The Imprecision of Precision Medicine in Cancer Drug Development: A Systematic Comparative Analysis

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TABLE OF THE CONTENTS

Abstract ..... **iii**

Résumé ..... **iv**

Acknowledgements ..... **v**

Preface ..... **vi**

Chapter 1 – Introduction: The Benefits and Limitations of Precision Medicine Cancer Drug Development **1**

Chapter 2 – Methodology for a Systematic Comparative Analysis on Published Literature of Novel, First-in-Class Cancer Drugs **13**

Tables & Figures **21**

Chapter 3 - Results of the Systematic Comparative Analysis Demonstrating the Gains and Limitations to Precision Medicine Drug Development **33**

Tables & Figures **42**

Chapter 4 – Reflections, Limitations, Recommendations, and Conclusions from the Results of the Systematic Comparative Analysis **57**

Appendix A: List of Studies Included in Systematic Comparative Analysis .. **vii**

ABSTRACT

Precision medicine (PM) in cancer typically involves matching patients to treatments based on molecular characteristics of their tumour. PM drug development is often viewed as more rapid and requiring fewer patients than non-precision medicine approaches. As drug development is an expensive process that exposes patients to significant risks, this vision for PM drug development is highly attractive. This thesis presents the rationale and results of a systematic comparative analysis of all published trials in first-in-class, novel oncology drugs that were first FDA-approved between 2009-2014. Fourteen drugs were included, five in the PM cohort and nine in non-PM cohort. We collected 339 trials – 109 trials in PM, and 230 trials in non-PM. PM took a comparable amount of time (median 1750 days in PM v. 1825 days in non-PM; range 1120-3458 in PM vs. 929-3127 in non-PM) and patients (median total n 1909 in PM v. 1265 in non-PM; range 986-2610 in PM v. 655-5009 in non-PM) between the first efficacy trial and the receipt of their first FDA licensing event when compared to non-PM. The PM cohort explored a comparable number of drug-indication trajectories, was more likely to use surrogate endpoints than "hard" clinical endpoints, was just as likely to have patients experiencing a Grade 3-4 adverse event, and dropped biomarker for eligibility in later trajectories when compared to non-PM. The thesis is a small, observational, retrospective analysis that may not be generalizable to all novel oncology drugs. Nevertheless, these findings suggest that precision medicine may not be as effective in sparing time and patients in drug development. Going forward, institutions, sponsors, and policymakers should be aware of this thesis's results and take the findings into consideration for actions concerning precision medicine drug development in oncology.

RÉSUMÉ

La médicine de précision (MP) en cancérologie consiste à prescrire des traitements selon les caractéristiques biologiques de la tumeur. Le développement pharmaceutique de la médecine de précision est souvent considéré comme potentiellement plus rapide et nécessitant moins de patients que les approches classiques. Cette perspective est très attractive, du fait que le développement pharmaceutique est un processus extrêmement couteux, et qui expose des patients à des risques importants.

Cette thèse présente le rationnel et les résultats d`une analyse comparative systématique des essais de nouvelles molécules *« first-in-class »* en oncologie ayant obtenu l`autorisation de mise sur le marché (AMM) de la FDA entre 2009 et 2014. La comparaison comprenait une cohorte de MP avec cinq médicaments et une cohorte de médicaments classique (non-MP) avec neuf médicaments. Nous avons collecté des données sur 339 essais – 109 essais de MP, et 230 essais de non-MP.

Le délai entre l`obtention d`AMM et le premier essai d`efficacité était comparable pour le groupe de médicaments MP et non-MP (médiane de 1750 jours vs. 1825 jours, respectivement; plage : 1120-3458 jours v. 929-3127 jours, respectivement). Le nombre de patients était similaire (médiane du nombre de patient par médicament : 1909 dans le groupe MP vs. 1265 dans le groupe non-MP ; plage : 986-2610 dans la groupe MP v. 655-5009 dans la groupe non-PM). Le nombre d`indication par médicament et la proportion de patients qui ont présenté un évènement indésirable de grade 3 ou 4 étaient comparable dans les deux groupes ; cependant le groupe MP utilisait plus fréquemment des critères de jugement intermédiaires que le groupe non-MP, et tendait à ne plus utiliser de critères d`inclusion basés sur les biomarqueurs dans les trajectoires tardives.

Cette étude est une étude rétrospective, observationnelle sur un petit nombre de molécules qui pourrait ne pas être généralisable à tous les traitements anticancéreux. Néanmoins, ces résultats suggèrent que la médecine de précision pourrait ne pas vraiment avoir d`impact en termes de réduction des délais et du nombre de patients. A l`avenir, les institutions, les promoteurs et les instances règlementaires de la recherche devraient reconsidérer ces paramètres pour le développement pharmaceutique de médicaments de médecine de précision.

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PREFACE

Chapter 1: Author Holly Sarvas conducted the literature review and writing of Chapter 1. Jonathan Kimmelman and Sean Zhang provided editorial assistance.

Chapter 2: Author Holly Sarvas determined primary and secondary outcomes, defined outcome boundaries (with input from previous research conducted in the lab), created Tables and Figures, and wrote Chapter 2. Jonathan Kimmelman designed the initial protocol of the study and provided editorial assistance.

Chapter 3: Author Holly Sarvas performed all data analysis, created all Tables and Figures (with code and templates partially provided by Benjamin Carlisle), and wrote Chapter 3. Jonathan Kimmelman and Adelaide Doussau provided input and editorial assistance.

Chapter 4: Author Holly Sarvas performed the literature review and writing of Chapter 4. Jonathan Kimmelman, Sean Zhang, Aden Feustel, and Benjamin Carlisle provided editorial assistance.

Chapter 1 Introduction: The Benefits and Limitations of Precision Medicine Cancer Drug Development

Precision medicine in cancer sets out to match patients to drugs based on molecular characteristics of a tumor [1]. There have been great successes in this field, including the HER2 targeting trastuzumab for breast cancer and the BCR-ABL inhibitor imatinib for Ph+ cancers [2]. Many believe that precision medicine drugs can target patients most likely to benefit, and produce fewer off-target adverse events [3].

With the completion of the Human Genome Project, lower costs for genetic sequencing, and a higher level of knowledge of cancer at the molecular level [3], treatments incorporating precision medicine have come to represent a 'norm' in oncology. The goal, for many, is to create a precision medicine framework that allows for "the right treatment, at the right time, every time to the right person" [4]. Such a proposition may come at a cost. For example, the Precision Medicine Initiative in the United States is budgeted at $215 million [4]. The FP7 and Horizon 2020 initiatives of Europe have already spent an estimated 3.2 billion euros from 2010 to June 2017 [5]. And precision medicine drugs can come with large price tags. For example, in 2016, the blockbuster drug imatinib's wholesale price was estimated at $146,000/year [6]. With such enormous stakes, it is imperative a critical lens is placed on the potential returns for drug development using precision medicine approaches.

Drug Development Process

Canonical development typically follows a regimented process. First, a drug must show efficacy and safety in pre-clinical models, including establishment of major toxicities and minimally effective dose [7]. The drug is brought to human testing, with Phase I testing dozens (median of 25 patients/trial [8]) of patients producing information on pharmacokinetics, pharmacodynamics,

safety (i.e. maximum tolerated dose), and preliminary efficacy [9]. The drug is advanced into Phase II testing if an adequate safety profile is established, where further exploration (n >100) of efficacy is performed, along with continued observation of safety [9]. Usually, the final step is Phase III testing, where a sample of 100s of patients determine if the new drug performs better than standard-of-care in both efficacy and safety [9]. If the drug shows significant efficacy over the standard-of-care, or similar efficacy and/or a significant improvement in safety profile, then the drug can be considered for an FDA-approved license [10].

Drug development is a lengthy process. According to some estimates one drug takes approximately 13 years [11] and over $2.7 billion [12] to get to market. These extended processes ensure adequate statistical power for estimating safety and efficacy [13]. Nevertheless, this lengthy process also means that access to new drugs is restricted to patients who participate in trials for prolonged periods. Some patient advocates urge earlier access to unproven drugs [13], and multiple trial designs have been proposed to optimize the drug-development process and allow more rapid patient access [14, 15]. Drug development also exposes a large number of participants to unproven and potentially unsafe drugs [16]. Often, patients are withheld from standard-of-care options [17, 18]. Designs are currently being implemented to increase effect size of the drug, so that fewer patient-participants are exposed to establish a drug's efficacy [14, 19].

Ethics of Drug Development

Patient-participants take on significant risks by choosing to enter into a trial. Risks include serious adverse events and fatalities from drugs [20]. Additional risks outside the experimental drug include risks from secondary tests (biopsies, scans, etc.) [21], and unanticipated toxicities when in combination with other treatments [22].

Because trials are not without significant risk, and the participants have intrinsic worth and dignity, investigators owe due care before initiating and enrolling participants into that trial. This position is emphasized by The Tri-Council Policy Statement 2 (TCPS2) of Canada [23] and Belmont Report [24] of the United States (US). The two documents outline the following ethical principles: Respect for Persons, Concern for Welfare (Beneficence), and Justice. To summarize briefly, these documents state research participants should be adequately informed of what will or could occur in the trial they are taking on, the investigator should ensure an adequate risk-benefit balance before initiating a trial, and no participant or group of participants should take on any additional unequal burden when entering into a trial [23, 24].

There appears to be a lack of awareness regarding how these principles would play out for the drug development process, as opposed to for individual trials. In particular justice and beneficence at the drug portfolio level. A drug portfolio is a collection of trials that includes all pursued trials in the development process of a drug pre- and post-licensure, which includes all indications and combinations [25]. Drug portfolios at the macro-level can impact the patient-participant at the micro-level. When examining the drug portfolios of sunitinib and sorafenib, a significant number of studies conducted were duplicative or in indications with only very minor modifications [26, 27]. Studies by Mattina [26] and Carlisle [27, 28] show that after the first licensed indication, trajectories in cancer drug development have exhaustive indication exploration with limited additional gains for future patients. Many 'label-extending' trials will be conducted through exploratory means and if one 'hits' then it can be developed further to extend the label, or just prescribed off-label without any additional efficacy information [28]. These activities call into question the principles of beneficence – as duplicative studies do not reflect an adequate risk-benefit balance with answers already being known, [25] and justice - as those

patients who enter later in the drug development trajectory are taking on more risk than those earlier on [25, 26, 27]. Without principal investigators and participants aware of the macro-scale development of the drug, participants may be consenting to enter a trial that is not likely to produce benefit either for the participant or downstream patients.

Benefits of Precision Medicine Drug Development

Ultimately, cancer drug developers seek to introduce drugs into human research that will take less time and fewer patients to bring to market. One possible method of achieving this is through precision medicine. Targeted agents can gain FDA approval faster, with fewer patients being needed to receive an approval [29]. One reason that this might be is through enrichment design. An enrichment design uses the presence of a marker to determine eligibility into the trial [30]. By sub-dividing the population to those believed to be most likely to respond, trials can detect a "signal" of efficacy with fewer patients [30]. If a drug does see significant difference in shorter endpoints, accelerated approval can often be granted to these precision medicine drugs ahead of phase 3 testing [14, 31]. Examples of this include the accelerated approval of imatinib on the basis of Phase II trials, and ceritinib on the basis of a Phase I trial [32].

In theory, precision medicine approaches should streamline drug development. By having extensive pre-clinical and biological studies performed ensuring a specific target and histology, more is often known about the drug before it enters clinical testing [33]. Upon entering clinical testing, the goal is to note effect in a specific drug-histology-biomarker triad, with minimal testing performed outside that trajectory.

Potential Limitations of Precision Medicine Drug Development

Precision medicine drug development is not without limitations, however. When using a smaller number of patient-participants prior to FDA approval, there is less power for safety signal detection [30]. Or, trials may involve less total patient exposure to a drug. This means rarer, or long-term adverse events are less likely to be detected compared to those non-precision medicine cancer drugs that went through more extensive, long-term testing [34]. As post-market monitoring of adverse events is often limited, [35, 36] there is a chance that patients can be given a harmful drug without proper knowledge of what risks they are taking on.

The more frequent use of surrogate endpoints throughout the precision medicine development process can also have negative consequences [14, 31]. By relying heavily upon short-term endpoints such as response rate, and progression-free survival, there is potential that these drugs will not actually provide any significant clinical benefit (namely, overall survival) when compared to their standard-of-care [37, 38]. This can be seen with vemurafenib for BRAFV600E+ metastatic melanoma, where the drug initially showed significant improvement in progression-free survival for metastatic melanoma, but once accounting for resistance during Phase III testing, did not have a large impact in overall survival [39].

Finally, precision medicine trials often involves more research burdens of the patient-participant, such as tumour biopsies to perform target profiling [21]. As such, screening may entail additional burden. Moreover, if biopsies are performed for exploratory molecular analyses, this can lead patients taking on additional non-negligible risks, including pneumothorax, bleeding, or infection, without any direct benefit [21].

Thesis Introduction

The most rigorous method for analysis of the literature is a systematic review. Systematic reviews involve a methodological approach that can minimize bias and increase precision. [40]. Systematic reviews involve establishing a clear research question, followed by a comprehensive and reproducible search strategy to identify the relevant literature [41]. Time and trial must be taken to ensure that the search strategy includes all relevant literature to the topic [41]. This is to diminish the chance of including reporting bias, and skewing results positively or negatively [42].

Most advances in precision medicine have occurred in the past couple decades [3]. While some systematic reviews have been conducted on precision medicine drug development such as drugs trajectories with respect to their pharmacogenomic marker inclusion criteria [43], and potential economic advantages [29], there is still limited analysis about the precision medicine drug process. To the author's knowledge, there has not yet been a comparative analysis of precision medicine drugs to non-precision with respect to their collective drug development portfolios (as described in Ethics of Drug Development). Reflection of the benefits in the precision medicine drug development process is imperative, given the many problems seen in previous non-precision medicine drug portfolios [27, 28]. However, this must also exist alongside what drawbacks can occur from a faster, less patient-intensive process.

The purpose of this thesis is to describe some of the gains and limitations of precision medicine approaches to drug development. Gains will be defined as more rapid and less patient exposure needed to receive a first FDA approval. Limitations will be defined as more limited safety signal at the point of FDA approval, less clinical endpoints use in later phase trials, and more exploratory biomarker testing. This will be achieved through a systematic comparative

analysis of a cohort of first-in-class, novel cancer drugs approved by the FDA from 2009 to 2014.

The search and screening methods and description of outcomes regarding first-in-class oncology drugs will be discussed in Chapter 2. Chapter 3 will present the findings of the comparative analysis including time to approval, number of patients to approval, exploration of biomarkers, frequency of serious adverse events experienced, and patients in successful trajectories. Chapter 4 will summarize the findings and then provide a brief ethical analysis and implications of the imprecise portions of precision medicine drug development alongside the current landscape of research oncology and how to address these implications.

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Chapter 2 Methodology for a Systematic Comparative Analysis on Published Literature of Novel, First-in-Class Cancer Drugs

The goal of Chapter 2 is to describe the data collection methods utilized to perform intense systematic review. Sections include: drug sampling, trial sampling, extraction, reconciliation & analysis, statistics, and outcomes. Tables and Figures relevant to the methods are present at the end of the Chapter. This Chapter will set-up how and for what purpose results were derived for Chapter 3.

Drug Sampling

We set out to identify all published trials of drugs that met the following criteria:

(a) A novel, first-in-class anti-cancer drug using the FDA definition [1]:

> Novel drugs and novel molecular entities (NMEs): Novel drugs are often innovative products that serve previously unmet medical needs or otherwise significantly help to advance patient care and public health. NMEs have chemical structures that have never been approved before. However, in some cases an NME may have actions similar to earlier drugs and may not necessarily offer unique clinical advantages over existing therapies.
>
> First-in-class: Drugs with a new and unique mechanism for treating a medical condition.

(b) Drug received first FDA approval between 2009-2014, inclusive. Drugs were excluded if they were minor modifications of already approved drugs. The timeframe of 2009-2014 was selected to ensure both relevance to the novelty of precision medicine, while also allowing some data for post-licensure events. The identified drugs were separated into two groups: precision and non-precision. These were defined based on whether they were only approved on the basis of a marker selected population for which there is a predictive claim. There were five drugs that fit

the precision medicine cohort and nine that fit the non-precision medicine cohort (See **Table 1**). Novel drugs were used both for feasibility purposes and to ensure we were reflecting the future of oncology drug practices.

Two drugs challenged this criterion. Blinatumomab was ultimately included in the Non-PM cohort, because it treats patients with acute lymphoblastic leukemia who are Philadelphia (Ph) chromosome negative [2]. Ultimately, blinatumomab is a salvage drug, providing some sort of therapy for those who cannot benefit from the effect of BCR-ABL inhibitors who are Ph chromosome-positive [2]. It does not work off the effect of the Ph chromosome per se [2].

While omacetaxine mepesuccinate was identified by the FDA as a novel, first-in-class non-precision oncology drug in the year 2012 it was ultimately excluded from our study due to its closeness to homoharringtonine [3]. Homoharringtonine was widely used in the 1990s for refractory chronic myeloid leukemia [3]. After the invention of imatinib, homoharringtonine was seen as obsolete [3]. The invention of its semi-synthetic derivative, omecetaxine mepesuccinate, was an attempt to re-invigorate the drug for use in CML patients [3]. Omacetaxine also presented difficulty in differentiating trials that were solely the natural product and those that used the semi-synthetic derivative. For the sake of ensuring our sample focused on drugs that were truly novel and reflected the drug of interest, we excluded omacetaxine.

Trial Sampling

Published trials were sought in EMBASE & Medline databases from June 2017 to August 2017. All searches were conducted using the OvidSP search platform. The databases included were Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE (dates of coverage from 1948 to 2018 [dates dependent]) and EMBASE Classic + EMBASE databases (dates of coverage from 1974 to 2018 [dates dependent]). This search strategy was used previously in two

systematic reviews of drug development [4, 5]. The search was reviewed by a university librarian during that time to ensure inclusivity of relevant studies. The search strategy for both EMBASE and Medline can be found in **Table 2** and **Table 3**, respectively. Specific search terminology for each drug can be found in **Table 4**.

