set with the package glmnet.[20]

Performance of the RESOLVED2 predictions for FDA-aFS was estimated by the concordance index (C-index) using both nonweighted (survcomp package) and weighted (inverse of the probability of censoring weighted estimate [IPCW]; pec package) methods. The area under the receiver operating characteristic curve (AUROC) was computed using the predicted probabilities and censored survival data at a cutoff of *t*-years (survivalROC package).

We compared RESOLVED2 predictions to those that are based on variables frequently used to estimate the success of a phase I trial: clinical activity detected (yes/no), whether complete responses are reported, and identification of DLT or MTD reached. The so-called EffTox model was trained using the same method and split rules as RESOLVED2, without penalization.

To facilitate interpretability and applicability of RESOLVED2, a binary classification model was computed from the previously computed scores. The main objective was to identify, and therefore prevent, the development of predicted nonapproved drugs to improve the current important attrition rate in drug development (ie, drugs that will fail to be approved after phase II/III trials). The training set was used to identify the cutoff that maximized the difference in observed FDA-aFS between predicted approved drugs and predicted nonapproved drugs (corresponding to minimizing the log-rank–derived *P* value). FDA-aFS was described using Kaplan-Meier curves and *t*-year event rate estimations. Significance was defined as $P < .05$.

RESULTS

FDA-aFS of ANAs

On the basis of the Medical Subject Headings term search, 2,606 PubMed entries were identified as early clinical trials that assessed ANAs (Data Supplement). Among these, 2,415 publication titles were found to quote one drug or more (Fig 1). There were 619 compounds that matched to 551 DrugBank5.0 entries (Data Supplement). Sixty-eight compounds derived from a parent compound were not registered in DrugBank5.0 (ie, liposome-encapsulated drugs, pegylated drugs, modified galenic forms) or were prodrugs/compounds not used as therapeutic agents (floxuridine for fluorouracil, exisulind for sulindac, ATP), and 314 drugs did not match any DrugBank5.0 entry (Data Supplement). Among the 551 DrugBank5.0 entries, 486 (88%) were developed initially as ANAs. For 24 drugs, the earliest phase I trial publications were identified, but abstracts were not available (Fig 1).

Finally, 462 drugs were selected for which the earliest phase I trial dates of publication ranged from June 1972 to October 2017, with 368 (80%) trials published after 2000. On the basis of abstract text, most phase I trials included all cancer types (68%) and mentioned a drug target (80%), at least one DLT observed or MTD reached (77%), and a clinical activity of efficacy (69%). Few abstracts mentioned a dose expansion cohort (16%) or a molecular biomarker (9%; Table 1).

The median follow-up was 134 months (range, 1 to 425 months; Q1-Q3, 77-203 months). At 3 and 6 years of follow-up, 13% (95% CI, 10% to 16%) and 20% (95% CI, 16% to 24%) of drugs have been approved, respectively. Overall, we observed that 131 (28%; 95% CI, 24% to 32%) of the 462 drugs obtained FDA approval. The nonapproved drug with the shortest follow-up was depatuxizumab mafodotin (10 months), whereas the longest was observed for treosulfan (495 months).

Training of the Models to Predict FDA Approval

PubMed abstract data and DrugBank5.0 annotations resulted in 1,411 binary variables. Ten drugs were removed because of unavailable data for clinical activity or DLT identified/MTD reached. The overall response rate was not considered because of too much unavailable data (Table 1).

The multivariable Cox model was penalized with the lasso procedure, which thus facilitated feature selection by filtering nonzero learned coefficients (Data Supplement). Twenty-eight features were finally selected (Fig 2; Data Supplement). Relevant treatment targets (*PDGFRα1*, *PD-L1*, *HDAC1*), pharmacokinetic properties (*CYP450* substrates/modulators; P-glycoprotein *ABCB1* substrates/modulators), and drug categories (kinase inhibitors, purine analogs, antibodies, proteins) were among the best predictors of FDA-aFS. Phase I trial results with complete

