OXFORD

JNCI J Natl Cancer Inst (2020) 112(8): djz212

doi: 10.1093/jnci/djz212
First published online November 13, 2019
Brief Communication

BRIEF COMMUNICATION

Impact of Precision Medicine on Efficiencies of Novel Drug Development in Cancer

Holly Sarvas, Benjamin Carlisle, Samantha Dolter, Esther Vinarov, Jonathan Kimmelman

See the Notes section for the full list of authors' affiliations.

Correspondence to: Jonathan Kimmelman, PhD, Studies of Translation, Ethics, and Medicine, McGill University Biomedical Ethics Unit, 3647 Rue Peel, Montreal, Quebec H3A 1X1, Canada (e-mail: jonathan.kimmelman@mcgill.ca).

Abstract

Precision medicine (PM) offers opportunities for reducing the costs, burdens, and time associated with drug development. We examined time, number of trials, indications tested, and patient burden needed to achieve first U.S. Food and Drug Administration license for all five novel anticancer PM drugs and all 10 novel non-PM drugs receiving U.S. Food and Drug Administration approval during 2010–2014. The 15 drug portfolios encompassed 242 trials: 87 for PM drugs and 155 for non-PM drugs. Embase and MEDLINE databases were searched for all prelicensure clinical trials, and data on time, patient numbers, indications tested, and total treatment-emergent grade 3–5 adverse events were measured from the first trial of each drug. We did not find patterns suggesting greater efficiencies in PM compared with non-PM. Gains in efficiency for PM drug development may be offset by challenges with recruitment.

Developing new drugs is costly and time consuming and exposes patients to potentially unsafe drugs (1,2). Precision medicine (PM) drug development strategies, which target patients most likely to benefit from a new drug using biomarkers, have the potential to reduce the time, cost, and burden associated with drug development (1). For example, development of imatinib for Ph+ cancers required less than 5 years from first patient enrollment date to U.S. Food and Drug Administration (FDA) approval (3).

Below, we compare the time, trials, patient burden, and additional licensures associated with research activities preceding the first FDA approval for all novel anticancer PM drugs with non-PM drugs approved by the FDA during 2010–2014. We selected all novel first-in-class (4) drugs receiving their first FDA approval as anticancer therapy from January 1, 2010, to December 31, 2014. This time frame captured drugs that are widely used currently while allowing at least 4 years since approval to assess secondary approvals. Nonnovel drugs were excluded because our focus was on the impact of PM on innovation. Eligible drugs ("index drugs") were classified as PM and non-PM based on whether first approval labels reflected a marker-selected indication. For a list of all drugs, their FDA approvals, exclusions, and how they were classified, see Supplementary Table 1 and Supplementary Figure 1 (available online).

Embase and MEDLINE databases were searched March 1, 2018, for trials of all index drugs, using Medical Subject Heading terms and other keywords alongside the drug names and synonyms. No date restrictions were applied. The complete search strategy (5), along with the 15-drug synonym lists, can be found in Supplementary Tables 2, 3, and 4 (available online).

Inclusion criteria for publications were full journal publication, trial initiated before first FDA approval, reporting primary results, testing a cancer indication, efficacy and/or safety endpoint, and English language. Exclusion criteria were secondary or interim reports in which the primary endpoint was not reached or completed, observational studies, case studies, and neoadjuvant, radiotherapy, cryotherapy, or phototherapy combination studies. Publication inclusion was censored at 4 years after a drug's initial FDA approval to ensure same follow-up

Received: July 17, 2019; **Revised:** October 13, 2019; **Accepted:** October 24, 2019