Entries from all searches were exported into Zotero, de-duped, and then screened. Inclusion criteria for the publications included the following (a) full journal publication, (b) initiated any time before FDA approval of the drug or up to five years after initial FDA approval (c) a prospective trial (d) reporting primary results or primary results with prospectively described marker stratification in a subsequent, linked publication (e) testing a cancer indication, (f) efficacy and/or safety endpoint and (g) English language. Exclusion criteria for trials included (a) retrospective analyses of samples gathered in trials (b) secondary reports, (c) interim reports, (d) meta-analyses/systematic reviews (d) laboratory analyses of ex vivo human tissues, (e) preclinical studies, (f) observational studies, (g) case studies, (h) solely healthy volunteer (i) neo-adjuvant, radiotherapy, cryotherapy combination studies.

Entries were initially screened on the basis of title alone. If the entry could not be eliminated on title alone then it was assessed based on abstract. Entries that could not be eliminated via abstract were finally eliminated through full-text reading. All screens were initially performed independently by screeners Esther Vinarov or HS. To assess for inter-coder agreement, a minimum 5% randomized concordance check was performed within Excel with an online random generator by the person who was not the initial screener. A minimum 95% concordance agreement in screening was met for each drug to be passed to extraction. The primary screener for vemurafenib and crizotinib was EV; HS was the primary screener of all other drugs.

Extraction, Reconciliation, & Analysis

We extracted the following from all trials meeting eligibility: a) basic demographics b) patient enrolment c) indications d) biomarker screening e) randomization f) efficacy outcomes g) safety data, and h) whether the development trajectory was productive. For the PM cohort items additional items extracted were a) biomarker testing and b) biomarker outcomes. An example of the precision medicine and non-precision medicine extraction template are provided in **Figure 1**, and **Figure 2**, respectively. Where possible, missing enrolment dates were inferred from the associated clinicaltrials.gov registration record. Where data were unavailable, corresponding authors were emailed. Response rates to the emails were 17 percent.

Indications were grouped based on anatomical site (i.e. breast, ovarian, liver); for hematologic cancers there was division for leukemias and lymphomas and then further sub-division for common sub-groups. For groupings of indications, see **Table 5**.

Trials using an efficacy primary endpoint were categorized as 1) positive, 2) inconclusive, or 3) negative based on whether a pre-defined primary efficacy endpoint was attained with statistical significance. In cases where trials used multiple primary endpoints and results were inconsistent or no pre-defined endpoints were provided, trials were deemed inconclusive. Efficacy endpoints were ranked from shortest (least likely to reflect clinical efficacy) to longest (most reflective of clinical efficacy) [6], respectively: overall response rate (ORR) (immune-response, RECIST, and haematologic criteria), progression-free survival (PFS), and overall survival (OS). We recorded the highest frequency treatment-related Grade 3-4 adverse event and the total number of treatment-related Grade 5 adverse events for each arm according to the National Cancer Institute Common Terminology Criteria of Adverse Events [7]. The highest frequency Grade 3-4 event was used for all trials regardless of phase and whether the

exact number of events was known. This method ensured we did not penalize drug trials that did report on all events, as safety reporting was highly variable between trials.

Trials were extracted independently by two coders (HS, EV, NA, SD, & SZ) using Numbat meta-analysis software (http://bgcarlisle.github.io/Numbat/) [8] and disagreements were resolved by discussion. Data were imported to R software. Analysis and graphing was done using R v. 3.4.1 [9].

Statistics

This analysis was primarily descriptive. Inferential statistics were occasionally performed for comparison of the two cohorts. Two-sided t-tests were performed and the p-value to determine significance was defined as 0.05.

Outcomes

The primary outcome was to determine the amount of time and patients it took for a drug to reach first-licensing event (FLE). Time was calculated by taking the enrollment date from the first efficacy trial in each drug and comparing it to the FLE. Patient numbers were determined by taking the total n of all trials (efficacy or non-efficacy) of each drug whose enrollment dates occurred before the FLE.

The first secondary endpoint determined how many drug-indication trajectories were explored. For these trajectories, biomarker stratification was considered for the PM cohort (i.e. melanoma BRAFV600+ vs. melanoma BRAFwt), however many biomarkers were grouped together to avoid over-analysis of indications (i.e. BRAF, BRAFV600, BRAFV600E/K+). A full review of biomarker groupings is available in **Table 6**. Drug-indication trajectories must have had at least one efficacy trial (not just observing safety), and the first trial must have started

before 2013-03 to allow for 5 years follow-up for capturing a license. To ensure the same about of follow-up for every drug, drugs that were approved in 2011 only had publications up to June 2014, those approved in 2012 had publications to June 2015, and those approved in 2013 to June 2016.

We then sought to determine how many patient-participants were in 'successful' trajectories in each cohort. We defined 'successful' not on whether the trial was positive, but whether the trial was in a drug-indication trajectory that eventually received FDA approval. We censored the indications that did not have at least 5 years of follow-up from the first trial, as above. We then stratified the patient-participants into label-seeking trials versus label-extending. Label-seeking was defined as all indications up to and including an indication that would get FDA approval. All indications after this were considered "label-extending." The same censoring technique for the drug-indications outcome was used in the 'successful' trajectories outcome.

We additionally sought to determine the number of adverse events experienced by patients in each cohort, and whether they were in label-seeking versus label-extending trajectories. We summed the number of Grade 3-4 and Grade 5 adverse events and then stratified trials based on whether their trajectory was label-seeking versus label-extending. The same censoring technique for the drug-indications outcome was used in the adverse-events outcome.

We examined the quality and extent of evidence used to determine licensure/abandonment of drugs in PM vs. non-PM. To do so, we pooled all efficacy phase II+ trials and determined what endpoints they used in each cohort. We recorded an efficacy endpoint as present if it was evaluated but not reached.

Finally, we established the volume of biomarker testing performed in license-seeking versus license-extending trials. Studies were defined as having biomarker testing if the testing was being performed as part of the study itself, either centrally or locally. Studies were defined as having biomarker eligibility if it was required that patients have a confirmed biomarker before entering into the study but testing could have been performed outside or inside study.

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Tables and Figures

Table 1: Precision Medicine and Non-Precision Medicine Cohorts for Systematic Review

Precision Medicine
Vemurafenib (kinase inhibitor) 2011-08-17: BRAFV600E+ unresectable or metastatic melanoma 2017-11-06: BRAFV600+ Erdheim-Chester disease
Crizotinib (kinase inhibitor) 2011-08-26: ALK+ locally advanced or metastatic NSCLC 2016-03-11: ROS1+ metastatic NSCLC
Ado-trastuzumab emtansine (antibody-drug conjugate) 2013-02-22: HER2+ recurrent, metastatic breast cancer
Trametinib (kinase inhibitor) 2013-05-29: BRAFV600E/K+ unresectable or metastatic melanoma 2014-01-08: BRAFV600E/K+ unresectable or metastatic melanoma **in combination with dabrafenib** 2017-06-22: BRAFV600E+ metastatic NSCLC **in combination with dabrafenib** 2018-04-30: BRAFV600E/K+ melanoma adjuvant treatment, with involvement of the lymph nodes, following complete resection **in combination with dabrafenib**
Olaparib (PARP inhibitor) 2014-12-19: BRCAm pre-treated advanced ovarian cancer 2017-08-17: maintenance treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy 2018-01-12: BRCAm, HER2- metastatic breast cancer
Non-Precision Medicine
Ipilimumab (CTLA4-blocking antibody) 2011-03-25: unresectable or metastatic melanoma 2015-10-28: Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy 2017-07-21: unresectable or metastatic melanoma in pediatric patients

2018-04-16: intermediate or poor risk, previously untreated advanced renal cell carcinoma, **in combination with nivolumab**
Abiraterone Acetate (CYP17 inhibitor) 2011-04-28: metastatic CRPC with prior therapy **in combination with prednisone** 2012-12-10: metastatic CRPC **in combination with prednisone** 2018-02-07: metastatic high-risk CSPC **in combination with prednisone**
Brentuximab Vedotin (CD30 directed antibody-drug conjugate) 2011-08-19: relapsed HL **or** sALCL 2015-0817: cHL at risk of relapse or progression as post-auto-HSCT consolidation 2017-11-09: pcALCL or CD30 expressing mycosis fungoides (MF) who had prior systemic therapy 2018-03-20: Previously untreated Stage III or IV cHL **in combination with chemotherapy**
Vismodegib (hedgehog pathway inhibitor) 2012-01-30: metastatic or locally advanced BCC who are not candidates for surgery or radiation
Cabozantinib (kinase inhibitor) 2012-11-29: progressive, metastatic medullary thyroid cancer 2016-04-25: advanced, relapsed RCC 2017-12-19: advanced RCC
Ibrutinib (kinase inhibitor) 2013-11-13: relapsed mantle cell lymphoma 2014-02-12: relapsed CLL 2014-07-28: CLL with 17p deletion 2015-01-29: Waldenström's macroglobulinemia 2016-03-04: CLL 2016-05-06: SLL with and without 17p deletion 2017-01-18: relapsed marginal zone lymphoma 2017-08-02: chronic graft vs host disease after failure of one systemic therapy
Idelalisib (kinase inhibitor) 2014-07-23: relapsed follicular B-cell non-Hodgkin lymphoma; relapsed SLL; relapsed CLL **in combination with rituximab**

Pembrolizumab (PD1-blocking antibody) 2014-09-04: unresectable or metastatic melanoma with prior ipilimumab treatment 2015-10-02: PDL1+ metastatic NSCLC 2015-12-18: unresectable or metastatic melanoma 2016-08-05: recurrent or metastatic HNSCC 2017-03-14: adult and pediatric patients with refractory, relapsed cHL 2017-05-10: in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC 2017-05-18: locally advanced, metastatic urothelial cancer not eligible for cisplatin or disease progression on or following platinum-containing chemotherapy 2017-05-23: adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumours or colorectal cancer 2017-09-22: recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PDL1
Blinatumomab (bispecific CD19-directed CD3 T-cell engager) 2014-12-03: relapsed/refractory Ph- B-cell precursor ALL 2017-07-11: relapsed/refractory B-cell precursor ALL **in children** 2018-03-29: B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1%

Table 2: EMBASE Search Strategy

#	Searches
1	exp “randomized controlled trial”/
2	exp “randomized controlled trial (topic)”/
3	exp “controlled clinical trial”/
4	exp “controlled clinical trial (topic)”/
5	exp randomization/
6	double blind procedure/
7	exp placebo/
8	“controlled clinical trial”.tw.
9	(random* or RCT$1 or placebo*).tw.
10	((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw.
11	or/1-10
12	exp clinical trial/
13	“clinical trial”.tw.
14	(volunteer or volunteers or open label* or non-random* or non random* or quasirandom* or quasi-random*).tw.
15	(longitudinal or prospective).tw.
16	((follow-up or followup) adj stud*).tw.
17	((multicenter adj stud*) or (multi-center adj stud*) or (multicentre* adj stud*) or (multi-centr* adj stud*)).tw.
18	((comparative adj study) or (comparative adj studies)).tw.
19	“head-to-head”.tw.
20	(pilot$1 or feasibility or “Proof of principle”).tw.
21	or/12-20
22	11 or 21
23	(editorial or letter or note).pt.
24	22 not 23
25	exp Animal/ not (exp Animal/ and Human/)
26	24 not 25
27	MeSH drug specific terms – **See Table 4**
28	26 and 27
29	removes duplicates from 28

Table 3: Medline Search Strategy

#	Searches
1	(controlled clinical trial or randomized controlled trial).pt.
2	exp randomized controlled trials as topic/ or exp controlled clinical trials as topic/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp placebos/
3	"controlled clinical trial".tw.
4	(random or FCT$1 or placebo*).tw.
5	(singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw.
6	Or/1-5
7	Clinical trials.pt.
8	(clinical trial phase I or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
9	Exp Clinical Trial/
10	Exp Clinical Trials as Topic/
11	"clinical trial".tw.
12	(volunteer or volunteers or open label* or non-random* or non random* or quasirandom* or quasirandom*).tw.
13	Exp Longitudinal Studies/ or exp Prospective Studies/ or exp Follow-Up Studies/
14	(longitudinal or prospective).tw.
15	((follow-up or followup) adj stud*).tw.
16	Multicenter Study.pt.
17	Exp Multicenter Study/ or exp Multicenter Studies as Topic/
18	((multicenter adj stud*) or (multi-center adj stud*) or (multicentre* adj stud*) or (multi-centr* adj stud*)).tw.
19	Comparative Study.pt.
20	((comparative adj study) or (comparative adj studies)).tw.
21	"head-to-head".tw.
22	Exp Pilot Projects/ or exp Feasibility Studies/
23	(pilot$1 or feasibility or "Proof of principle").tw.
24	or/7-23
25	6 or 24
26	(comment or editorial or guideline or practice guideline or interview or letter).pt.
27	25 not 26
28	Exp Animals/ not (exp Animals/ and Humans/)
29	27 not 28
30	MeSH Drug specific terms – **see Table 4**
31	29 and 30
32	Remove duplicates from 31

Table 4: Search Terms Used in EMBASE #27 and Medline #30 for Oncology Drugs

Non-Precision; First-in-Class
Abiraterone acetate (“abiraterone acetate” or “CB 7630” or “CB-7630” or CB7630 or Zytiga or “154229-18-2” or “154229 18 2” or 154229182 or “UNII-EM5OCB9YJ6” or UNIIEM5OCB9YJ6 or “UNII EM5OCB9YJ6” or EM5OCB9YJ6 or CHEBI68639 or “CHEBI-68639” or “CHEBI 68639” or “abiraterone acotate” or “CB7630 acetate”).tw.
Brentuximab vedotin (“brentuximab vedotin” or “antibody-drug conjugate SGN-35” or “antibody drug conjugate SGN-35” or “antibody-drug conjugate SGN35” or “antibody drug conjugate SGN35” or “ADC SGN-35” or “ADC SGN35” or “anti-CD30 ADC SGN-35” or “anti-CD30 ADC SGN35” or “anti-CD30 antibody-drug conjugate SGN-35” or “anti-CD30 antibody drug conjugate SGN-35” or “anti-CD30 antibody-drug conjugate SGN35” or “anti-CD30 antibody drug conjugate SGN35” or adcetris or “cac10-vcmmae” or “cac10 vcmmae” or cac10vcmmae or “SGN-35” or “SGN 35” or SGN35).tw.
Ipilimumab (ipilimumab or “anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody” or “MOAB CTLA-4” or “MOAB CTLA4” or “monoclonal antibody CTLA-4” or “monoclonal antibody CTLA4” or yervoy or “MDX-CTLA-4” or “MDX CTLA 4” or MDXCTLA4 or “BMS-734016” or “BMS 734016” or BMS734016 or “MDX-010” or “MDX 010” or MDX010).tw.
Cabozantinib (cabozantinib or “BMS 907351” or “BMS-907351” or BMS907351 or cometriq or “XL 184” or “XL-184” or “XL184 cpd” or XL184 or “849217-68-1” or “849217 68 1” or 849217681 or cabometyx or “UNII-1C39JW444G” or “UNII 1C39JW444G” or UNII1C39JW444G or CHEBI72317 or “CHEBI-72317” or “CHEBI 72317” or 1C39JW444G or “XL184 free base” or CHEMBL2105717” or “CHEMBL-2105717” or “CHEMBL 2105717” or “cabozantinib-s-malate”).tw.
Pembrolizumab (pembrolizumab or keytruda or “MK-3475” or “MK 3475” or “SCH 900475” or “SCH-900475” or SCH900475 or MK3475 or “anti-PD-1 monoclonal antibody MK-3475” or “anti-PD1 monoclonal antibody MK-3475” or “anti-PD-1 monoclonal antibody MK3475” or “anti-PD1 monoclonal antibody MK3475” or “anti-PD-1 MOAB MK-3475” or “anti-PD1 MOAB MK3475” or “immunoglobulin G4, anti-(human programmed cell death 1)).tw.

Blinatumomab (blinatumomab or "MT103" or "MEDI-538" or MEDI538 or "MEDI 538" or “MT 103” or AMG103 or “AMG-103” or “AMG 103” or “MT-103” or “bispecific T-cell engager” or blincyto or “anti-CD19/anti-CD3 recombinant bispecific monoclonal antibody”).tw.
Ibrutinib (ibrutinib or “PCI 32765” or “PCI-32765” or PCI32765 or 936563961 or “936563-96-1” or “936563 96 1” or imbruvica or “UNII-1X70OSD4VX” or “UNII 1X70OSD4VX” or UNII1X70SD4VX or CRA032765 or “CRA-032765” or “CRA 032765” or 1X70OSD4VX or CHEBI76612 or “CHEBI-76612” or “CHEBI 76612” or “PCI-32765-00” or ibrutinibum or ibruvica or “PC-323675” or CHEMBL1873475 or “CHEMBL-1873475” or “CHEMBL 1873475” or “Bruton’s tyrosine kinase inhibitor PCI-32765” or “BTK inhibitor PCI-32765”).tw.
Vismodegib (vismodegib or erivedge or “GDC 0449” or “GDC-0449” or GDC0449 or HhAntag691 or “NSC 747691” or “NSC-747691” or NSC747691 or “R 3616” or “R-3616” or R3616 or “R3616 cpd” or “RG 3616” or “RG-3616” or RG3616 or “879085-55-9” or “879085 55 9” or 879085559 or “UNII-25X868M3DS” or “UNII 25X868M3DS” or UNII25X868M3DS or CHEMBL473417 or “CHEMBL-473417” or “CHEMBL 473417” or “CHEBI-66903” or “CHEBI 66903” or CHEBI66903 or vismodegibum or “Hh-Antag691” or “HhAntag 691” or “hedgehog antagonist GDC-0049” or “hedgehog antagonist GDC0449” or “hedgehog antagonist GDC 0449).tw.
Idelalisib (idelalisib or zydelig or “CAL 101” or “CAL-101” or CAL101 or “GS-1101” or “GS 1101” or GS1101 or “870281-82-6” or “870281 82 6” or 870281826 or “UNII-YG57I8T5M0” or “UNII YG57I8T5M0” or UNIIYG57I8T5M0 or YG57I8T5M0 or CHEMBL2216870 or “CHEMBL-2216870” or “CHEMBL 2216870” or “CHEBI-82701” or “CHEBI 82701” or CHEBI82701 or “phosphoinositide-3 kinase delta inhibitor CAL-101” or “PI3K delta inhibitor CAL-101”).tw.
Precision – First-in-Class
Ado-trastuzumab Emtansine ("ado trastuzumab emtansine" or "ado-trastuzumab emtansine" or "ado-transtuzumab" or "transtuzumab emtansine" or "transtuzumab-emtansine" or "transtuzumab-DM1" or "transtuzumab-MCC-DM1" or "transtuzumab-MCC-DM1 antibody-drug conjugate" or "transtuzumab-MCC-DM1 immunoconjugate" or kadcyla or "T-DM1" or TDM1 or PRO132365 or "PRO-132365" or RO5304020 or "RO-5304020").tw.