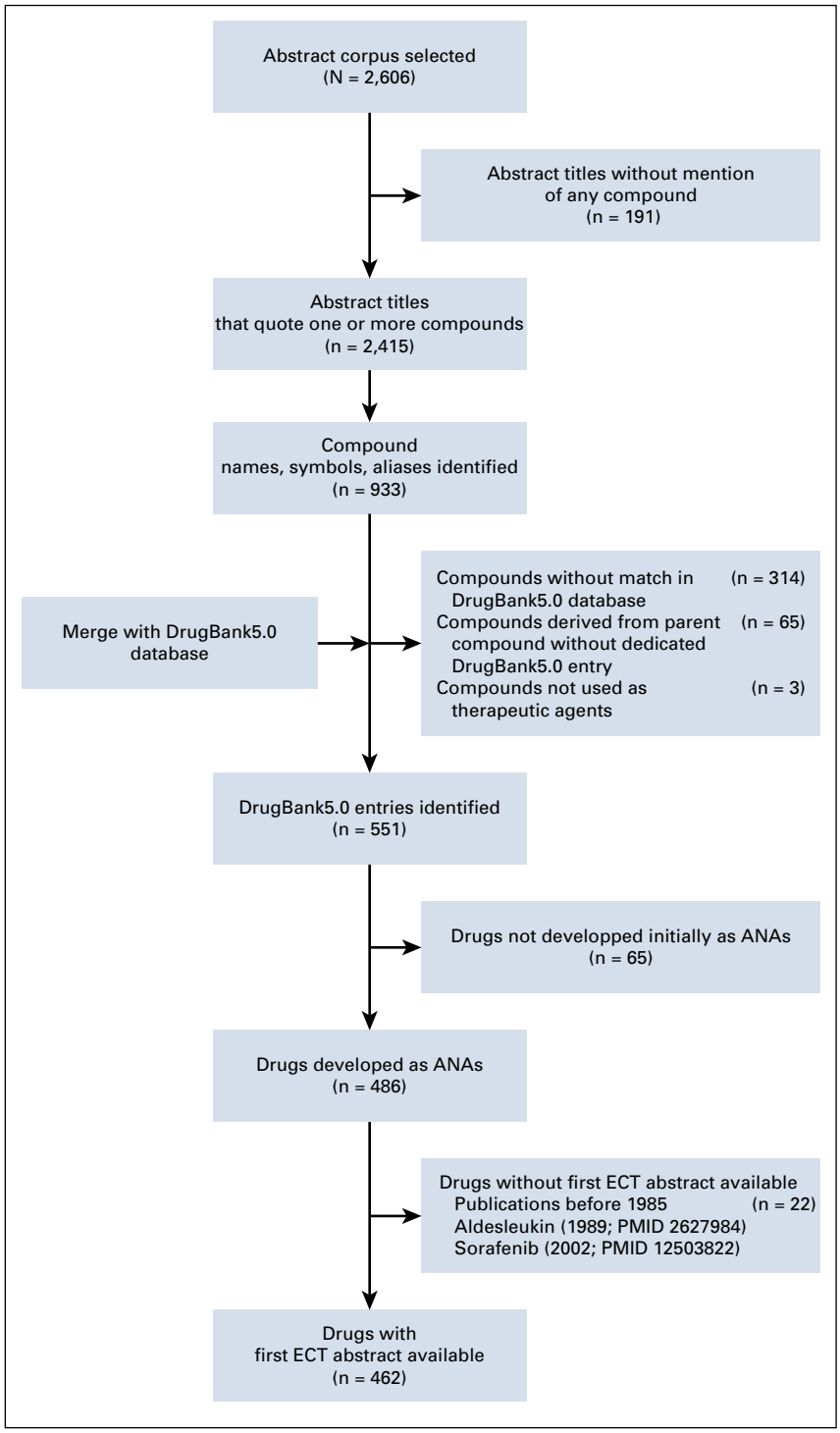

FIG 1. Flow chart for drug selection. ANA, antineoplastic agent; ECT, early clinical trial.

response reported and trial designs such as tumor type enrichment or selection, dose expansion cohort, and molecular biomarker (Fig 2) also were identified as important features (see Data Supplement for DrugBank5.0 feature definitions and drug annotations with model features).

The predictive score for FDA-aFS was used for classification. The cutoff found in the training set that maximized the FDA-aFS difference between predicted approved drugs and predicted nonapproved drugs (Data Supplement; Fig 3A) also was applied and evaluated in the independent test set.