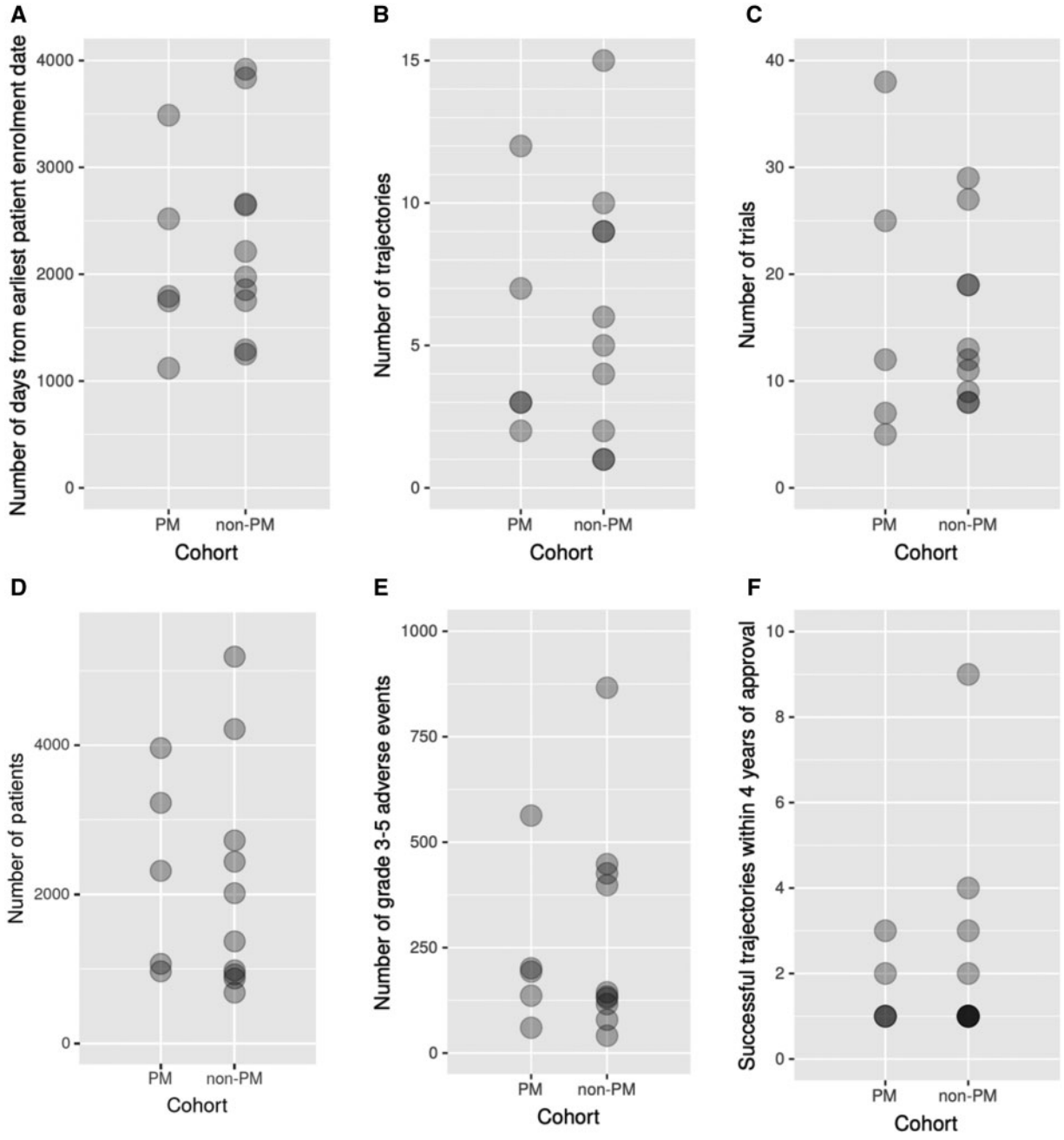

Figure 1. A comparison of drug development efficiencies prelicensure between precision medicine (PM) and non-PM novel, first-in-class oncology U.S. Food and Drug Administration (FDA)-approved drugs from 2010 to 2014. **A)** Time: time elapsed between first enrollment date of the first trial and date of first FDA approval. **B)** Indication trajectories: number of prelicense drug-indication or combination-indication pairings tested. **C)** Trials: number of published prelicense trials. **D)** Patients: number of enrolled patients in published prelicense efficacy or safety trials. **E)** Grade 3–5 adverse events: number of enrolled patients in published prelicense efficacy or safety trials, total number of treatment-emergent grade 3–5 adverse events. **F)** Successful trajectories including first license: the first license trajectory and the number of prelicense trajectories resulting in additional FDA approvals within 4 years of the first approval. Each circle represents an index drug in each cohort.

time for each drug. A PRISMA flow diagram is available in Supplementary Figure 2 (available online).