Olaparib (olaparib or “AZD 2281” or “AZD-2281” or AZD2281 or “AZD 221” or “AZD-221” or AZD221 or Lynparza or “763113-22-0” or “763113 22 0” or 763113220 or “KU-0059436” or “KU 0059436” or KU0059436 or “UNII-WOH1JD9AR8” or “UNII WOH1JD9AR8” or UNIIWOH1JD9AR8 or “acylpiperazine analogue 47” or CHEMBL521686 or “CHEMBL 521686” or “CHEMBL-521686” or “CHEMBI 83766” or “CHEMBI-83766” or CHEMBI83766 or olaparibum).tw.
Trametinib (trametinib or “871700-17-3” or 87170017 or “871700 17 3” or GSK1120212 or “GSK 1120212” or “GSK-1120212” or mekinist or “JTP 74057” or “JTP-74057” or JTP74057 or “UNII-33E86K87QN” or “UNII 33E86K87QN” or UNII33E86K87QN or 33E86K87QN or “trametinib dimethyl sulfoxide” or “CHEBI-75998”or “CHEBI 75998” or CHEBI75998 or CHEMBL2103875 or “CHEMBL-2103875” or “CHEMBL 2103875” or TMT212 or “TMT-212” or “TMT 212”).tw.
Vemurafenib (“PLX 4032” or “PLX4032” or “R05185426” or “RG7204” or vemurafenib or Zelboraf or “918504-65-1” or “PLX-4032” or “1029872-54-5).tw.
Crizotinib (877399-52-5 or “53AH36668S” or “PF 02341066” or “PF—02341066” or “PF02341066” or xalkori or crizotinib or “PF-2341066” or “(R)-crizotinib” or “PF 2341066”).tw.

Figure 1: Extraction Template for Precision Medicine Drugs

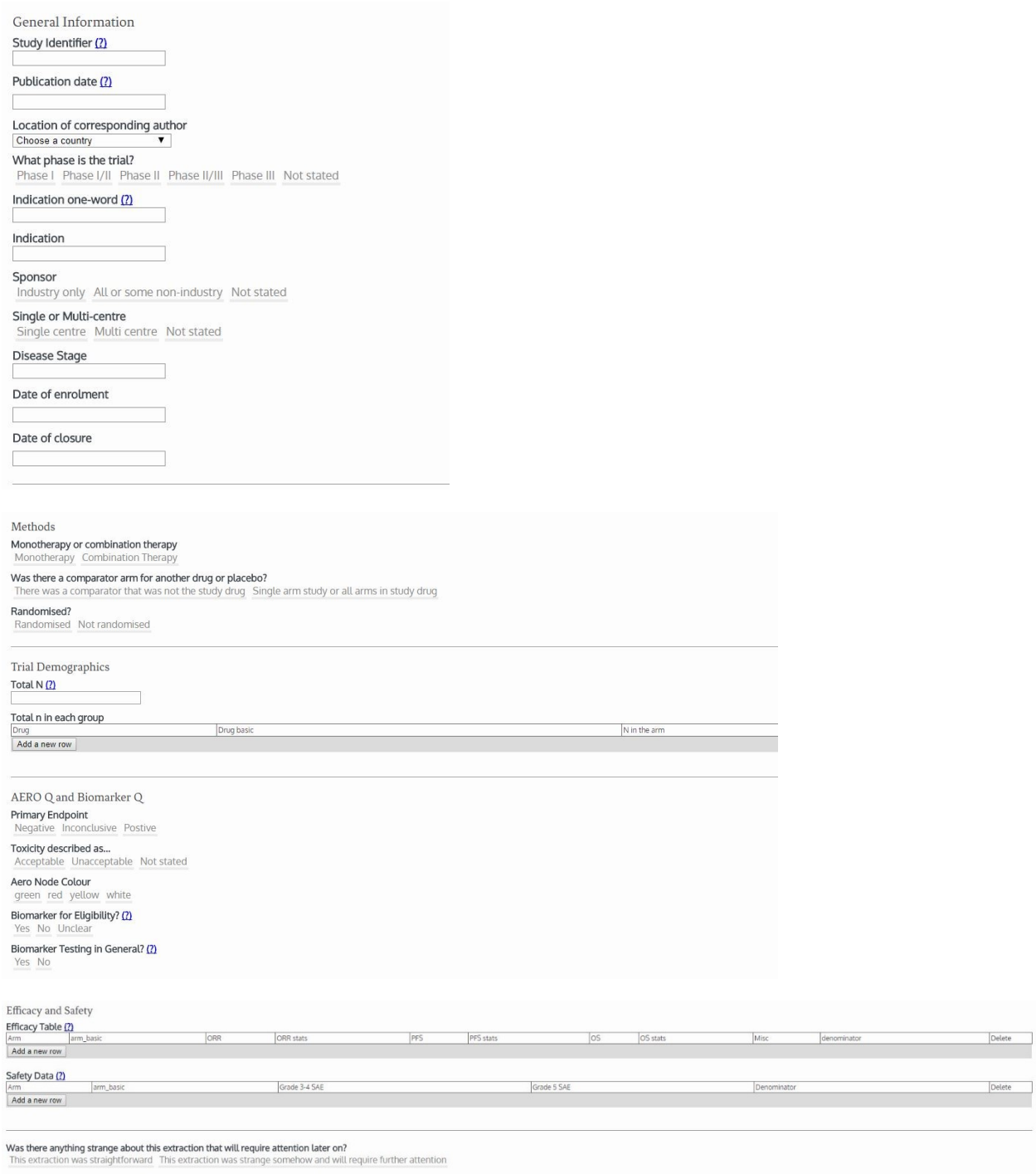
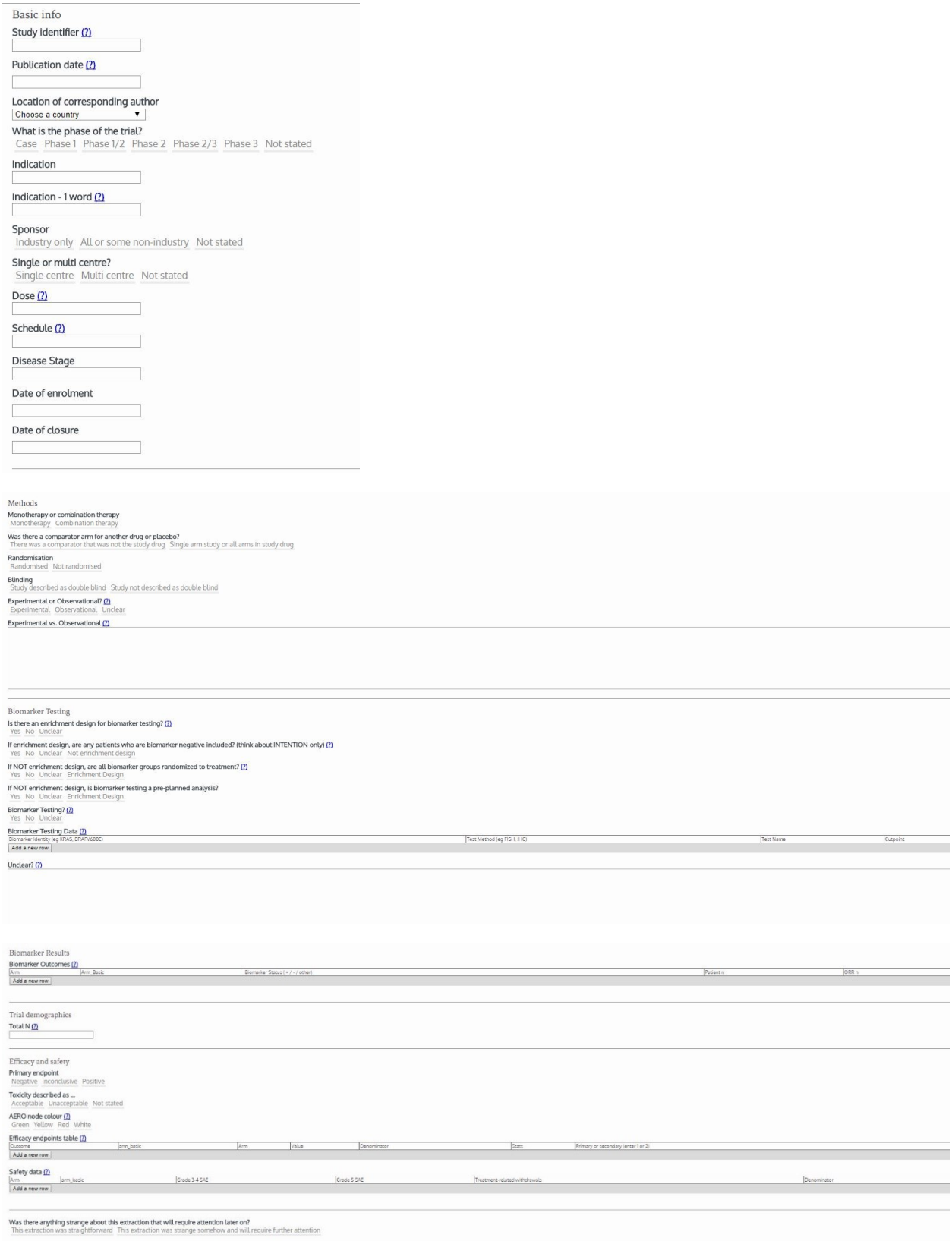


Figure 2: Extraction Template for Non-Precision Medicine Drugs



Basic info

Study identifier (?)

Publication date (?)

Location of corresponding author

Choose a country

What is the phase of the trial?

Case | Phase 1 | Phase 1/2 | Phase 2 | Phase 2/3 | Phase 3 | Not stated

Indication

Indication - 1 word (?)

Sponsor

Industry only | All or some non-industry | Not stated

Single or multi centre?

Single centre | Multi centre | Not stated

Dose (?)

Schedule (?)

Disease Stage

Date of enrolment

Date of closure

Methods

Monotherapy or combination therapy

Monotherapy | Combination therapy

Was there a comparator arm for another drug or placebo?

There was a comparator that was not the study drug | Single arm study or all arms in study drug

Randomisation

Randomised | Not randomised

Blinding

Study described as double blind | Study not described as double blind

Experimental or Observational? (?)

Experimental | Observational | Unclear

Experimental vs. Observational (?)

Biomarker Testing

Is there an enrichment design for biomarker testing? (?)

Yes | No | Unclear

If enrichment design, are any patients who are biomarker negative included? (think about INTENTION only) (?)

Yes | No | Unclear | Not enrichment design

If NOT enrichment design, are all biomarker groups randomized to treatment? (?)

Yes | No | Unclear | Enrichment Design

If NOT enrichment design, is biomarker testing a pre-planned analysis?

Yes | No | Unclear | Enrichment Design

Biomarker Testing? (?)

Yes | No | Unclear

Biomarker Testing Data (?)

Biomarker identity (eg KRAS, BRAFV600E)	Test Method (eg FISH, IHC)	Test Name	Cutpoint

Add a new row

Unclear? (?)

Biomarker Results

Biomarker Outcomes (?)

Arm	Arm_Basic	Biomarker Status (+ / - / other)	Patient n	ORR n

Add a new row

Trial demographics

Total N (?)

Efficacy and safety

Primary endpoint

Negative | Inconclusive | Positive

Toxicity described as ...

Acceptable | Unacceptable | Not stated

AERO node colour (?)

Green | Yellow | Red | White

Efficacy endpoints table (?)

Outcome	arm_basic	Arm	Value	Denominator	Stats	Primary or secondary (enter 1 or 2)

Add a new row

Safety data (?)

Arm	arm_basic	Grade 3-4 SAE	Grade 5 SAE	Treatment-related withdrawals	Denominator

Add a new row

Was there anything strange about this extraction that will require attention later on?

This extraction was straightforward | This extraction was strange somehow and will require further attention

Table 5: Indication Grouping

Leukemias	Lymphomas	Mixed non-solid	Solid	Mixed solid and non-solid
ALL	cHL/HL		Breast	
Hairy Cell Leukemia	T-cell lymphomas		Ovarian	
	B-cell lymphomas - CLL/SLL - DLBCL - MCL - MZL - Waldenstrom macroglobulinemia - FL - CNS lymphoma		Women's Cancer (Ovarian & Breast)	
	Mixed lymphoma		NSCLC	
			SCLC	
			Prostate	
			Melanoma	
			Sarcoma	
			Pancreatic	
			HNSCC	
			Thyroid	
			Renal	
			Bladder	
			BCC	
			Medullablastoma	
			Glioma	
			Liver	
			Cholangiocarcinoma	
			Merkel-cell	
			Gastric	
			Urothelial	
			Endometrial	
			Colorectal	
			Anal	
			Erdheim-Chester	
			OCSCC	
			Mixed solid	

Table 6: Biomarker Groupings

Biomarker	**Subgroup 1**	**Subgroup 2**	**Subgroup 3**	**Subgroup 4**
BRAF	BRAFV600	BRAFV600E	BRAFV600K	Not BRAFV600E/K
RAS	NRAS	KRAS		
BRCA	BRCA1	BRCA2	BRCA1/2	
Triple Negative	ER-, PR-, HER2-			
ALK				
ROS1				
HER2				
RAS/RAF				
PDL1				
CD30				
Ph-				
Ph+				
BCR-ABL or MLL-AF4 translocation				
HLA-A*201				
del17p/del11q/TP53				
Richter's Transformation				
ATMlow				
KIT				
SHH				
EGFR				
CD20				
ER				
PR				
AR				

Chapter 3 Results of the Systematic Comparative Analysis Demonstrating the Gains and Limitations to Precision Medicine Drug Development

The purpose of this thesis is to determine how precision medicine (PM) drug development strategies effect the speed and patient burden associated with clinical translation efforts. Our hypothesis is precision medicine drugs will achieve initial regulatory approval more rapidly with less patient exposure, but at the cost of lower statistical power to detect safety signal. Secondarily, we were interested in the amount of indication exploration, proportion of patients in successful trajectories (defined in **Chapter 2**), the quality of evidence used to determine licensure/abandonment of a drug-indication, and the extent of biomarker testing performed. We anticipated that precision medicine drug development would have less indication exploration (a more streamlined process) and a greater proportion of patients in successful trajectories, but less quality evidence used to determine the licensure/abandonment of the drug-indication, when compared to non-PM. With this, we can begin to explore policy dimensions of PM - including how risk/benefit should be assessed, how priorities are established, and how informed consent is obtained. This chapter presents results of the methods described in Chapter 2.

Properties of Drugs in our Sample

Fourteen drugs were included in this comparative analysis: five in the PM cohort, and nine in the non-precision medicine (non-PM) cohort. The PM cohort included three kinase inhibitors, one PARP inhibitor, and one antibody-drug-conjugate. The non-PM cohort included three kinase inhibitors, two checkpoint inhibitors, two antibody therapies, one CYP17 inhibitor and one hedgehog pathway inhibitor. For a review of which drugs are in each category, mechanisms of action, and approved indications, refer back to **Chapter 2 Table 1.**

Properties of Studies

From our literature search for trials of the above drugs, 339 studies met eligibility for inclusion; 109 trials in the PM group and 230 trials in the non-PM cohort. For a list of all studies included, refer to **Appendix A**. A PRISMA diagram with the screening process is available in **Figure 1**. The most frequent reasons for exclusion from full-text included being linked to an already published trial (36%), the study was observational or retrospective in nature (21%) or the publication was a poster/conference abstract/oral presentation (9%).

Most trials were single-arm (79%), multi-centre (80%) and industry sponsored (65%). Noted differences between the two cohorts were: number of trials outside North America (26% Non-PM v. 38% PM) and number of trials that were Phase II (47% Non-PM v. 37% PM). **Tables 1**, **2**, and **3**; and **Figures 2, 3,** and **4** overview demographic data of the PM and Non-PM cohorts.

The majority of trials tested in solid malignancies (77%), with the most frequent indications being melanoma (21%), prostate (13%), and non-small cell lung cancer (NSCLC) (7%). In the non-PM cohort 39% of combinations were with antibodies, inhibitors, or immunotherapies, and 12% were cancer vaccines. In the PM cohort 58% of combinations were with antibodies or inhibitors, and one trial used adoptive cell therapy. **Figures 5** and **6** provide information on drug indications explored within each cohort.

Plotting of Drug-Indication Trajectories

Figures 7 and **8** describe the drug-indication trajectories for each drug in the PM and non-PM cohorts. These figures include information regarding the indications explored, when each trajectory began, the phases, and whether the primary endpoint was reached. Refer to the legend present at the end of the figures for more information.

Time and Patients to First-Licensing Event

The mean number of days from the first efficacy trial to first-licensing event was 1933d in PM vs 1801 in non-PM (p=0.8). The median number of days was 1750 in PM versus 1825 in non-PM. The range of days was 1120 to 2063 for PM versus 929 to 3127 in non-PM. **Figure 9**, and **Tables 4** and **5** illustrate the distribution of dates in both cohorts.

The median number of patients in efficacy trials from first efficacy trial to first licensing event was 1909 in PM compared to 1265 in non-PM (p=0.75). The mean number of patients in efficacy trials was 1755 in PM compared to 2012 in non-PM. The range of patients to first-licensing event was 986 to 2610 in PM, compared to the non-PM range of 655 to 5009. **Figure 10**, and **Tables 6** and **7** illustrate the distribution of patients to first-licensing event in both cohorts.