Generalization of Predicted FDA Approval on the Test Set

The predictions of RESOLVED2 were highly related with the observed FDA-aFS of ANAs included in the previously unseen test set. For the time-dependent scores, the nonweighted C-index was 0.90, and the weighted C-index (IPCW) was 0.89. Moreover, the AUROCs on the basis of

TABLE 1. ECT Data Extracted From Abstracts

Feature (No. of ECTs with available data)	No. (%)
Median (Q1-Q3) No. of patients included (440)	32 (22-51)
Date of publication (462)	
Before 1989	24 (5)
1989-1993	21 (5)
1994-1998	40 (9)
1999-2003	77 (17)
2004-2008	92 (20)
2009-2012	105 (23)
2013-2017	103 (22)
ECT that enrolled all tumor types (462)	312 (68)
ECT enriched in a particular tumor type (462)	187 (40)
Drug target mentioned in ECT abstract (462)	370 (80)
Healthy volunteers included (462)	7 (1.5)
Dose expansion cohort (462)	76 (16)
Median (Q1-Q3) No. patients included in expansion cohort (76)	26 (15-37)
Molecular biomarkers considered (462)	43 (9)
Pathologic biomarkers considered (462)	28 (6)
Circulating biomarkers considered (462)	9 (2)
Clinical antitumor activity mentioned (456)	315 (69)
DLT identified or MTD reached (458)	354 (77)
Median (Q1-Q3) best objective response rate reported (356)	5 (0-20)
Complete response reported (456)	74 (16)
Grade V* TRAE reported (462)	13 (3)
Cardiac† TRAE reported (462)	41 (9)
Neuropsychological† TRAE reported (462)	34 (7)

NOTE. For feature definitions, see Data Supplement.

Abbreviations: DLT, dose-limiting toxicity; ECT, early clinical trial; MTD, maximum tolerated dose; Q1-Q3, interquartile range; TRAE, treatment-related adverse event.

*According to the Common Terminology Criteria for Adverse Events (version 4.0).

†Defined as any cardiac, neurologic, or psychiatric condition mentioned as a TRAE in the abstract.

Kaplan-Meier curves were 0.97 and 0.94 at 3 and 6 years, respectively (Data Supplement).

As a comparison, performances of the EffTox model in the test set (Data Supplement) were lower in terms of concordance (C-index, 0.79; IPCW, 0.69) and in terms of sensitivity and specificity (survival AUROCs were 0.76 and 0.84 at 3 and 6 years, respectively; Data Supplement).

The classifier version of RESOLVED2 predicted that 81% of ANAs from the test set would be nonapproved. Predictions were strongly related with observed FDA-aFS (Fig 3B). For example, at 3 years of follow-up, 95% (95% CI, 91% to 99%) of predicted nonapproved drugs were not approved, whereas 50% (95% CI, 27% to 66%) of predicted approved drugs were indeed approved. For a later follow-up of 6 years, we found that 92% (95% CI, 87% to 98%) of predicted nonapproved drugs were still not approved, whereas 73% (95% CI, 49% to 86%) of predicted approved drugs were indeed approved. A predicted approved drug was 16 times more likely to be approved than a predicted nonapproved drug (hazard ratio, 16.4; 95% CI, 8.40 to 32.2; $P < .001$). Proportional hazard assumption was verified (cox.zph R function).

Applications of RESOLVED2

We applied RESOLVED2 on recent examples of early drug development (Table 2; Data Supplement). Rovalpituzumab tesirine is a bispecific antibody developed for a hard-to-treat cancer type, namely small-cell lung cancer. Epacadostat is an indoleamine 2,3-dioxygenase 1 inhibitor developed in combination with immune checkpoint blockers for melanoma. On the basis of available data from single-agents publications (epacadostat being not yet indexed in DrugBank5.0), RESOLVED2 found that rovalpituzumab tesirine had a probability of FDA approval within 6 years of 73%, whereas epacadostat had a 92% risk of nonapproval. Only longer follow-up will confirm or not these predictions. We also applied RESOLVED2 predictions for treatments with relatively complex development and finally approved (Table 2). Of note, four of five treatments were indeed predicted approved, and the one missed by RESOLVED2 had nevertheless a relatively high score. Several false-positives of the classifier should be mentioned (14 drugs predicted nonapproved but finally approved among 109 predicted nonapproved drugs in the test set); however, scores of these 14 drugs were also relatively high, close to the classifier threshold (Data Supplement).