We extracted the following items from all trials: study design, patient enrollment, indications, whether patients were screened for biomarkers on trial entry, safety data, and whether the development trajectory led to FDA approval or was unproductive (based on a search conducted on June 1, 2018 of FDA-approved indications). Where possible, missing enrollment dates were imputed from associated clinicaltrials.gov registration records. Where data were unavailable, corresponding authors were emailed.

Trials were extracted independently by two coders, and disagreements were resolved by discussion. Analysis and graphing (*ggplot2* package) were conducted using R v. 3.4.1 (6).

Table 1. Comparison of PM and non-PM primary endpoints

Cohort	Patients, No.	Days, No.	Trials, No.	Adverse events, No.	Trajectories, No.	Successful trajectories, No.	Patients in successful trajectories, %*
PM	—	—	—	—	—	—	—
Ado-trastuzumab	2316	2519	12	201	2	1	96.4
Crizotinib	968	1120	5	60	2	1	86.6
Olaparib	3962	3488	38	563	9	3	43.1
Trametinib	3227	1793	25	193	7	2	79.7
Vemurafenib	1069	1750	7	136	3	1	91.7
PM median (mean)	2316 (2308)	1793 (2134)	12 (17)	193 (231)	3 (5)	1 (2)	86.6 (79.5)
Non-PM	—	—	—	—	—	—	—
Abiraterone	2723	1974	13	79	1	1	100.0
Blinatumomab	981	3837	8	144	1	1	100.0
Brentuximab	873	1752	11	116	4	2	83.4
Cabozantinib	928	2646	9	130	2	1	53.5
Eribulin	2016	2658	19	866	9	1	62.8
Ibrutinib	2438	1292	19	448	9	4	61.2
Idelalisib	1370	2213	12	398	6	3	37.4
Ipilimumab	5187	3919	29	426	10	1	36.1
Pembrolizumab	4216	1252	27	134	15	9	94.4
Vismodegib	683	1855	8	41	5	1	13.8
Non-PM median (mean)	1693 (2142)	2094 (2340)	13 (16)	139 (278)	6 (6)	1 (2)	62.0 (64.3)

*Percentage of patients enrolled in efficacy trials from indications put into testing before licensure that led to an FDA approval within 4 years' follow-up from first FDA licensing events, compared with patients in efficacy trials from all indications put into testing before licensure. FDA = U.S. Food and Drug Administration; PM = precision medicine.

The primary goals of this study were to compare PM vs non-PM prelicense clinical development activities based on time elapsed between first enrollment date of the first trial and date of first FDA approval, number of prelicense drug-indication or combination-indication pairings tested, number of published prelicense trials, number of enrolled patients in published prelicense efficacy or safety trials, total number of treatment-emergent grade 3–5 adverse events according to the Common Terminology Criteria for Adverse Events (2), and the number of prelicense trajectories resulting in additional FDA approvals within 4 years of the first approval. For this last item, we reasoned that knowledge about markers acquired in prelicense testing might lead to attainment of additional indication labels within a few years of approval. Statistical analysis was not performed because of the small cohort of drugs available; all assessments were qualitative.

In total 15 drugs were included in our cohort: five that were PM and 10 that were non-PM. Their drug portfolios encompassed 242 trials: 87 trials for PM drugs and 155 trials for non-PM drugs. A list of all trials is available in the Supplementary Methods (available online).