Indication Exploration

When data were censored for same time follow-up from publication date, the average number of drug indication trajectories explored for PM was 3 compared to 3 in non-PM (medians 3 v. 2). In both PM and non-PM the minimum number of drug-indications explored was 1 and the maximum explored was 6. Non-PM was slightly more likely to explore beyond second indication than PM.

The average number of drug indication trajectories explored up to the indication for first license was 1.0 for PM and 1.4 for non-PM (medians 1 v 1). The majority of indications that eventually received FDA approval were in the first 3 indications put into testing in PM and non-PM. **Figures 11** and **12** demonstrate the number of drug indication trajectories explored (x-axis) alongside the number of FDA drug approvals received at each drug indication trajectories (y-axis) in PM and non-PM.

Patients in Successful Trajectories

When data were censored for same time follow-up as in *Indication Exploration*, in PM, 65% of patients were enrolled in successful trajectories compared to 58% in non-PM. PM patient-participants had a 42% chance of being enrolled in label-seeking studies compared to 57% of non-PM patient-participants. There was a 98% chance of a patient-participant being in a successful PM label-seeking trajectory compared to 79% in non-PM. There was a 41% chance of a patient-participant to be in a successful label-extending PM trajectory compared to 30% in non-PM. These proportions are represented graphically in **Figures 13** and **14** for Venn diagrams on PM and non-PM, respectively.

Adverse Events Experienced

When data were censored for same time follow-up as in *Indication Exploration*, in the PM cohort, 12% (n = 316) of patients experienced a Grade 3-4 adverse event in label-seeking compared to 16% (n = 659) in label-extending. Grade 5 adverse events were experienced by 0.7% (n = 20) of PM label-seeking patients, compared to 0.5% (n = 20) of label-extending patients.

In contrast, 11% (n = 825) of non-PM patients experienced a Grade 3-4 adverse event in label-seeking, and 20% (n = 1036) experienced one in label-extending. Grade 5 adverse events were experienced by 1.3% (n = 103) of non-PM label-seeking patients, compared to 1.7% (n = 90) of label-extending patients. These proportions are represented graphically in **Figures 15** and **16** for Venn diagrams on PM and non-PM, respectively.

Quality of Evidence at FDA Approval

In phase II testing, progression-free survival was used 90% of the time in PM compared to 66% in non-PM ($p < 0.005$). There was a lower usage of overall survival endpoints in phase III testing in the PM cohort (58%) compared to the non-PM cohort (72%) ($p = 0.4$). Overall (both Phase II and III) there was a higher usage of progression-free survival as the final endpoint for PM (41%) compared to non-PM (23%). In phase III testing, progression-free survival was used as the final endpoint 42% of the time in PM, compared to 24% of the time in non-PM. The following was not censored for follow-up and therefore present unadjusted estimates of quality of evidence to FDA approval.

Biomarker Testing

We established the amount of biomarker testing performed in label-seeking versus label-extending trials for both cohorts. In the label-seeking stage, PM required a biomarker for eligibility in 100% of trials, whereas biomarker testing was performed in 74% of trials. For PM label-extension, 50% of trials had biomarkers for eligibility and 50% had biomarker testing.

In contrast the non-PM cohort required biomarkers for eligibility in 24% of trials and biomarker testing was performed in 60% of trials in label-seeking. In label-extending trials 29% had biomarkers for eligibility and 75% had biomarker testing.

Purely exploratory biomarker testing, defined as performing a biomarker assay within the study but not requiring the biomarker for eligibility for the trial, was employed in 61% of trials in the non-PM cohort. In PM, 31% of trials had biomarker testing when the trial did not require a biomarker for eligibility.

Factors that Increase the Probability Patients will be in Successful Trajectories

Drug Classes

The largest subgroup of drug class was kinase inhibitors. There were three kinase inhibitors in the PM cohort (crizotinib, vemurafenib, trametinib) and three in the non-PM cohort (cabozantinib, ibrutinib, idelalisib). When comparing these drugs against each other they enrolled a similar number of patients (mean 1614 PM v 1461 non-PM) and number of days (mean 1381 PM v 1695 non-PM) to first-licensing event. Similar to the whole cohort, PM explored, on average, 3 drug-indication trajectories compared to 3 in the non-PM cohort. First approval was seen, on average, in the first drug-indication trajectory explored for both cohorts. PM had 41% of patients in label-seeking trials, with 95% of those patients being in successful trials. 59% of patients were in label-extending trials and of those, 63% were in successful trials. Non-PM had only 28% of patients in label-seeking trials with 95% of patients in successful trials. Of the 72% of patients in label-extending trials, only 29% were in successful trials.

Checkpoint inhibitors and immunotherapies are an important new class of drugs coming to oncology [1]. Our cohort included two novel checkpoint inhibitors in the non-PM cohort (pembrolizumab and ipilimumab). Pembrolizumab explored five drug-indication trajectories; four received FDA approval. Ipilimumab, in comparison, explored six trajectories and one received FDA approval. Pembrolizumab had 92% of patients in successful trajectories compared to 19% in ipilimumab. Pembrolizumab had 17 Phase I, 8 Phase II and 4 Phase III trials compared to ipilimumab which had 22 Phase I, 32 Phase II and 9 Phase III. Pembrolizumab was quick to first-licensing event with 1252d but took 3874 number of patients; ipilimumab took a significant amount of time 3127d and a significant amount of patients, 5009, to first-licensing event.

Combination Trials

The number of patients enrolled in combination therapy was 17645 (27% in PM v 73% in non-PM). Of this 15% were enrolled in successful trajectories (48% in PM v 3% in non-PM). There were 0% of trials that were label-seeking in PM and 18% label-seeking in non-PM (see Venn diagram **Figures 17** and **18**). On average 4 combination drug-indication trajectories were explored in PM and 0 received FDA-approval. For non-PM, two combination drug-indication trajectories were explored and zero received FDA-approval.

Biomarker Eligibility

Do biomarkers for eligibility have an impact on whether or not a patient-participant is in a successful trajectory? When censored for follow-up, as explained above, in PM 100% of trials at the label-seeking stage required a biomarker for eligibility and 98% were in successful trajectories. In the label-extending stage 67% required a biomarker for eligibility, but if a biomarker was required there was a 14% greater chance of being in a successful trajectory than biomarker agnostic. For non-PM 37% of trials at the label-seeking stage required a biomarker for eligibility and 73% of the 37% were in successful trajectories. In the label-extending stage 31% required a biomarker for eligibility, if a biomarker was required for eligibility there was a 22% greater chance of being in a successful trajectory than biomarker agnostic.

Do biomarkers for eligibility have an impact on the risk for patient-participants? For the PM cohort, if a biomarker was required for eligibility, there was a 13% chance of a patient-participant experiencing a Grade 3-4 adverse event and a 0.6% chance of experiencing a Grade 5 adverse event. If a biomarker was not required, the patient-participant had an 18% chance of experiencing a Grade 3-4 adverse event, and a 0.6% chance of experiencing a Grade 5 adverse event.

Phase I Trial Endpoints

As precision medicine drugs are getting approved at earlier stages [2] it is important to characterize Phase I trials. A total of 2165 (16%) patients were enrolled in PM phase I trials and 3775 (11%) in non-PM. Of the 122 Phase I trials (51 PM vs 71 non-PM), 28 had efficacy as one of their primary endpoints (20% PM v 25% Non-PM). Of the trials that used efficacy as one of their endpoints 62% used response rate as their final endpoint (69% PM v 50% Non-PM) and 38% used progression-free survival as their endpoint (31% PM v 50% Non-PM). Primary non-efficacy endpoints could include safety, maximum-tolerated dose, and pharmacodynamics or pharmacokinetics.

Conclusion

The results of our primary endpoint are not consistent with the primary hypotheses we set out to test. Namely, precision medicine drug development approaches took the same amount of time and patients to first-licensing event rather than doing so more rapidly with less patients exposed. Secondary endpoints mainly supported our stated hypotheses, with indication exploration, persons in successful trials, and endpoint use acting as anticipated, whereas biomarker testing and screening showed unexpected results. Some factors had large influences on whether a patient was in a successful trajectory, including whether that drug was in combination, or the trial had a biomarker for eligibility. Specific drug classes did not show correlation with a patient being in a successful drug trajectory. Phase I trials continue to use non-efficacy endpoints and short-term surrogate endpoints, and combination trials show different trajectories than whole drug portfolios. Reflections on these results, limitations of our analysis, as well as recommendations for future researchers will be addressed in the next Chapter.

References

1. Brahmer JR, Pardoll DM. Immune checkpoint inhibitors: making immunotherapy a reality for the treatment of lung cancer. *Cancer Immunol Res*. 2013;1(2):85-91.
2. Chabner BA. Approval after phase I: ceritinib runs the three-minute mile. *Oncologist*. 2014;19(6):577-578. doi:10.1634/theoncologist.2014-0143

Tables and Figures

Figure 1: PRISMA Flow Diagram

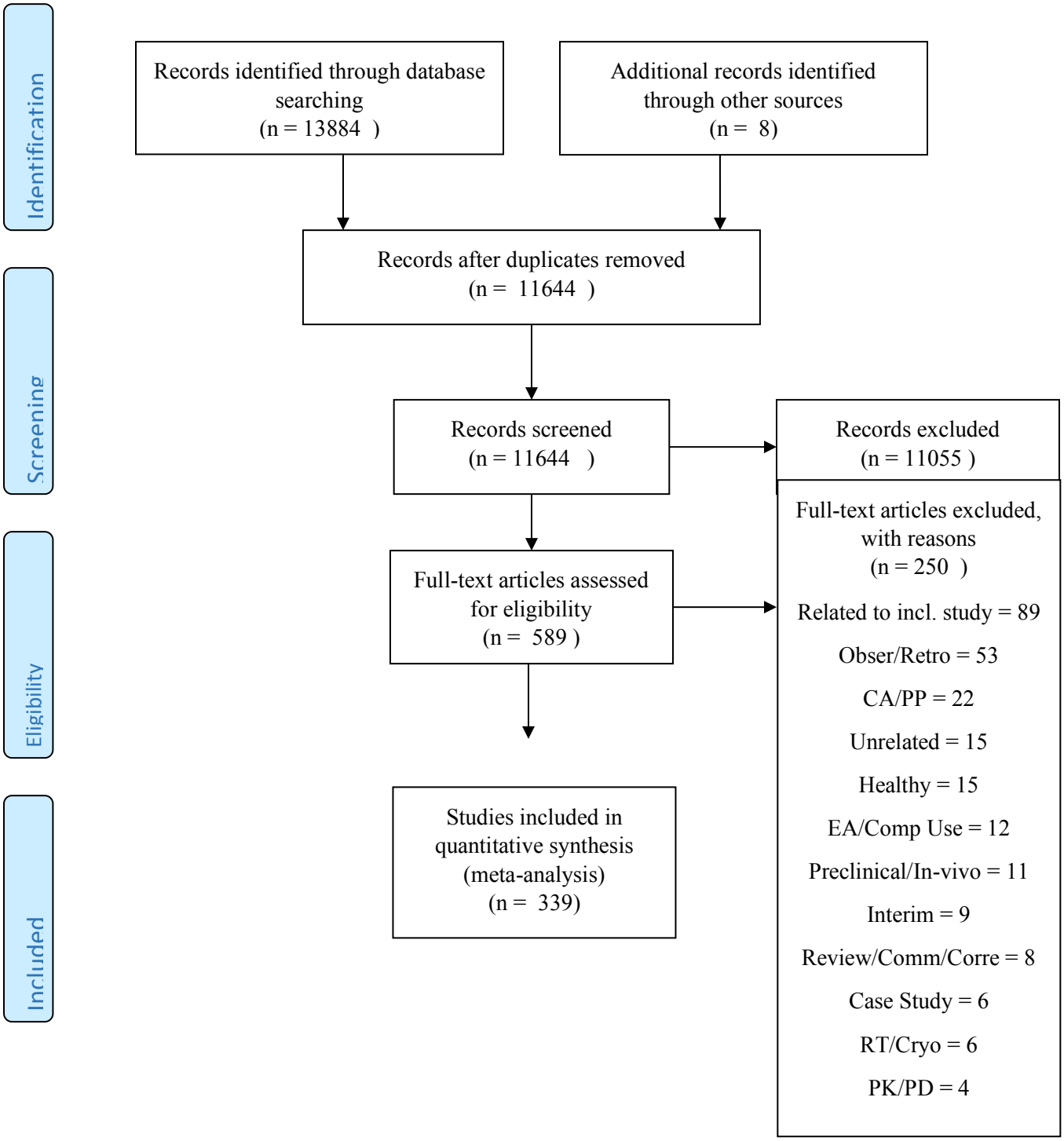


Figure 2: Distribution of Trial Phases in Precision Medicine versus Non-Precision Medicine