DISCUSSION

Given the limited success rate of recent ANA development in oncology, the improvement of an early go/no-go decision after a phase I clinical trial is a timely challenge. RESOLVED2 used the earliest phase I PubMed abstracts and simple pharmacologic characteristics to predict the likelihood of FDA approval for individual ANAs. When RESOLVED2 was used for classification, it was highly correlated with time to approval in the independent evaluation test set; within the first 6 years of follow-up, RESOLVED2 predictions were correct for 73% of approved drugs and for 92% of nonapproved drugs. RESOLVED2 potentially could reduce by 81% the number of ANAs undergoing further development and that would fail to achieve FDA approval.

Features included in the RESOLVED2 model supported its external validity. For instance, we found that targeting the immune checkpoint inhibitor programmed cell death-ligand 1 was associated with successful development.[21,22] The model also included drug characteristics related to antibodies, such as complement C1q subcomponent subunit A target, antibodies, and proteins, or related to targeted therapies, such as kinase inhibitors and known targets (platelet-derived growth factor receptor α-1, histone deacetylase 1). Trial designs also played an important role

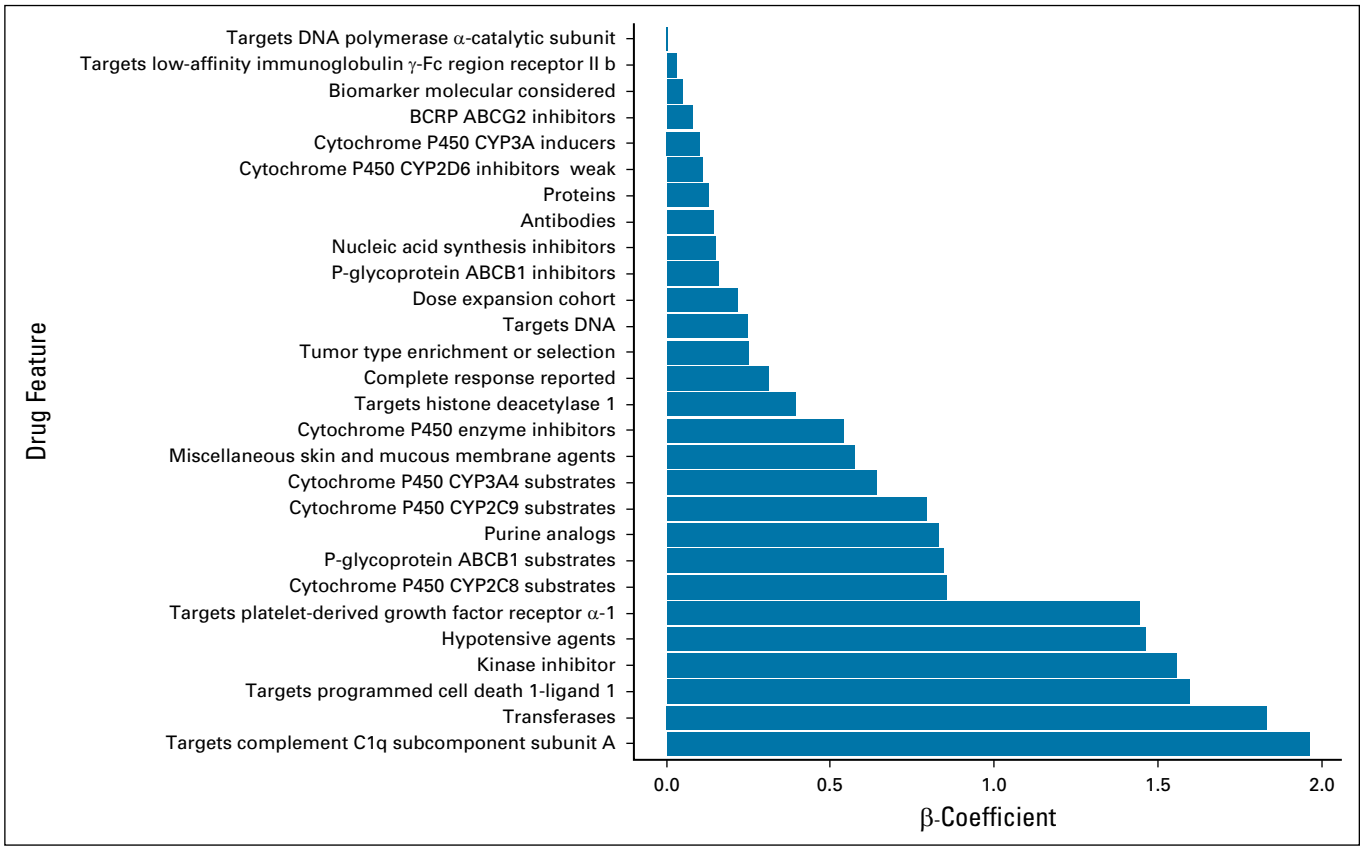

FIG 2. RESOLVED2 model. β-Coefficients from lasso-penalized Cox model. For feature definitions, see the Data Supplement. The best lasso penalization parameter (λ_{min}-value) was determined using a 100-fold cross-validated Cox regression model on the training set (Data Supplement). Evolution of penalized β-coefficients with λ-values are depicted in the Data Supplement. A Cox regression model L1 (lasso) penalized with the λ_{min}-value identified by cross-validation ($6.59.10^{-2}$) was fit to allow feature selection and associated β-coefficient computation.