There was a large variation in the number of patients (968–3692 for PM and 683–5187 for non-PM), days (1120–3488 for PM and 1252–3919 for non-PM), trials (5–38 for PM and 8–29 for non-PM), and adverse events (60–593 for PM and 41–866 for non-PM) to first FDA licensure across the drug cohorts, and visual inspection of Figure 1 did not suggest substantial differences between PM and non-PM drugs. No pattern was found in the number of new licenses obtained 4 years postlicensure between PM and non-PM. PM may have a small advantage in number of malignancies tested prelicensure (Figure 1B). A description of the results is found in Table 1.

Improvements in drug development efficiencies as a result of using PM approaches were modest in our sample of drugs. Compared with novel, first-in-class drugs that were not initially developed using a PM strategy, PM drugs did not show striking improvements on most measures of efficiency, with the possible exception of number of indications explored. One plausible explanation for the lack of gains for PM drugs is that accrual may be slower for biomarker-enriched trials because of screening requirements (7). Whereas 25.8% prelicense trials used enrichment designs, 60.9% used prelicense trials testing PM used enrichment designs.

Our study has limitations. First, a small number of drugs was available for inclusion (8). Second, our analyses were based only on full-text published reports, because registration records during this period did not generally contain adverse event information (9). However, a search of clinicaltrials.gov for first trial date did not meaningfully change our results (Supplementary Table 5 available online). Third, our classification of drugs as PM vs non-PM is not a perfect distinction given a mechanism of action may be PM despite not having a biomarker indication, or drugs may acquire PM or non-PM properties later. One example is the CD-30–directed brentuximab vedotin, for which we found no large changes if it was reclassified as PM (Supplementary Table 6; Supplementary Figure 3 [available online]). However, our classification was driven by our goal of distinguishing between drugs that relied primarily on biomarker indications at initial license.

Drug development continues to demand a large amount of resources, time, and patients to get a drug to market. Although our study does not rule out the possibility that PM approaches have improved drug development efficiencies, the effects have not been dramatic.

Funding

This work was supported by the Canadian Institute for Health Research (PJT-148726) and Genomics Canada (PACEOMICS).

Notes

Affiliation of authors: Studies of Translation, Ethics, and Medicine, McGill University Biomedical Ethics Unit, Montreal, Quebec, Canada (HS, BC, SD, EV, JK).

The funder had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

JK serves on a data and safety monitoring board for Ultragenyx Pharmaceuticals. The authors declare they have no other competing interests.

The authors thank Noga Aharony and Sean Zhang for assistance with the extraction and reconciliation work for this manuscript. The authors thank Adelaide Doussau de Bazignan for her advice regarding data analysis and interpretation of findings for this study.

References

1. Collins FS. Reengineering translational science: the time is right. *Sci Transl Med*. 2011;3(90):90cm17.
2. US Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE) Version* 5.0. 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed August 15, 2019.
3. Sacha T. Imatinib in chronic myeloid leukemia: an overview. *Mediterr J Hematol Infect Dis*. 2014;6(1):e2014007. doi:10.4084/MJHID.2014.007.
4. US Food and Drug Administration Center for Drug Evaluation and Research. Novel Drugs Summary; 2016. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm534863.htm. Accessed April 20, 2018.
5. Mattina J, Carlisle B, Hachem Y, Fergusson D, Kimmelman J. Inefficiencies and patient burdens in the development of the targeted cancer drug sorafenib: a systematic review. *PLoS Biol*. 2017;15(2):e2000487.
6. R Core Team. *The R Project for Statistical Computing*. https://www.r-project.org/. Accessed April 20, 2018.
7. Freidlin B, McShane LM, Korn EL. Randomized clinical trials with biomarkers: design issues. *J Natl Cancer Inst*. 2010;102(3):152–160.
8. Personalized Medicine Coalition. Personalized medicine at *FDA: 2017 Progress Report*. 2017. http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_at_FDA_2017_Progress_Report.pdf. Accessed August 15, 2019.
9. Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009;(1):MR000006.