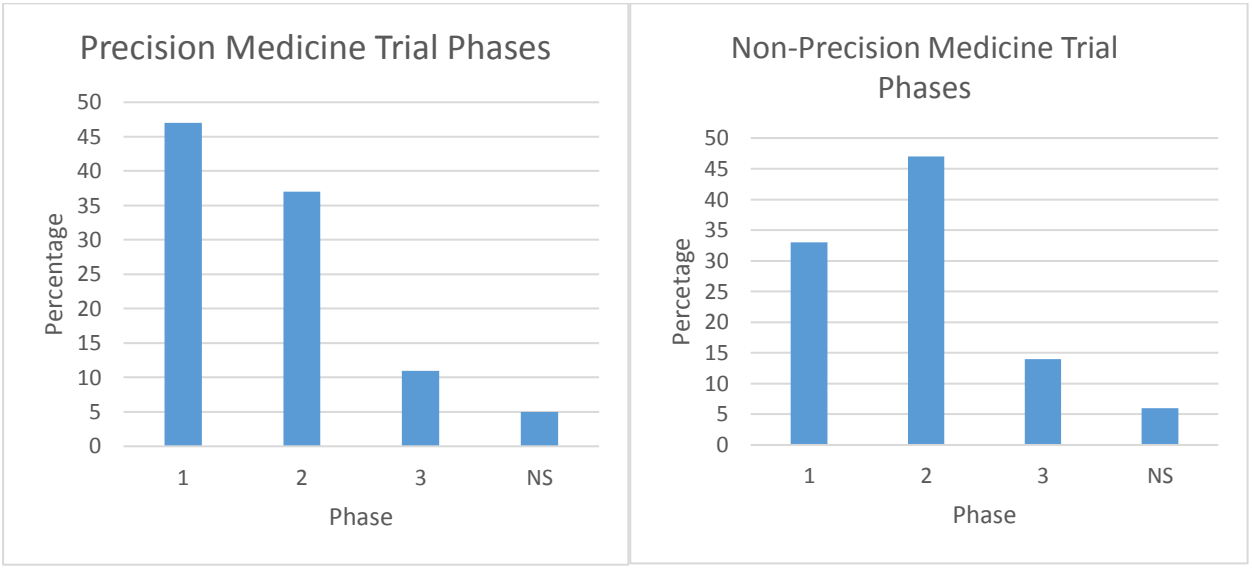


Figure 3: Distribution of Funding Sources in PM versus Non-PM

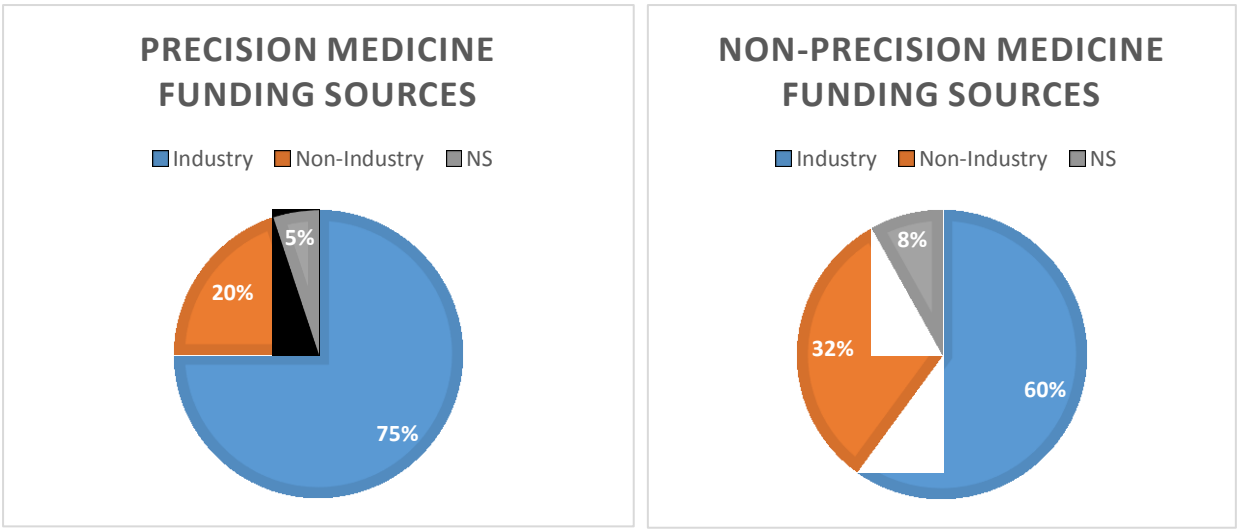


Figure 4: Distribution of Locations of Corresponding Author in PM versus Non-PM

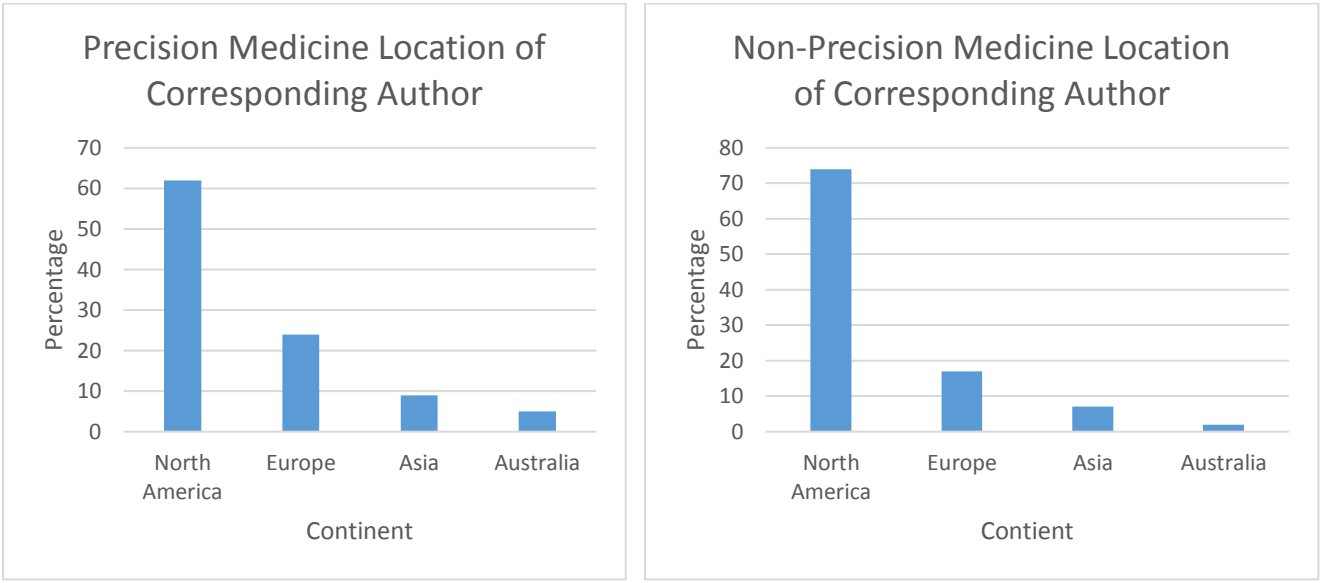


Figure 5: Indication Exploration of PM and Non-PM cohorts

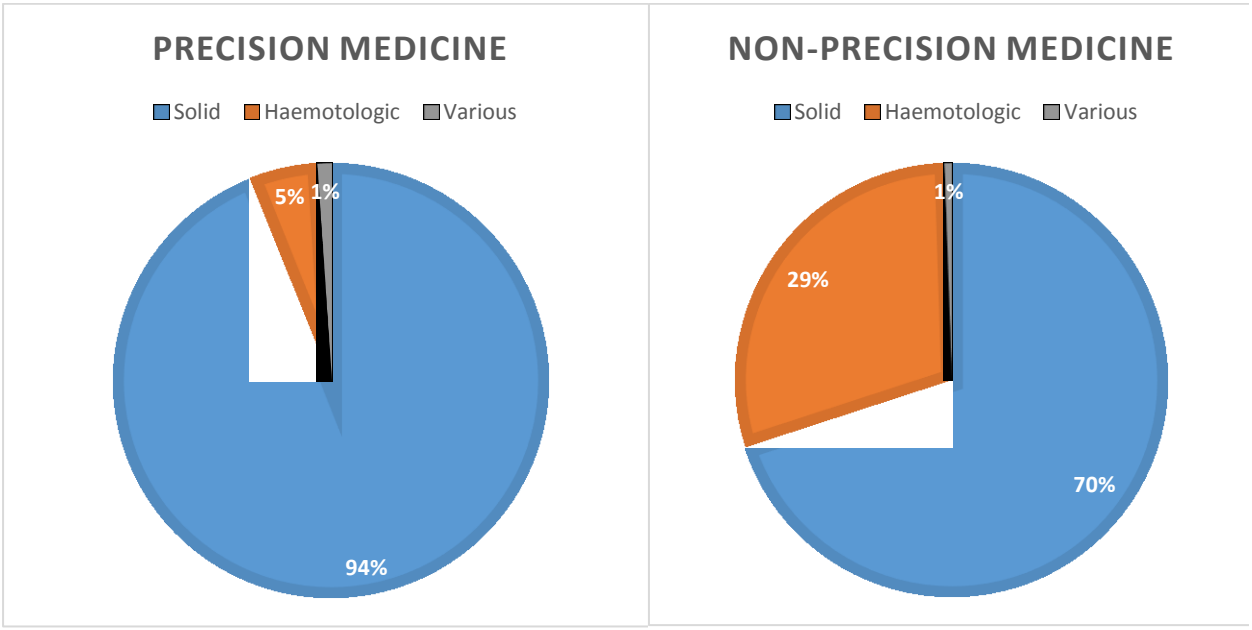


Figure 6: Percentage of Trials with Metastatic Population in Eligibility Criteria

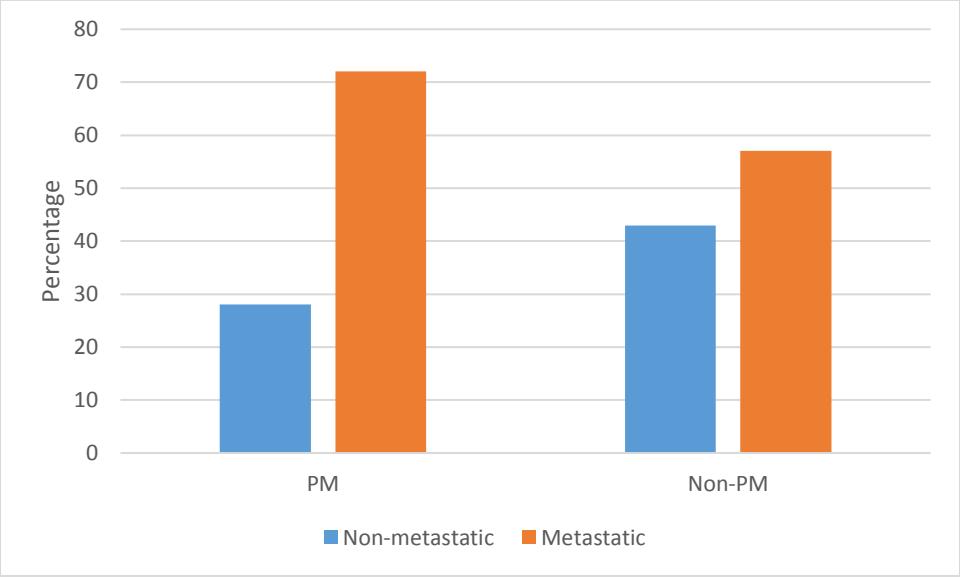


Table 1: Description of Demographics in Non-Precision Medicine Studies*

Drug	Number of Trials	Phases (%)				Sponsors (%)			Centres (%)			Mono-Combo (%)	
		1	2	3	NS	Ind	Non-Ind	NS	Multi	Single	Not Stated	Mono	Combo
Abr	32	31	44	19	6	56	31	13	84	6	9	72**	28**
Bli	7	14	71	14	NA	71	29	NA	100	NA	NA	100	NA
Bre	19	37	47	11	5	84	16	NA	100	NA	NA	74	26
Cab	21	29	57	14	NA	48	43	9	86	4.7	9.5	81	19
Ibr	23	30	52	17	NA	57	43	NA	74	26	NA	57	43
Idl	12	33	42	25	NA	83	17	NA	100	NA	NA	42	58
Ipi	71	31	45	13	11	50	37	13	59	4	37	35	65
Pem	30	57	27	13	3	80	17	3	87	3	10	87	13
Vsm	15	20	67	NA	13	40	47	13	73	20	7	67	33

*Numbers will not add up to 100% at all times due to rounding

** If abiraterone acetate was solely combined with prednisone it was considered monotherapy

Table 2: Description of Demographics in Precision Medicine Studies*

Drug	Number of Trials	Phases (%)				Sponsors (%)			Centres (%)			Mono-Combo (%)	
		1	2	3	NS	Ind	Non-Ind	NS	Multi	Single	Not Stated	Mono	Combo
Adt	13	23	62	15	NA	92	NA	8	100	NA	NA	62	38
Crz	10	50	40	NA	10	80	10	10	90	10	NA	80	20
Olp	35	63	34	3	NA	69	26	5	86	11	3	51	49
Trm	29	52	38	10	NA	76	24	NA	83	14	3	34	66
Vem	22	27	41	14	18	73	23	4	73	18	9	68	32

*Numbers will not add up to 100% at all times due to rounding

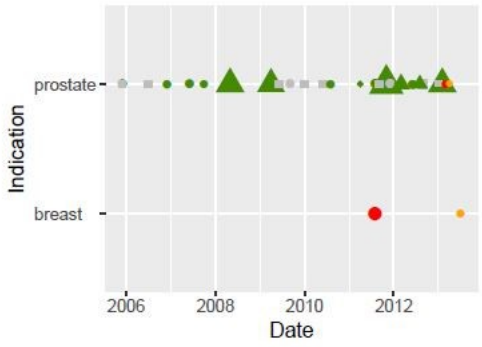
Table 3: Description of Demographics comparing the PM and Non-PM Cohorts*

Drug	Number of Trials	Phases (%)				Sponsors (%)			Centres (%)			Mono-Combo (%)	
		1	2	3	NS	Ind	Non-Ind	NS	Multi	Single	Not Stated	Mono	Combo
Non-PM	230	6	33	47	14	60	32	8	78	4	18	61	39
PM	109	47	38	11	5	75	20	5	84	7	8	54	46

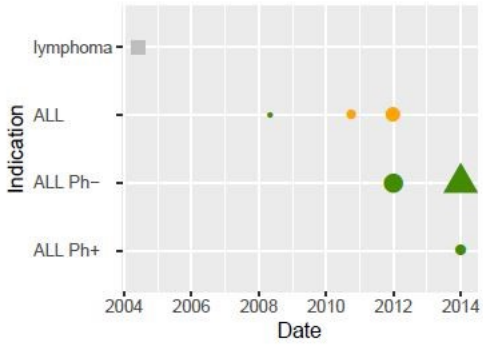
*Numbers will not add up to 100% at all times due to rounding

Figure 7: Drug Portfolios of Non-Precision Medicine Cohort

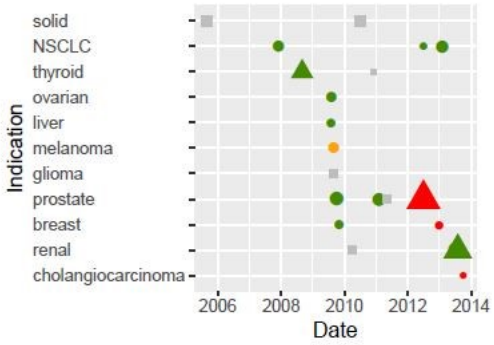
Abiraterone Acetate



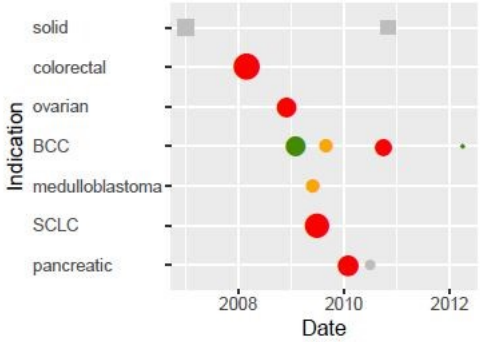
Blinatumomab



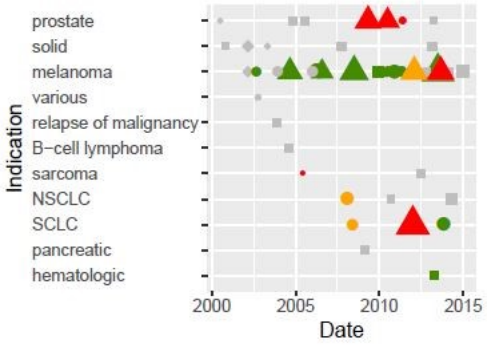
Cabozantinib



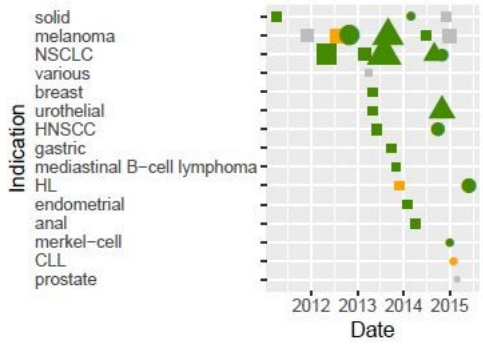
Vismodegib



Ipilimumab



Pembrolizumab



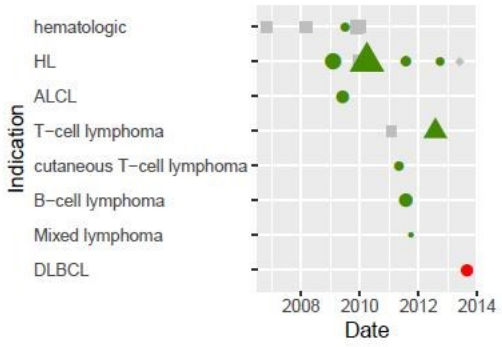
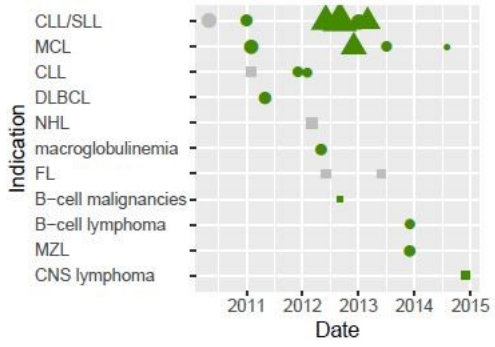
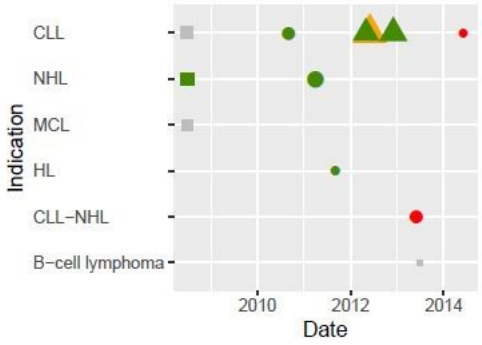
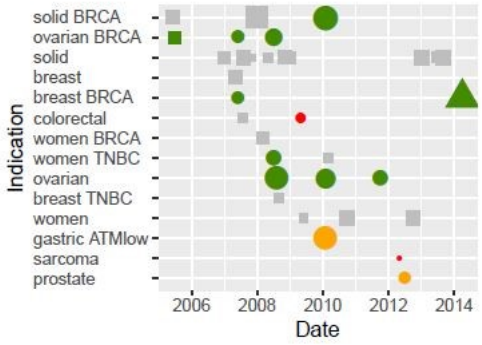
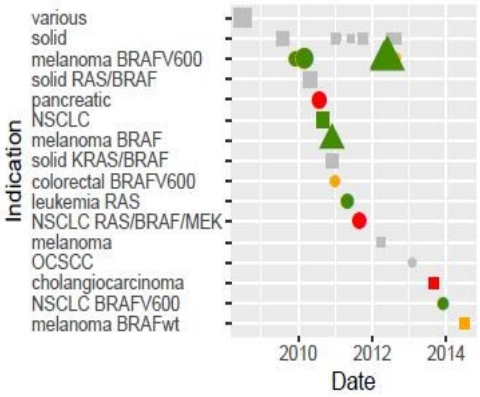
Brentuximab  	Ibrutinib 
Idelalisib  	**Legend:** All indications explored within that drug's development are plotted on the y-axis, with those explored earliest at the top, and latest at the bottom. Phases are described using shapes, with squares representing Phase I, circles for Phase II, triangles for Phase III, and diamonds as not stated. Colours state whether the trial reached its primary efficacy endpoint, with green being positive, yellow inconclusive, red negative, and white as a non-efficacy trial. Dates are listed along the x-axis.

Figure 8: Drug Portfolios of Precision Medicine Cohort

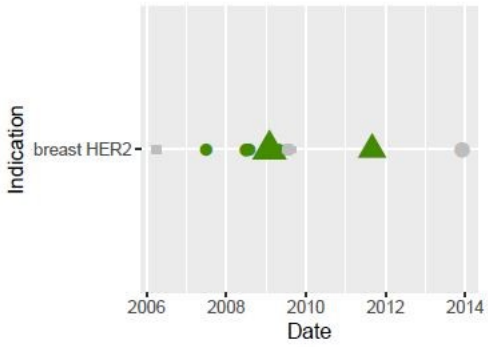
Olaparib



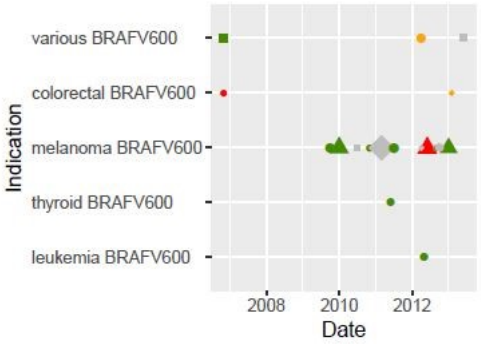
Trametinib



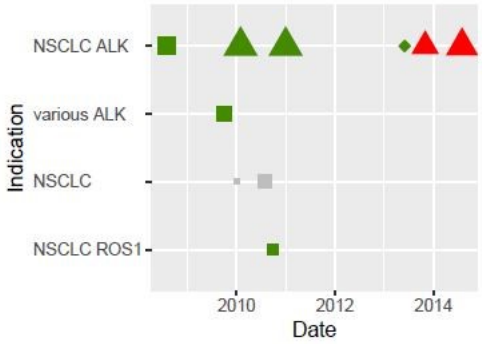
Ado-trastuzumab



Vemurafenib



Crizotinib



Legend: All indications explored within that drug's development are plotted on the y-axis, with those explored earliest at the top, and latest at the bottom. Phases are described using shapes, with squares representing Phase I, circles for Phase II, triangles for Phase III, and diamonds as not stated. Colours state whether the trial reached its primary efficacy endpoint, with green being positive, yellow inconclusive, red negative, and white as a non-efficacy trial. Dates are listed along the x-axis.