in RESOLVED2 predictions, such as the use of molecular biomarkers, cohort enrichment with specific tumor types, and a dose expansion cohort. These findings are consistent with the positive impact of biomarker-based strategies in oncology[10] along with the rise of precision medicine both in clinics[23,24] and in the drug development landscape.[1,25] Features that describe cytotoxic chemotherapy targets or categories also were found as predictive of drug approval, such as purine analogs and DNA interacting agents. Overall, RESOLVED2 used features that describe therapeutic breakthroughs, which could suggest that the development of innovative drugs should be preferred to development of me-too drugs.

Some limitations should be stressed. With regard to the data used, among 619 ANAs retrieved in PubMed, 314 were not recorded in DrugBank5.0. The approval rate in our cohort was 28%, which was higher than the 5% likelihood of approval reported elsewhere.[3] This could be explained by the selection of compounds reported in both the PubMed and the DrugBank5.0 databases. A publication bias also could have influence our model (ie, delayed phase I publication that reports a promising drug; restriction to English-written abstracts). To date, RESOLVED2 provides a probability of approval for compounds given as monotherapy. Predicting approval for treatment combinations is a current challenge that would require dedicated data and/or a flexible modeling approach that can be derived from RESOLVED2.

As reported in 2018, FDA approval regulations evolve quickly[26] to improve the balance between enhanced drug access and patient safety.[27,28] The Cox model assumes that the strength of predictors is constant over time. Because it has been trained on data from a long time interval (1972 to 2017), RESOLVED2 predictions may have been influenced by approval rules evolution. Despite that the good performance of RESOLVED2 was confirmed on an independent test set with a similar time distribution, it would benefit from future independent prospective validation. Another assumption of the Cox model is that events are independent: Here, drug A approval could have influenced drug B approval. Nevertheless, the strength of such dependencies is arguable. For example, me-too drugs are approved equivalently for the treatment of tumor types such as kidney cancer (four anti-angiogenic ANAs), *BRAF*-mutated melanomas (two *BRAF* inhibitors), and *EGFR*-mutated lung adenocarcinomas (six small molecules)

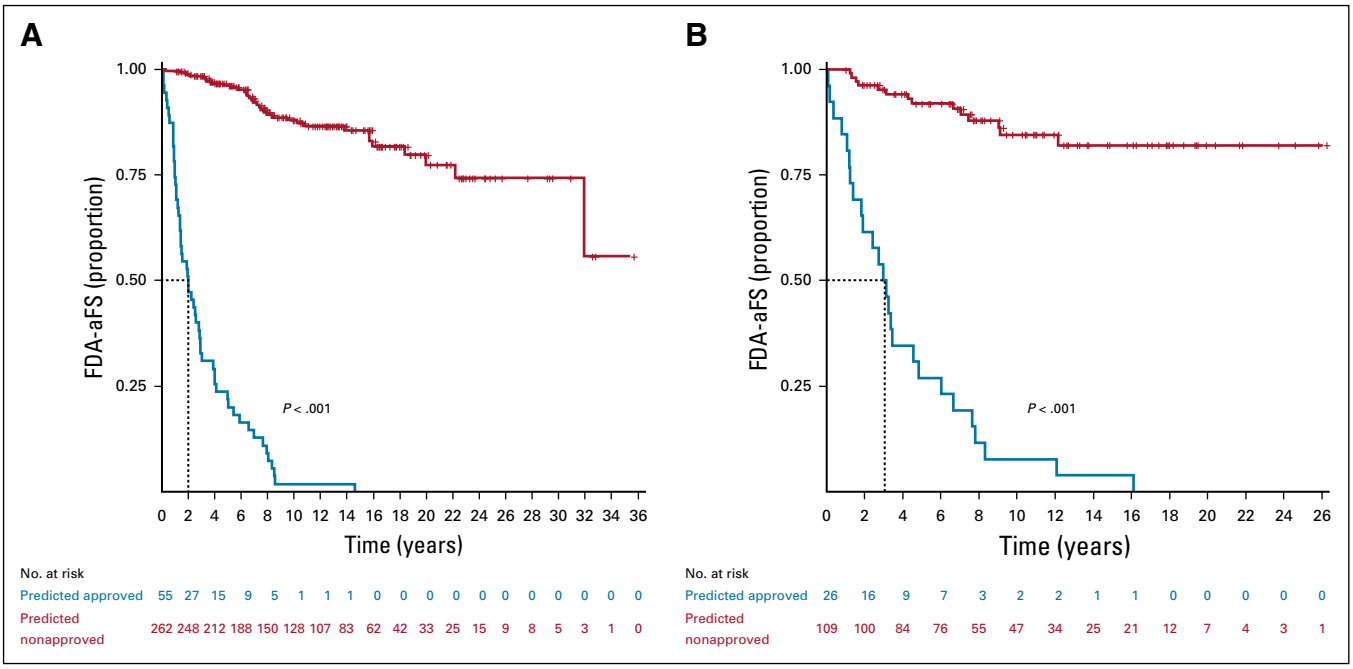

FIG 3. US Food and Drug Administration approval-free survival (FDA-aFS). Kaplan-Meier curves of FDA-aFS. (A) FDA-aFS according to the RESOLVED2 classification in the training set. Predicted approved and nonapproved antineoplastic agents refer to binary predictions performed using the RESOLVED2 classifier on the basis of RESOLVED2 scores. In this plot, the training set was split using the optimal cutoff calibrated on a minimal log-rank derived *P* value (see Methods section). (B) FDA-aFS according to the RESOLVED2 classification in the test set. The test set was split using the optimal cutoff in RESOLVED2 scores identified in the training set (see Methods section).

(https://www.nccn.org/professionals/physician_gls/default.aspx[29,29a]). On the other hand, me-too drugs also can fail to obtain approval because of poor activity or safety. For example, panitumumab has failed approval in head and neck cancers, whereas cetuximab is a long-standing standard of care.[30] To evaluate the added value of RESOLVED2 compared with the current approach, we designed EffTox as a proxy on the basis of variables most frequently used to estimate the success of a phase I trial when limited information on a drug is available. Despite that the final approval decision is highly contextual and uses more information, standardized decisions in this context are becoming more frequent.[31,32] A basic approach such as EffTox and an advanced approach such as RESOLVED2 could be applied to support decisions in this context.