Figure 9

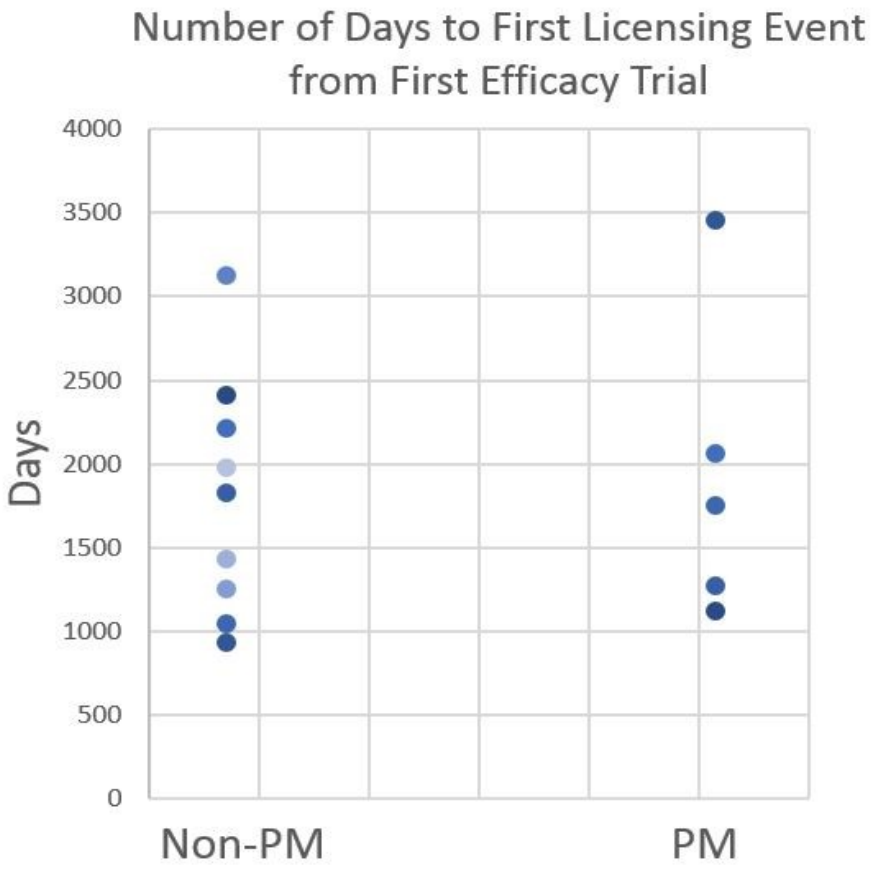


Table 4: Non-Precision Medicine Days to First-Licensing Event by Drug

Drug	Abr	Bli	Bre	Cab	Ibr	Idl	Ipi	Pem	Vsm
# of days to First Licensing Event	1974	2409	929	1825	1047	2213	3127	1252	1430

Table 5: Precision Medicine Days to First-Licensing Event by Drug

Drug	Adt	Crz	Olp	Trm	Vem
# of days to First Licensing Event	2063	1120	3458	1275	1750

Figure 10

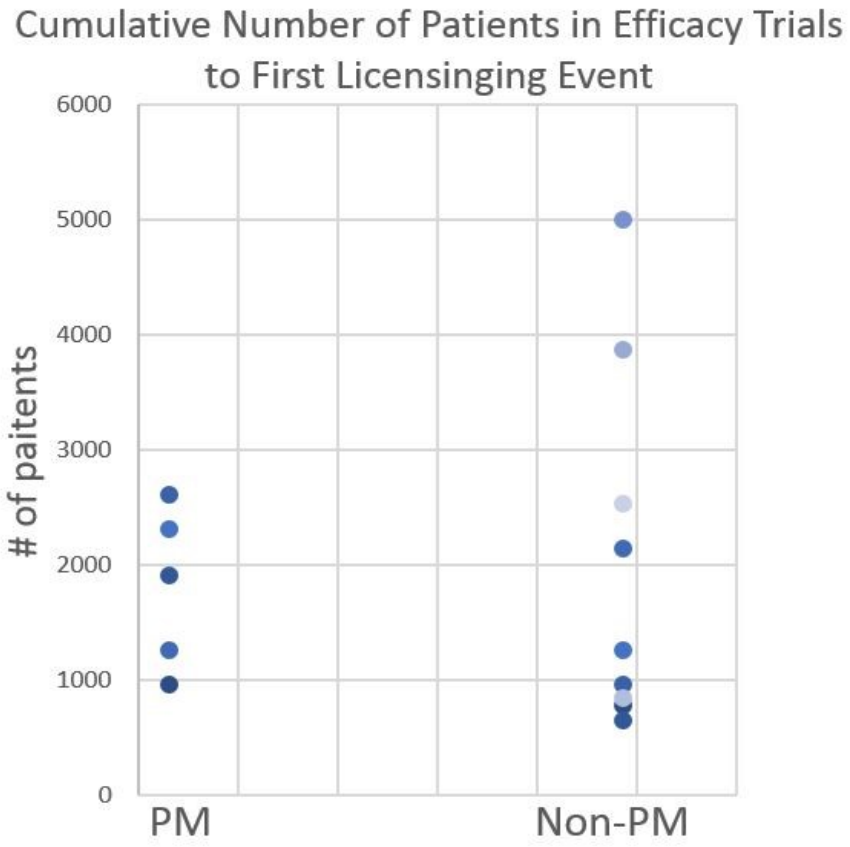


Table 6: Non-Precision Medicine Patients to First-Licensing Event by Drug

Drug	Abr	Bli	Bre	Cab	Ibr	Idl	Ipi	Pem	Vsm
# of patients to First Licensing Event	2543	789	655	970	2148	1265	5009	3874	852

Table 7: Precision Medicine Patients to First-Licensing Event by Drug

Drug	Adt	Crz	Olp	Trm	Vem
# of patients to First Licensing Event	2316	968	1909	2610	1265

Figure 11: Non-PM Drug-Indication Trajectories that Received FDA Approval

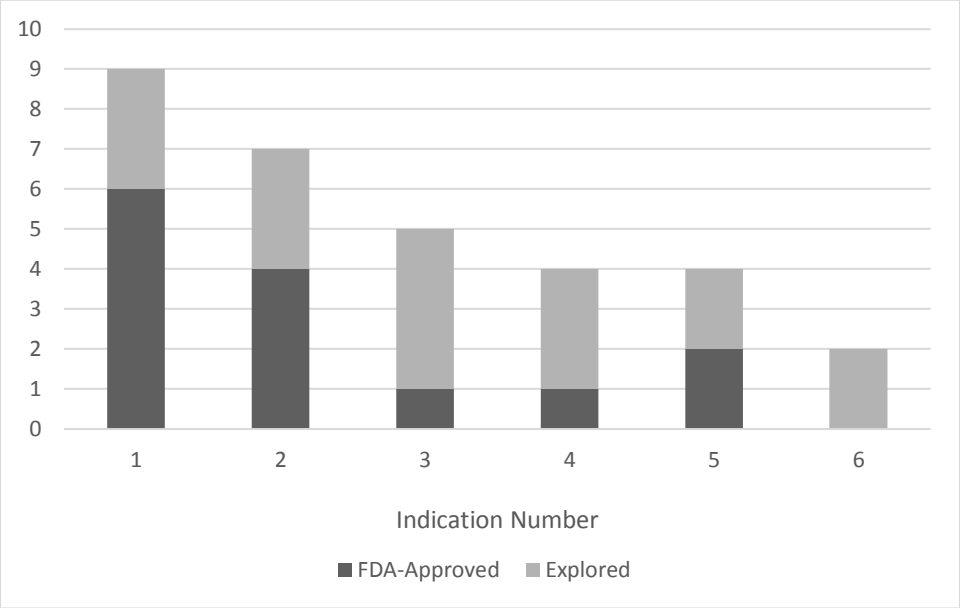


Figure 12: PM Drug-Indication Trajectories that Received FDA Approval

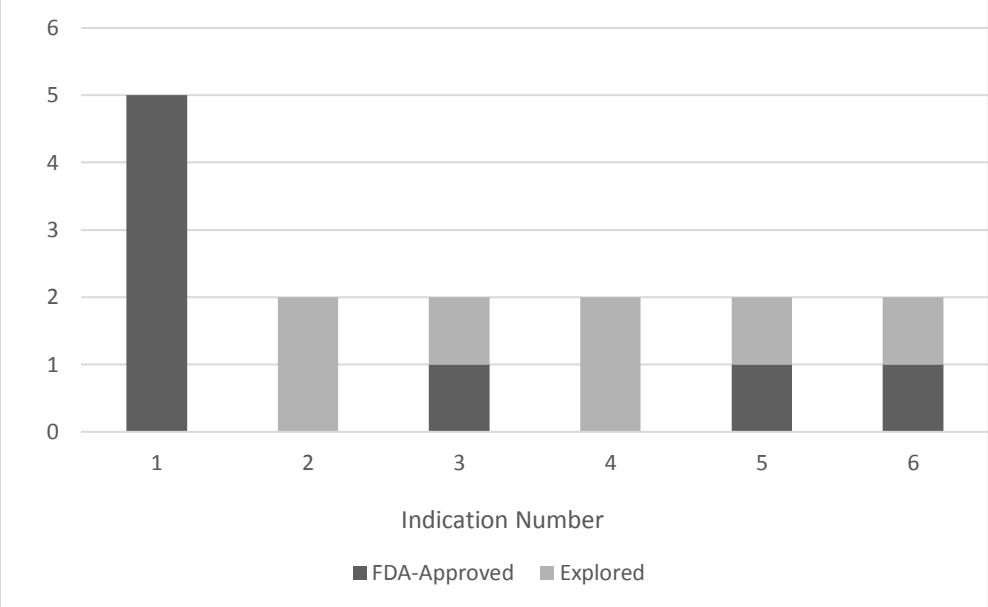
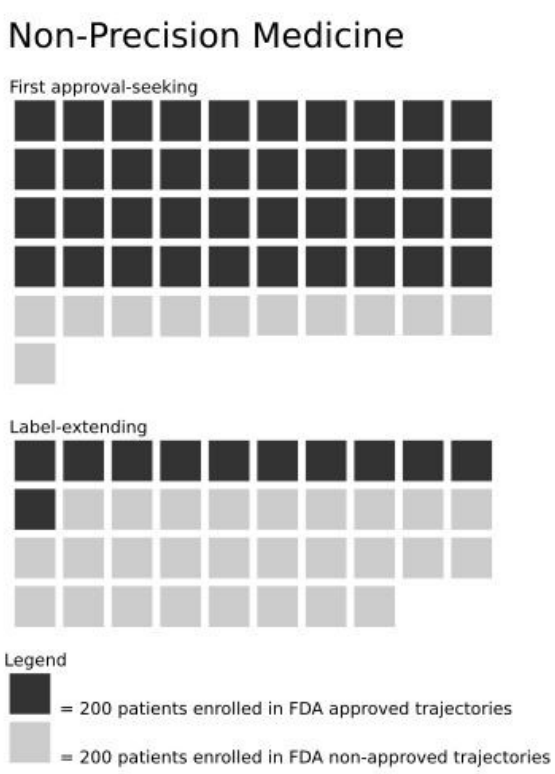


Figure 13: Non-PM Venn Diagram for Proportion of Patients in Successful Trials



Venn diagrams representing the proportion of patient enrolment in approval-seeking vs label-extending activities, and within each, the proportion of efforts within trajectories that met with FDA approval or positive phase 3 trial result (black) or not (gray)

Figure 14: PM Venn Diagram for Proportion of Patients in Successful Trials

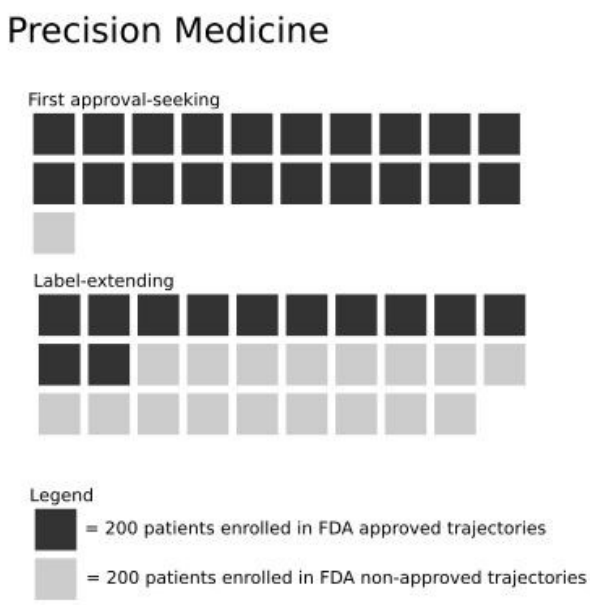


Figure 15: Non-PM Venn Diagram for Proportion of Patients who experienced the most frequent Grade 3-4 Adverse Event

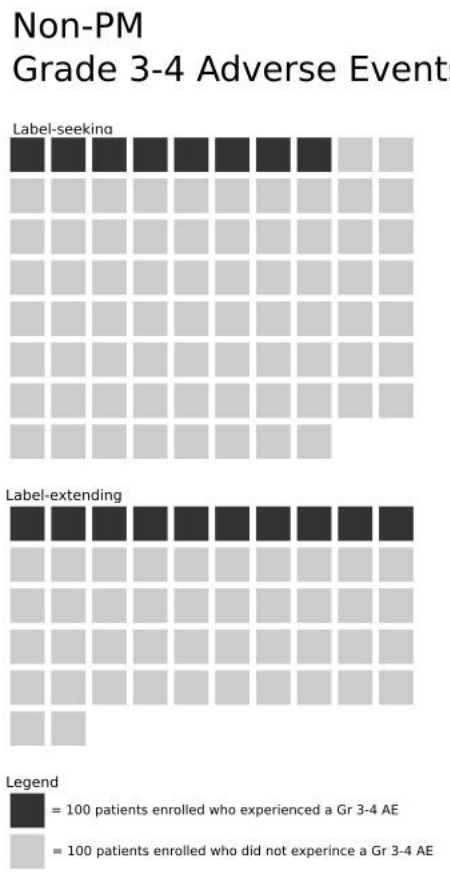


Figure 16: PM Venn Diagram for Proportion of Patients who experienced the most frequent Grade 3-4 Adverse Event

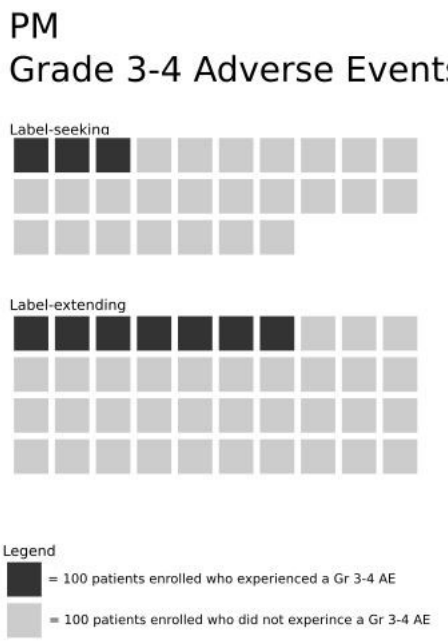


Figure 17: PM Venn Diagram for Proportion of Patients in Successful Combination Trials

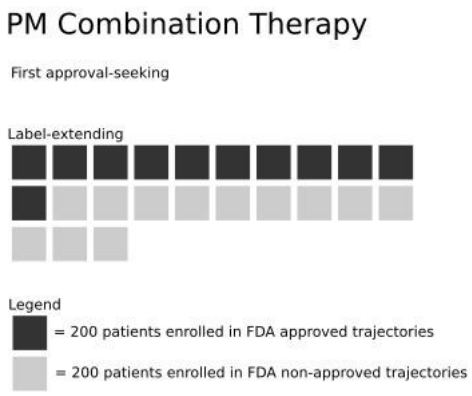
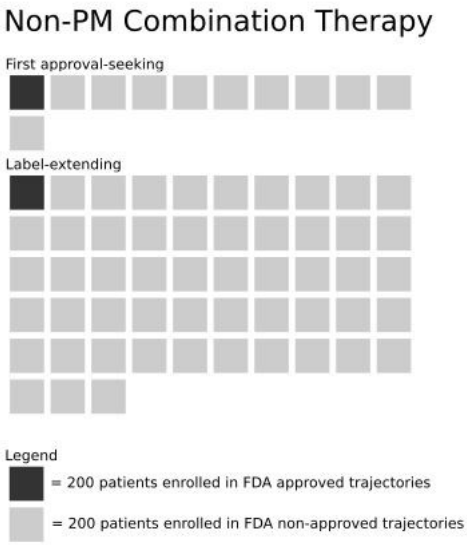


Figure 18: Non-PM Venn Diagram for Proportion of Patients in Successful Combination Trials



Chapter 4: Reflections, Limitations, Recommendations, and Conclusions from the Results of the Systematic Comparative Analysis

Chapter 4 discusses the results from Chapter 3 including all primary and secondary outcomes with reflection from the literature. Special consideration is given to anomalies, unanticipated results, and significant findings. The chapter will continue with a description of limitations of the thesis design and recommendations for government, policymakers, sponsors, and researchers from the results. The chapter will end with a brief conclusion of the entire thesis.

Primary Outcomes

We anticipated that novel, first-in-class, precision medicine (PM) drugs would take less time and fewer participants to reach a first licensing event when compared to Non-PM drugs that were licensed in the same timeframe. Unexpectedly, PM takes a comparable amount of time and participants to first-licensing event.

Number of Patients to First-Licensing Event

From a macro-level perspective, it is unclear why a similar number of participants would be required for PM compared to non-PM. Further analysis of additional novel oncology drugs or analysis at the trial level to better understand factors at play, including mechanisms of action, number of Phase 3 trials, or types of indications tested, should be performed. When looking at the specific development pathways for this cohort, there are several potential explanations for the large patient numbers incurred by PM drugs prior to first-licensing event.

One explanation for the substantial number of participants to first-licensing event in the PM cohort is a tendency for drug developers to cast a wide net of testing among multiple indications and drug combinations. For example, trametinib (MEK inhibitor) and olaparib (PARP inhibitor) underwent exploration of numerous indications and combinations early on

before the discovery of the indication that led to first FDA approval [1, 2]. Trametinib was initially believed by its developers to be effective in BRAF-mutated solid indications irrespective of tissue type, but later discovered to only be effective in BRAF-mutated melanoma and non-small cell lung cancer [1]. Olaparib was originally tested in three indication trajectories: breast, ovarian, and prostate cancer [2]. Ado-trastuzumab's (antibody-drug conjugate) trajectory was in one indication but tested various combinations prior to first approval including capecitabine, chemotherapy, and pertuzumab. The ado-trastuzumab + pertuzumab combination went to Phase III testing [3], which may explain the large number of patients needed for first approval. A second explanation for the number of patients is that drugs had unexpected events during their development. Vemurafenib (BRAF inhibitor) development encountered unexpected safety events, including development of other carcinomas, and eventual resistance to vemurafenib [4, 5]. This may have led to regulatory demands for greater patient exposure for both safety signal detection and effect size. One positive consequence of similar pre-license patient exposure in PM and non-PM is that the prospects of detecting safety signal is similar for the two modes of cancer drug development [6].