Using a model for censored data to predict drug approval is new, accounts for heterogeneity in follow-up, and maximizes the amount of data used, including recent examples. The lasso-penalized Cox model offers the advantage of only one hyperparameter to train, which is valuable in the context of a limited number of examples. Moreover, it facilitates the interpretation of the model by automated feature selection and generation of hazard ratios per feature, which is valuable compared with ensemble modeling

TABLE 2. Applications of RESOLVED2: Examples

Drug	Corresponding DrugBank5.0 Entry	PMID	Granted FDA Approval	Date of Approval	Delay (in months) From Date of Early Phase I CT to FDA Approval or Censoring (July 2018)	RESOLVED2 Score	RESOLVED2 Binary Prediction
Cabazitaxel	Cabazitaxel	19147780	Yes	June 17, 2010	17.4	13.138	Predicted approved
Abiraterone	Abiraterone	15150570	Yes	April 28, 2011	82.7	4.170	Predicted nonapproved
Cabozantinib	Cabozantinib	21606412	Yes	November 29, 2012	17.0	31.834	Predicted approved
Palbociclib	Palbociclib	21610706	Yes	February 3, 2015	91.9	19.822	Predicted approved
Olaratumab	Olaratumab	24452395	Yes	October 19, 2016	33.5	5.556	Predicted approved
Rovalpituzumab tesirine	Rovalpituzumab tesirine	27932068	No	NA	18.9	15.671	Predicted approved
Epacadostat	Not indexed	28053021	No	NA	12.9	1.000	Predicted nonapproved

Abbreviations: CT, clinical trial; FDA, US Food and Drug Administration; NA, not applicable; PMID, PubMed identifier.

technics or neural networks, for example.[33] With regard to the choice of data, numerous drug databases with various topics and aims are available[34,35]; DrugBank5.0 had the advantage to provide qualitative, accurate, and manually curated annotations on pharmacologic properties and drug targets.[13]

In conclusion, the seminal RESOLVED2 experience showed that machine learning models could efficiently support early go/no-go decisions before phase II/III trials.[36,37] Such models could improve the current landscape of drug development for patients, academic centers, and the pharmaceutical industry.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Research Funding: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi, Bayer, Johnson & Johnson, Eli Lilly, Medimmune, NH TherAGuiX

Other Relationship: AbbVie, Agios Pharmaceuticals, Amgen, Argen-X BVBA, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca, Aveo, Bayer Healthcare AG, BBB Technologies BV, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corporation, Chugai Pharmaceutical, Clovis Oncology, Daiichi Sankyo, Debiopharm SA, Eisai, Eli Lilly, Exelixis, Forma, Gamamabs, Genentech Glaxosmithkline, H3 Biomedicine, Hoffmann La Roche AG, Innate Pharma, Iris Servier, Janssen Cilag, Kyowa Kirin Pharmaceutical Research, Loxo Oncology, Lytix Biopharma AS, Medimmune, Menarini Ricerche, Merck Sharp & Dohme-Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology NV, Oncoethix, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Pfizer, Pharma Mar, Pierre Fabre, Roche, Sanofi Aventis, Taiho Pharma, Tesaro Xenco

Antoine Hollebecque

Honoraria: Merck Serono

Consulting or Advisory Role: Amgen, Spectrum Pharmaceuticals, Eli Lilly

Research Funding: AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringher Ingelheim, Janssen Cilag, Johnson & Johnson, Eli Lilly, Medimmune, Merck, NH TherAGuiX, Novartis, Pfizer, Roche, Sanofi

Travel, Accommodations, Expenses: Servier, Amgen, Eli Lilly

Other Relationship: AbbVie, Agios Pharmaceuticals, Amgen, Argen-X BVBA, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca, Aveo, Bayer Healthcare AG, BBB Technologies BV, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corporation, Chugai Pharmaceutical, Clovis Oncology, Daiichi Sankyo, Debiopharm SA, Eisai, Eli Lilly, Exelixis, Forma, Gamamabs, Genentech, GlaxoSmithKline, H3 Biomedicine, Hoffmann La Roche AG, Innate Pharma, Iris Servier, Janssen Cilag, Kyowa Kirin Pharmaceutical Research, Loxo Oncology, Lytix Biopharma AS, Medimmune, Menarini Ricerche, Merck Sharp & Dohme-Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology NV, Oncoethix, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Pfizer, Pharma Mar, Pierre Fabre, Roche, Sanofi Aventis, Taiho Pharma, Tesaro Xencor

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Honoraria: Pierre Fabre, OmniSeq

Consulting or Advisory Role: Adaptherapy, Pierre Fabre

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