Non-PM drugs had higher variability in the number of patients to first licensing event compared to PM drugs. The range for non-PM is 655-5009 patients compared to 968-2610 patients in PM. To better understand this variability in range, an analysis into the trajectories that took the minimum and maximum number of patients for non-PM will be provided.

In the non-PM cohort, ipilimumab's trajectory had 5009 patients enrolled from its first efficacy trial to the first licensing event. Ipilimumab is an immunotherapy and a CTLA4 checkpoint inhibitor [7]. Its mechanism of action means there are greater risks for serious immune-related adverse events [8]. These novel adverse events required new criteria outside

Common Terminology Criteria of Adverse Events (CTCAE) [9] and more vigilant assessment than previous chemotherapies [8]. In early trials, participants in ipilimumab trials were not meeting the objective response rate (ORR) of tumour reduction according to RECIST criteria [8, 10]. Nevertheless, responses were noted months later, as were improvements in progression-free survival [10]. Researchers determined that a new surrogate endpoint, immune-related response criteria, was needed for immunotherapies [10]. This endpoint better reflected the longer time and less acute decrease in response for ipilimumab [10]. These endpoints were validated during the initial development of ipilimumab in melanoma trials, and prior to first FDA approval [10]. The development of the new immune-related adverse event and immune-related response criteria may be two large factors that attributed to the large number of patients needed to answer efficacy and safety questions in ipilimumab's initial trajectory.

Brentuximab vedotin, another non-PM drug, took the fewest patients (655) to first licensing event. Brentuximab vedotin is a CD30-targeted antibody-drug conjugate [11]. CD30 is present in all Hodgkin's lymphomas and anaplastic large-cell lymphoma [11]. Like other antibody-drug conjugates (ado-trastuzumab [3], inotuzumab ozogamicin [12]), significant discovery work had already been conducted to identify a compatible antibody, small chemotherapeutic drug, and proper linker for the drug and antibody [11]. Thus, previous understanding of anticipated patient population and mechanism of action could provide insight into why brentuximab vedotin had an efficient trajectory once clinical trials began.

Number of Days to First-Licensing Event

The distribution of number of days to first-licensing event for PM and non-PM were similar in both mean, median, and range. One possible explanation for the similar amount of time is that PM biomarker-enriched trials require screening of patient biomarkers for eligibility. The accrual

process of PM biomarker-enriched trials may therefore take longer than non-PM trials, which are biomarker agnostic and do not require screening [13]. We determined that all label-seeking PM trials required a biomarker for eligibility. This may suggest that accrual does affect time to first-licensing event, and that this screening process should not be ignored for precision medicine drug development efficiency. A more in-depth analysis into individual drugs are provided below.

Olaparib had a lengthy trajectory at 9.5y. As stated above, olaparib was initially tested in three indications: prostate, ovarian, and breast [2]. There were varying levels of promise in each indication, causing differing levels of follow-up [2]. The divided attention at the outset of drug development may be one reason for the time taken from first efficacy trial to initial licensing. However, this attention to multiple indications may have been warranted, as olaparib was eventually approved for triple-negative HER2- breast cancer, and ovarian maintenance therapy [14]. No label for prostate cancer has yet been achieved as of June 2018.

Crizotinib [15] had the fastest trajectory at 3.1y from first efficacy trial to first-licensing event. Crizotinib received accelerated approval based on a large effect size observed early on in ALK+ non-small cell lung carcinoma (NSCLC) during the first trials [15]. This effect was observed first in one of crizotinib's initial trials conducted on humans, and the trajectory narrowed in on the NSCLC indication until approval [15]. This early discovery, along with an active choice to maintain the streamlined path, may be the reason behind such a rapid trajectory.

In the non-PM cohort, ipilimumab had the longest time (10y), and brentuximab the shortest time (2.5y), from first efficacy trial to first-licensing event. The reasons for this amount of time taken may be reflective of the reasons for their number of patients to first-licensing event (see *Number of Patients to First-Licensing Event*). For ipilimumab, developing a new safety/efficacy criteria, and measuring patients against that criteria can take a significant amount

of time [7, 9]. For brentuximab, possessing knowledge about the presumed responsive patient population before clinical trials began could have influenced the small number of patients needed to first-licensing event [11].

Primary Endpoints in Relation to Current Scholarly Literature

Many commentators portray PM as taking less time and fewer patients to first-licensing event [16, 17, 18]. Examples include imatinib [16, 17], crizotinib [16], vemurafenib [17]. However, when authors ignore or downplay the swiftness and efficiency of non-PM drug development such as brentuximab and ibrutinib, or the slowness and inefficiency of PM drug development such as trametinib and olaparib, they overestimate the productivity of PM drug development in relation to non-PM drugs.

Skepticism surrounding precision medicine drug development is beginning to emerge in both research [19, 20] and expert opinion [21, 22, 23]. Authors reflect on how precision medicine trials and trajectories are showing little difference in efficacy over non-precision medicine [19, 23], removing the assumed power of large effect size. Precision medicine drug development also consumes a number of resources in discovery and pre-clinical studies to find actionable mutations without having those findings translate to clinically meaningful results [19, 22]. Finally, precision medicine financial incentives rely on lower-level evidence to gain FDA-approval (PM drugs require Phase II trials with large differences in surrogate endpoints to get approved, while non-PM drugs require two Phase III trials) and then rely on off-label use for efficacy afterwards [21].

The hype surrounding precision medicine efficiency is still present [18, 24], however, with commentators suggesting that precision medicine simply needs more time to prove itself than is currently being provided [24]. Funding in the hundreds of millions to billions of dollars

[18, 25] is being provided to precision medicine drug development despite growing literature about how PM may be of low impact in terms of efficacy and efficiency. Our primary endpoint results will add to the literature surrounding skepticism about the value of precision medicine in terms of streamlining drug development.

Secondary Outcomes

Indication Exploration

PM drug development efforts involved a similar number of drug-indication exploration trajectories compared to non-PM efforts. PM had a slight chance (1.0 trajectories in PM v 1.4 trajectories in non-PM) to identify an indication that would lead to license indication sooner than non-PM. Nevertheless, after first-licensing event, both PM and non-PM conducted trials in a number of indications that did not receive FDA approval. This result is comparable to previous studies showing inefficiencies in drug development trajectories [26, 27].

There were very efficient drug-indication explorations in both the PM and non-PM cohorts. For example, ado-trastuzumab was an anomaly, as it only explored one indication. Trastuzumab, a drug approved in 1998, was a monoclonal antibody also approved in HER2+ breast cancer [28]. While ado-trastuzumab emtansine is unique, as the first antibody-drug conjugate to be used in solid tumours, it is a derivative of its monoclonal antibody, trastuzumab, and thus has similar properties [3]. As such, the trajectory for success was well anticipated, explaining the remarkably streamlined development. Abiraterone acetate and brentuximab vedotin only explored one indication when data were censored for follow-up (explained in **Chapter 3**). Abiraterone is a CYP17 inhibitor, unique to other mechanisms of action [29]. This drug class is known for addressing the cancer through hormonal pathways, including estrogen and androgen [29]. Because of abiraterone's drug mechanism of action, this explains exploration

only in cancer indications that use hormonal pathways. Brentuximab, an antibody-drug conjugate, had a small number of trajectories explored during its clinical research development, likely due to knowing the responsive patient population, determined early on in research development [11].

In contrast, there were a number of seemingly inefficient drug trajectories in PM and non-PM. In the non-PM cohort, ipilimumab's drug development examined six drug-indication trajectories with only one receiving FDA approval. Ipilimumab's development had a few early phase trials that demonstrated preliminary efficacy in NSCLC, SCLC, prostate cancer, melanoma and renal cell carcinoma [9]. Previous immunotherapies had little effect on NSCLC or SCLC, but there is some retrospective and discovery phase testing to state why ipilimumab may work on lung cancers [9]. As of June 2018, ipilimumab is only approved in melanoma. For PM, trametinib and olaparib had numerous indications believed to be effective pre-clinically that were discovered to be ineffective in early phase clinical trials, thus explaining their numerous drug-indication trajectories.

Vismodegib is unusual insofar as its development initiated exploration of two other indications before a third, basal-cell carcinoma, was identified and led to a regulatory approval. In pre-clinical testing, vismodegib was tested in medulloblastoma allograft and colorectal xenograft models to determine pharmacokinetic/pharmacodynamic (PK/PD) modeling [30]. In the discovery phase, ovarian fibromas were seen to be largely impacted by alterations in the Hedgehog pathway [30]. This can explain the colorectal and ovarian testing before basal cell carcinoma and medulloblastoma testing immediately after, demonstrating the impact the drug discovery and pre-clinical phases can have on indication exploration.

Patients in Successful Trajectories

Generally, PM patients had a better chance of participating in a successful trajectory at both the label-seeking (98% PM v 79% non-PM) and label-extending stages (41% PM v 30% non-PM). Nevertheless, both PM and non-PM cohorts had a significant drop in patients in successful drug-indication trajectories during the label-extension research. These patterns are similar to other cancer drug-indication trajectories studies performed [26, 27], showing that PM is not immune to unsuccessful exploration after initial approval.

This unsuccessful label-extending exploration may be related to the tissue agnosticism theory: many researchers expect their PM drug will work on any histology as long as a certain biomarker is present [31, 32]. Additionally, researchers may work with sponsors or organizations that focus on patients with rare or severe indication, and choose to explore these indications despite the likelihood of success being low [33]. This concept is explored further in the *Biomarker Testing and Eligibility* section.

The proportion of patients in successful trajectories for PM compared to non-PM (65% PM v 58% non-PM) may indicate that the preclinical and discovery stages of research give better insight into what indications are likely to be effective. Novel PM drugs are known to have an extensive discovery phase [34] and this knowledge may cause principal investigators to be hesitant to stray from the supposed efficacious drug-tissue-biomarker pathways. The burden of proof, in terms of investigator brochures and funding applications, may be greater for indications that are not referenced in the discovery and pre-clinical phases.

Biomarker Testing and Eligibility

The PM cohort used biomarker eligibility criteria in a greater proportion during the label-seeking stage (100%) when compared to the label-extending stage (50%). A recent article published in

Scientific Reports demonstrated that for 22 oncology drugs that required genetic testing on FDA labels, most approvals (69%) were based on trials using enriched populations [35]. This review was designed to demonstrate a need to test on biomarker-negative patients to determine whether the biomarker was predictive [35]. Nevertheless, it may also demonstrate that approvals occur in those that are enriched rather than those that are biomarker agnostic or biomarker-negative.

One possible explanation trials in the PM label-extension stage drop biomarker eligibility is the indications they explore. Rare occurrence indications (sarcomas) or indications with very poor outlooks (pancreatic) were more frequently seen in label-extension, including 2 of 5 PM drugs and 6 of 9 non-PM in this cohort. Some oncology researchers argue that it is ethically permissible to run a trial with less stringent eligibility criteria, if it gives patients with rarer indications an 'option' for therapy that was not present previously [36, 37]. The counterargument is that without taking into account important inclusion criteria [38], and ensuring careful methodological insight [39], patients are not properly respected as research participants and may be put at unnecessary risk [38].

Exploratory biomarker testing was common in both non-PM (75%) and PM cohorts (50%), especially at the label-extending stage. Specifically, non-PM label-extending has a large division between trials that needed a biomarker for eligibility (29%) and trials that performed exploratory biomarker testing (75%). Mandatory tumour biopsies may be a barrier to enrollment for cancer trials, especially repeat biopsies [40]. Researchers in oncology have encouraged investigators to develop biomarker assays with respect to clinical need, such as eligibility, measurement of outcome, or assignment of treatment [41]. Exploratory biomarker testing can play an important role in drug development, but patients should have an option to opt out, even if they are exceptional responders [42].

Adverse Events Experienced

Due to the targeted nature of PM drugs, researchers hypothesize that these drugs will have less off-target adverse events, and fewer adverse events overall experienced by patients when compared to non-PM drugs [43]. Our findings indicate patients experienced a similar number of Grade 3-4 adverse events at the label-seeking and label-extending stage in both the PM and non-PM cohort. Patients in the PM cohort were slightly less likely to experience a Grade 5 adverse event compared to non-PM. Explanations for these finding may be that these adverse events are on target, but just as grave as before, or that novel drugs as a whole are getting better safety profiles regardless of their biomarker eligibility status.

Both cohorts had a slight increase in patients experiencing Grade 3-4 adverse events at the label-extending stage, compared to the label-seeking stage. These findings relate to previous studies showing increased burden as drug development trajectories continue forward [26, 27]. Later on the drug development trajectory, researchers were more likely to test in drug combinations, or in rare indications. Testing in combination can lead to unexpected toxicities or adverse events [44], and testing in rare indications is riskier as less is known about the cancer etiology [45]. Those who enter into the drug development trajectory later are taking on greater risk than those who enter during the label-seeking stage.

Quality of Evidence to FDA Approval

Overall survival (OS), often considered the gold-standard clinical endpoint in oncology [46], was used more frequently in non-PM late stage trials than in PM trials. PM trials were more likely to use the longer-term surrogate endpoint progression-free survival (PFS) earlier on, in Phase II testing, than non-PM trials. Generally, PM trials will stop at PFS, whereas non-PM will follow through to OS, especially in Phase III testing.

Regulators encourage the use of hard clinical endpoints when possible over surrogate endpoints [33, 47]. This is because often the surrogate endpoints being used are poor indicators of the clinical endpoint, and post-marketing follow-up of downstream patients is delayed [33, 47]. Nevertheless, recent articles critique the expectation of OS use every time in cancer drug development, as OS can have crossover confounding results [31] and be contaminated by post-progression therapies [48]. At the same time, there has yet to be a single time where PFS has been found to be a valid surrogate of OS in any cancer histology [49]. At a minimum, these findings of endpoint usage and concerns raised about surrogate endpoints in the literature demonstrate the need for long-term follow-up, of which PM drug development does not seem to be encouraging [50].

Factors that Influence Whether a Patient is in a Successful Trajectory

Drug Classes

While future researchers are encouraged to perform more in-depth analyses into specific drug classifications (expanded upon in *Recommendations*), we began performing subgroup analyses on prominent classes from our cohort, including kinase and checkpoint inhibitors.

Kinase inhibitors outcomes from the PM and non-PM cohort compare to the findings of the whole cohort. Kinase inhibitors had similar numbers of patients in the PM vs. non PM-cohort (1614 PM v 1461 non-PM), days to first-licensing event (1381d PM v 1695d non-PM), number of drug-indication trajectories explored (3 PM v 3 non-PM), and number of patients in successful trajectories (label seeking: 95% PM v 95% non-PM; label-extending: 63% PM v 29% non-PM). The literature suggests that kinase inhibitors are among the more impactful drug classes both within oncology and other disease drug development [51, 52]. This subgroup analysis may demonstrate that our findings translate across classifications, and that kinases may share novelty

like other drug classes. It is important to note that there are still many classes of kinase inhibitors [53] and our analysis grouped all kinase inhibitors together.

Immunotherapies, and specifically checkpoint inhibitors, are expected to play a critical role in the future of oncology drugs [24]. Briefly, immunotherapies assist in boosting the body's own immune system to recognize and fight the cancer, rather than directly killing the cancerous cells [7]. Reflecting on the two checkpoint inhibitors in our cohort, there are drastic differences in drug development efficiency between the two. Ipilimumab took a significantly longer time to licensing (explained in *Primary Outcome*), had more unsuccessful trajectories explored, and had more patients in unsuccessful trials when compared to pembrolizumab. Ipilimumab paved the way for future immunotherapies including pembrolizumab with the development of immune-related response and safety criteria [7, 9, 10]. More analysis will have to be performed on non-first-in-class checkpoint inhibitors approved after ipilimumab (i.e. nivolumab, avelumab), to see whether their trajectories followed the efficiency of pembrolizumab drug development.

Combination Testing

Combinations therapies can improve patient outcomes by acting synergistically and additively [44]. But they can also be more toxic [44]. Our cohort had a substantial percentage of trials that acted in combination (44%) and 4 of the 14 drugs eventually had an FDA label for a combined oncology drug-indication with indications that had 5-years follow-up.

PM trials tested in combination with another cancer drug 46% of the time, whereas non-PM trials tested in combination only 39% of the time. In our analysis, the majority of trials conducted in drug combinations did not result in an FDA license. Combinations were frequently performed with other novel therapies, including inhibitors, antibodies, and cancer vaccines. PM

was slightly more prone to combination testing with other cancer therapeutics than non-PM drugs.

Testing in combination can be attributed to pharmaceutical companies competing with other drug companies to gain first-line therapy, or maintaining patents on one of the two drugs in combination [44]. The proposed combination may be initiated to manage unwanted side effects, or to increase physician confidence in the efficacy of the drug over other drugs [54]. There has been recent criticism of immunotherapies testing in combination, with an estimated 1100 combination clinical trials in progress, about whether the risk of toxicity and serious economic burden of combination therapy is worth the slightly added efficacy [55].

Our findings demonstrate that drug-combination trajectories rarely result in FDA licenses. Drug combination trials should be initiated with caution, as numerous patients are exposed to unknown risks in the process. Having a combination with another novel agent does not guarantee that the combination will the efficacious.

Biomarker Eligibility

Our systematic review demonstrated that when a biomarker was required for eligibility in the label-extending stage, there was a 14% greater chance that the drug-indication would receive FDA-approval within the next 5 years. This held true for both the PM and non-PM cohort.

Researchers and institutes who encourage precision medicine drug development frequently cite the use of targeted therapy to individualize the patient tumour as one of the reasons for its success and novelty [18, 24]. Researchers who see the failures or shortcomings of PM drug development often state that it will get better with more genetic knowledge and understanding of tumour heterogeneity [19]. Yet our findings demonstrate biomarker eligibility

is quickly abandoned after initial licensing in PM, and that when the biomarker eligibility is kept, the trajectory has a higher chance of receiving a new FDA label. Given that researchers and experts clearly comprehend the importance of the biomarker, what factors are at play for early abandonment of the biomarker after the label-seeking trajectory?

Our study suggested that when the drug was designed with a biomarker in mind, that biomarker played a role in the drug's first FDA approval. The trajectories that were biomarker agnostic were less likely to receive FDA approval, and often were in indications that had poor prognoses to begin with. Principal investigators, funding agencies, and research ethics boards should be mindful of whether a drug required a biomarker initially, and what level of evidence is being presented for a trial with a biomarker-agnostic indication, to determine if that trial should proceed as designed.

Phase I Testing

Ceritinib received approval after Phase I testing, and imatinib received approval after two Phase II tests [56]. In our cohort, 8 out of 14 drugs were granted orphan drug status or accelerated approval ahead of Phase III testing, including 3 of 5 PM drugs and 5 of 9 non-PM drugs. Phase I trials and the information they collect will continue to play an integral role for drugs that receive accelerated approval. Despite this, Phase I trials only used efficacy endpoints 20% of the time in PM. The majority of the time this was ORR, which is often a poor reflection of overall survival [57]. Phase I trials represented 16% of the total patient population for testing. With such a small percentage of the population being represented, there is a greater likelihood that rarer and long-term adverse events are easily missed [58]. Despite Phase I trial information being more heavily relied upon with accelerated approval, it appears that the Phase I trials of novel, first-in-class drugs do not possess substantive new, lengthy, or rigorous information for downstream patients.

Limitations

This study has several limitations. Our examination of novel drugs had significantly less follow-up than previous drug-trajectory examinations [26, 27] due to the recentness of our sample. Currently we cannot conclude whether novel drugs or precision medicine drugs perform fewer drug-indication trajectories in the label-extension stage. Follow-up is warranted for both cohorts to determine if PM drug development is more streamlined in time and number of patients to first-licensing event, and if novel oncology drugs in general are becoming more focused in the number of trajectories they are exploring.

Our study included a relatively small cohort of drugs, especially from the PM cohort. Therefore, we urge caution in attempting to generalize our findings beyond our sample. This choice did allow for direct comparison with non-PM drugs approved in the same timeframe. Ensuring we were comparing drugs that had similar levels of novelty was important as expanding the PM time-frame relative to non-PM would come with additional limitations in comparing older drugs to newer ones. Few PM drugs using biomarker testing are currently FDA licensed (10% of approvals were PM in 2007 and grew to only 21% of new approvals by 2014 [59]), meaning that a large sample size within the same timeframe would be voluminous work regardless. Using drugs that were approved more recently would not have allowed for enough time for follow-up.

We only used full-text published reports for our systematic review. Due to publication bias, published studies are more likely to report positive findings than negative [60]. While this may elevate the positivity in our results, it should not affect our comparison, as only published trials were used in both cohorts.

For our comparative analysis we had to designate each drug to one cohort: PM or non-PM. However, an initial designation of PM or non-PM by the first FDA license is not necessarily reflective of that drug's class. For example, pembrolizumab, a non-PM drug, eventually had PM attributes, being used in PDL1+ NSCLC and gastric cancer, and MSI-H colorectal cancer [61]. Contrarily, olaparib, a PM drug, was eventually approved in a non-PM use for maintenance therapy for ovarian cancer [2]. Brentuximab precisely targets CD30 and uses the microtubule-disrupting agent MMAE to treat B-cell malignancies, yet its classification does not revolve around a subdivision of individuals that requires biomarker testing, [11] so we designated it as non-PM. If our definition did not exist on the presence of a test but on the specific mechanism of action, or on whether the drug eventually had a biomarker component, then this could have drastically altered the primary outcome, especially considering the lengthiness of olaparib and rapidness of brentuximab initial drug development. Not all comparisons may adequately reflect PM vs. non-PM but may more appropriately be described as initially PM vs. initially non-PM.

We chose what indications were label-seeking versus label-extending based on the first indication that received FDA-approval. This method has inherent faults in design. For example, pembrolizumab was initially approved for melanoma, but the first efficacy trial for enrollment was non-small cell lung cancer, and subsequently melanoma. To state that melanoma was label-extending is not necessarily accurate, as both indications were explored in tandem given the tissue agnosticism of pembrolizumab immunotherapy [61]. Our definition of the proportion of patients in label-extending trials is ultimately biased towards placing patients in the label-extending cohort.

Our definition of a 'successful' trajectory for the Venn diagrams (see Chapter 3 *Tables and Figures*) was narrow. This definition was only based on mono- or combination therapy, and

the histologic (non-PM) or histologic-biomarker (PM) indication. Important factors such as dosing, schedule, line of treatment, and patient population (i.e. refractory, age range) were not taken into account. These items can have a substantial impact on whether a downstream patient will receive the drug, but are longer to code, and difficult to stratify. For this reason, a simplified definition was used in the comparative analysis.

Implications for Research Ethics

Informed Consent: Hype or Hope?

PM has entered the mainstream, with headlines in TIME magazine and Forbes touting the successes of targeted oncology therapy [62, 63]. Patients, and laypersons, may have the impression that every one of these drugs is a 'magic bullet', or 'miracle pill' [62, 63].

Patients must enter into trials with informed consent [64, 65]. Despite this, patients who enter into trials often experience therapeutic misconception or therapeutic overestimation [66]. Therapeutic misconception is the belief that research is meant to benefit them as a patient; therapeutic overestimation is the belief that there is a great chance of the patient benefiting compared to the actual prospect in the trial [66]. With the publicity of PM, it is easy for patients who see a PM trial to believe that drug is more likely to benefit them than one that does not have a PM component. Our results have demonstrated that patients in PM drug trials had as likely a risk of experiencing a serious adverse event when compared to patients in non-PM drugs trials, and did not result in a more efficient process to approval. While we did not look directly at benefit, our results did indicate that the PM cohort used lower quality evidence up to approval, and that this lower quality evidence had consequences, such as the determination of vemurafenib resistance after FDA-approval [5].

To assume that patients are uninfluenced by media and the world surrounding them is imprudent. Cancer patients may be deeply immersed in investigating their disease, and they frequently use media to research their disease trajectory, possible treatments, and current research trials [67]. Knowing this, healthcare providers obtaining informed consent must situate the patient in the context of that individual trial. Our research would encourage healthcare providers to assess patients for therapeutic overestimation surrounding PM, and mitigate that bias, as there is emerging skepticism about the impact PM drugs will play in oncology.

Beneficence: Biomarkers and Biopsies

Investigators have a duty to ensure a fair balance of risks and benefits to the research participant [64, 65]. Research must be consistent with competent care, there must be expert consensus that the drug is at least equal to standard-of-care, and risks that are outside therapeutic procedures must be minimized [64, 65].

In our study, when a PM trajectory dropped the biomarker eligibility criteria, that trajectory was less likely to be successful and gain FDA-approval. Patients enrolling into the biomarker-agnostic trials were taking on greater risk in terms of Grade 3-4 adverse events experienced. This systematic review should encourage future researchers, and research ethic boards, that biomarker-agnostic trials in biomarker-approved drugs should be initiated with caution, as patients may be taking on additional risks, without actionable clinical information.

Our study demonstrated that purely exploratory biomarker testing increased during the label-extending stage of drug development for both cohorts. Biopsies for biomarker testing are above minimal risk, and can result in serious adverse events [68]. When the purpose of a biopsy is to determine whether the drug will be effective in that patient, it is a therapeutic procedure. However, if the biopsy is solely for research purposes then the patient is taking on a non-

negligible risk without any prospect of direct benefit, and it is a non-therapeutic procedure. Non-therapeutic procedures can be justified - if they have sound scientific design and relevant knowledge is gained [69]. When researchers propose that a biopsy be performed for exploratory purposes, there should be a plan for how to use those biopsies, and if not, the biopsies should be optional [70]. Large-scale trials, such as the FOCUS-4 trial, are already putting this into place with a separate consent form for biopsy collection [71].

Justice: Equal Burden

According to the Belmont Report and Tri-Council Policy Statement 2, no group of persons should take on greater burden in research than any other group of persons [64, 65]. This protects vulnerable groups, and makes investigators and sponsors reflect on their inclusion and exclusion criteria before initiating a trial [64, 65]. From our results, whether patients were entering into PM or non-PM trials, if they entered in the label-extending stage, they were taking on greater burden than those in label-seeking. The patients were more likely to experience a Grade 3-4 adverse event, and in the non-PM cohort were also more likely to experience a Grade 5 adverse event (Death) if they were in later trajectories. These patients were also less likely to be in a trial or trajectory that will have implications for future clinical practice. These inequities are reflective of previous drug development trajectory studies of sunitinib and sorafenib [26, 27].

Cancer patients who enter clinical trials can arguably be deemed a vulnerable population, as these patients are often out of curative options, and feel desperate for a treatment to their disease, no matter how slim the chance of benefit [72]. Our study found that most trials were open to persons with refractory or metastatic disease, demonstrating that these patients have little prospect of benefit in the clinical realm. This desperation may be further amplified when cancer

patients have an indication that is rare or has a poor prognosis. Indications that were rare or with poor prognoses were more prevalent in the label-extending phase.

Investigators and Research Ethics Boards have a duty to protect participants from taking on greater burden than is necessary. When a trial is initiated in a rare indication that it was not originally intended for, or is on a much later indication exploration, special consideration should be given if that trial is warranted for that patient population. By taking the time to recognize where the drug is in its development, and reflect it to the trial at hand, patients may be saved from undergoing greater risk than those who entered earlier in the drug trajectory profile.

Recommendations

Our findings suggest that, regardless of PM or non-PM class, drug development in oncology continues to be a lengthy process that involves many patient-participants. Even when the majority of PM trials are biomarker-enriched, this does not largely impact the number of patients needed to come to a conclusion on the efficacy and safety of the drug before FDA licensing. Our recommendations focus on ensuring PM trials provide quality evidence moving forward, and meta-analysis researchers continue to hold oncology drug development accountable for any inefficiencies in the future.

Companies, sponsors, and policy makers must be made aware and base decisions around the fact that indications at the label-extending stage are unlikely to produce actionable information and should not be conducted without appropriate justification [26, 27]. Our results now demonstrate this is true in both PM and non-PM drugs at the extension stage. Principal investigators should take it upon themselves to verify the current drug portfolio and make informed decisions about how to move forward, rather than exploring exhaustively or without proper justifying evidence [73].

Cancer drug trials should follow through with hard clinical endpoints in PM and non-PM. This includes both overall survival (censored for crossover) and quality-of-life. If not, attempts should be made to validate progression-free survival for incoming novel drugs. There are limitations to using softer endpoints such as PFS or response rate. This was seen with vemurafenib where patients often acquired resistance soon after therapy and experienced serious adverse events such as squamous cell carcinoma, leading to an insignificant difference in overall survival [5, 74].

Biopsies have been known to cause severe adverse events on occasion and are not a negligible procedure [68]. Participants need to be protected when entering into a study and make an informed decision about what risks they incur [64, 65]. Therefore, principal investigators must have an ethical and scientific justification for biomarker testing without eligibility when participants are entering into a cancer drug trial. If exploratory testing is to be performed, it should be an optional procedure that ideally exists alongside another clinically relevant procedure to minimize patient risk and maximize patient autonomy.

Future research may benefit from performing systematic reviews based on drug class, additionally stratified to precision and non-precision medicine. The classes could include, but are not limited to: antibodies (monoclonal and antibody-drug conjugate), tyrosine kinase inhibitors or checkpoint inhibitors. This can address the limitation of using a wide comparison of drugs and allows for a more streamlined analysis of where the inefficiencies may be in oncology drug development.

Biomarker outcome and biomarker exploration studies in novel precision and non-precision medicine drugs have yet to be properly analysed by meta-analysis research. This thesis exclusively analysed interventional studies. If researchers analyse the specific biomarker studies,

they may uncover answers regarding the decline in biomarker eligibility for precision medicine and increase in biomarker exploration for non-precision medicine. Researchers may also look at the impact of assay testing, cut-points used for biomarker stratification, and biomarker levels as clinical endpoints [75].

After a few years, to ensure adequate follow-up, researchers should observe the impact of novel trial designs such as basket, umbrella, and platform trials on time and patients to first licensing event, number of indication explorations, and biomarker testing in cancer drug development. Briefly, basket trials are a single trial that tests one drug under multiple tissue types (usually with a similar biomarker), umbrella trials tests one tissue type under different biomarkers, and platform is usually a combination of basket and umbrella [31]. These designs can already be seen in our cohort, with vemurafenib using basket trials [76], and pembrolizumab having the notable KEYNOTE platform design [77]. Predictions for these novel trial designs are optimistic, suggesting that they will allow for more indication exploration while using less patients and less time [31]. Researchers should determine whether novel drugs that used these designs actually meet these predictions, and at what cost (including financial, safety signal detection or false negatives/positives).

Researchers may take this data and expand to a larger cohort of novel, first-in-class oncology drugs. Creating a larger cohort, especially in the precision medicine section, can increase confidence in the results provided. This would likely mean included drugs that were approved in 2015-2016 as few novel precision medicine drugs were approved prior to 2009.

Conclusion

This is the first systematic review to compare novel precision medicine drug development efficiency to non-precision medicine in the same timeframe. Our results show that precision

medicine is not as efficient as previously hypothesized, and uses the same number of patients and days to reach a first-licensing event compared to their non-PM counterpart. Precision medicine has additional limitations, including more frequently using less valid clinical endpoints compared to non-PM and dropping their biomarker eligibility after the initial label-seeking stage.

Limitations of this thesis included the smaller cohort of drugs, the strict definition of a precision medicine drug, the gray definition of label-seeking versus label-extending, and the incomplete definition of a successful trial or trajectory. Future research from our study could include expanding the timeframe or excluding the first-in-class label to allow a larger cohort, focusing on one drug classification over a longer span of time, focusing on the biomarker testing and outcomes, and following up on how novel trial designs will ultimately impact drug development efficiency.

With respect to these limitations, researchers and policymakers can begin to take note of inefficiencies in precision medicine drug development. At the policy and macro-level precision medicine should be encouraged to use hard endpoints and keep biomarkers for eligibility where possible. Drug development in oncology as a whole should have clear guidelines for when biomarkers for eligibility and biomarker testing should be performed. Trials at the label-extending stage should be held under close observation with proper accountability for those found to be solely exploratory, without plan for follow-up, or anticipated to be negative.

Until now, precision medicine has been viewed in a positive light and believed to be a beacon towards the future of cancer drug development. Going forward, precision medicine should be carefully watched and held accountable for inefficiencies and limitations as seen in this review. Precision medicine drug development must be seen with its success stories alongside

its failures and mediocrities, and with that, a better drug development paradigm in oncology can begin to unfold.

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Appendix A: List of Studies Included in Systematic Review

Precision Medicine Studies
Ado-trastuzumab Martin M, Fumoleau P, Dewar JA, Albanell J, Limentani SA, Campone M, Chang JC, Patre M, Strasak A, de Haas SL, Xu J. Trastuzumab emtansine (T-DM1) plus docetaxel with or without pertuzumab in patients with HER2-positive locally advanced or metastatic breast cancer: results from a phase Ib/IIa study. Annals of Oncology. 2016 Apr 6;27(7):1249-56. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéras V, Guardino E, Fang L. Trastuzumab emtansine for HER2-positive advanced breast cancer. New England Journal of Medicine. 2012 Nov 8;367(19):1783-91. Krop IE, Kim SB, González-Martín A, LoRusso PM, Ferrero JM, Smitt M, Yu R, Leung AC, Wildiers H. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. The lancet oncology. 2014 Jun 1;15(7):689-99. Watanabe J, Ito Y, Saeki T, Masuda N, Takano T, Takao S, Nakagami K, Tsugawa K, Nakagawa S, Kanatani K, Nakayama T. Safety Evaluation of Trastuzumab Emtansine in Japanese Patients with HER2-Positive Advanced Breast Cancer. in vivo. 2017 May 1;31(3):493-500. Burris III HA, Rugo HS, Vukelja SJ, Vogel CL, Borson RA, Limentani S, Tan-Chiu E, Krop IE, Michaelson RA, Girish S, Amler L. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)–positive breast cancer after prior HER2-directed therapy. Journal of Clinical Oncology. 2010 Dec 20;29(4):398-405. Miller KD, Diéras V, Harbeck N, Andre F, Mahtani RL, Gianni L, Albain KS, Crivellari D, Fang L, Michelson G, De Haas SL. Phase IIa trial of trastuzumab emtansine with pertuzumab for patients with human epidermal growth factor receptor 2–positive, locally advanced, or metastatic breast cancer. Journal of Clinical Oncology. 2014 Apr 14;32(14):1437-44. Hurvitz SA, Dirix L, Kocsis J, Bianchi GV, Lu J, Vinholes J, Guardino E, Song C, Tong B, Ng V, Chu YW. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2013 Mar 20;31(9):1157-63. Gupta M, Wang B, Carrothers TJ, LoRusso PM, Chu YW, Shih T, Loecke D, Joshi A, Saad O, Yi JH, Girish S. Effects of Trastuzumab Emtansine (T-DM1) on QT Interval and Safety of Pertuzumab Plus T-DM1 in Patients With Previously Treated Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer. Clinical pharmacology in drug development. 2013 Jan 1;2(1):11-24. Krop IE, Modi S, LoRusso PM, Pegram M, Guardino E, Althaus B, Lu D, Strasak A, Elias A. Phase 1b/2a study of trastuzumab emtansine (T-DM1), paclitaxel, and pertuzumab in HER2-positive metastatic breast cancer. Breast Cancer Research. 2016 Dec;18(1):34. Yamamoto H, Ando M, Aogi K, Iwata H, Tamura K, Yonemori K, Shimizu C, Hara F, Takabatake D, Hattori M, Asakawa T. Phase I and pharmacokinetic study of trastuzumab emtansine in Japanese patients with HER2-positive metastatic breast cancer. Japanese journal of clinical oncology. 2014 Oct 20;45(1):12-8.

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Trametinib

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Non-Precision Medicine

Vismodegib

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Idelalisib

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Brentuximab Vedotin

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Ibrutinib

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