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Research Paper

Representation of older patients in the safety analysis of protein kinase inhibitor registration studies

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ABSTRACT

Introduction: Older patients (≥65 years old) make up the majority of the cancer population. Older patients seem to experience more adverse events (AEs) from protein kinase inhibitors (PKIs) in clinical practice. Yet they are underrepresented in clinical trials. We aimed to evaluate whether age-related safety differences were described at authorization of PKIs. Representation of older patients in registration studies was also evaluated.
Materials and Methods: European Public Assessment Reports (EPARs) of PKIs authorized between 2010 and 2015 were evaluated for the description of age-related safety- and pharmacokinetic differences. The International Council for Harmonization of Technical Requirement for Pharmaceuticals for Human Use (ICH) E7 guideline was applied to EPARs to assess the representation of older patients. Study results were presented descriptively.
Results: Eighteen PKIs with 19 EPARs were analyzed. Age-related safety differences were described in 14 out of 19 EPARs, and age-related pharmacokinetic differences in 1 out of 19 EPARs. More than 100 older patients were included in half of the studies. Older patients were not excluded solely by age, although other inclusion and exclusion criteria negatively influenced enrollment of older patients. None of the PKIs met all criteria from the ICH E7 guideline.
Discussion: Age-related safety differences are described for most PKIs. Older patients were underrepresented in PKI registration studies. Adequate representation of older patients in clinical trials for PKIs is vital, since they make up most of the cancer population.

1. Introduction

Older patients make up the majority of the total cancer population, although the proportion of older patients is dependent on the site and type of cancer [1,2]. For instance, the median age at diagnosis for lung cancer is 71 years, resulting in a mainly older population, while the median age at diagnosis for thyroid cancer is 51 years [2]. Overall, more than half of the new cancer cases are in patients older than 65 years. Due to the increased life expectancy and demographic shifts, the older patient population with cancer is expected to increase in both absolute and relative numbers [2–4].

Despite older patients representing the majority of patients with cancer, this population is underrepresented in clinical studies [5]. Data from clinical trials may not be suitable for extrapolation to older adults [6], as aging comes with several pharmacokinetic and pharmacodynamic changes [7–10]. Changes include a different volume of distribution due to a decreased lean body mass, reduced renal and hepatic function, diminished reserve capacity, and changes in receptor number and affinity [6,11]. Older patients are also more prone to develop adverse events (AEs) [7–10]. The importance of adequate representation has been a point of discussion for years [12–15], however, older patients still seem to be underrepresented.

Protein kinases play a critical role in mechanisms regulating different cellular functions, such as cell growth, proliferation, and differentiation. Alterations in their expression and mutations may lead to cancer and other diseases, such as rheumatoid arthritis and psoriasis

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[16,17]. Since the approval of imatinib in 2001, protein kinase inhibitors (PKIs) have become a major class of small-molecule, orally available drugs for the treatment of cancer [18,19]. Tofacitinib, approved for rheumatoid arthritis, was the first rationally designed PKI approved for a disease other than cancer [17]. However, few PKIs are approved for indications other than cancer [16,17,20]. It is predicted that the development of novel PKIs continues to be a growth area over the next 20 years [17].

This study assessed whether safety differences were evaluated and exist between older and younger patients in the registration studies for PKIs. As a secondary objective, the representation of older patients within the registration dossiers was evaluated by assessing adherence to the International Council for Harmonization of Technical Requirement for Pharmaceuticals for Human Use (ICH) E7 guideline and the supplementary Questions and Answers [21]. These documents provide guidance on the clinical evaluation of drugs in older patients, with special consideration of differences in pharmacokinetics, pharmacodynamics, and dose response studies in older patients. The general principle of these guidelines is that patients entering clinical trials should be "reasonably representative of the target population." The European Public Assessment Reports (EPARs) contain detailed information on the medicines assessed by the Committee for Medicinal Products for Human Use (CHMP) [22]. Data submitted to regulatory agencies are collected based on International Council for Harmonization (ICH) guidelines. The definitions and terminology associated with clinical safety experience are described in ICH Topic E2 A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [23]. Therefore, the data collected from the regulatory sources is standardized which enables a systematic analysis based on protein kinase inhibitor level [24]. Clinical study reports of registration studies are in general confidential, while EPAR data is publicly available. EPARs of PKIs registered from 2010 through 2015 are the main data source to assess the representation and safety evaluation of older patients in registration studies.

2. Methods

2.1. Drug Selection

This study focused on PKIs registered for human use in oncology that were granted marketing authorization in the period from 2010 to 2015 in the European Union (EU). The EPARs of these PKIs were selected from the European Medicines Agency (EMA) Excel table: 'Medicines output European public assessment reports', retrieved from the EMA website on September 1, 2021 [20]. Generic drug authorizations were excluded since limited or no new clinical efficacy and safety data were available nor expected.

Drugs were included by Anatomical Therapeutic Chemical classification system (ATC) code based on the World Health Organization (WHO) classification. The ATC code for PKIs is L01E. However, the classification was updated in October 2019, and changes were not yet fully implemented in the EMA database at the time of the search [25]. Therefore, L01E and L01XE were both included in the search. Drugs that were authorized for a non-oncological indication were excluded. The process of drug selection is shown in Fig. 1.

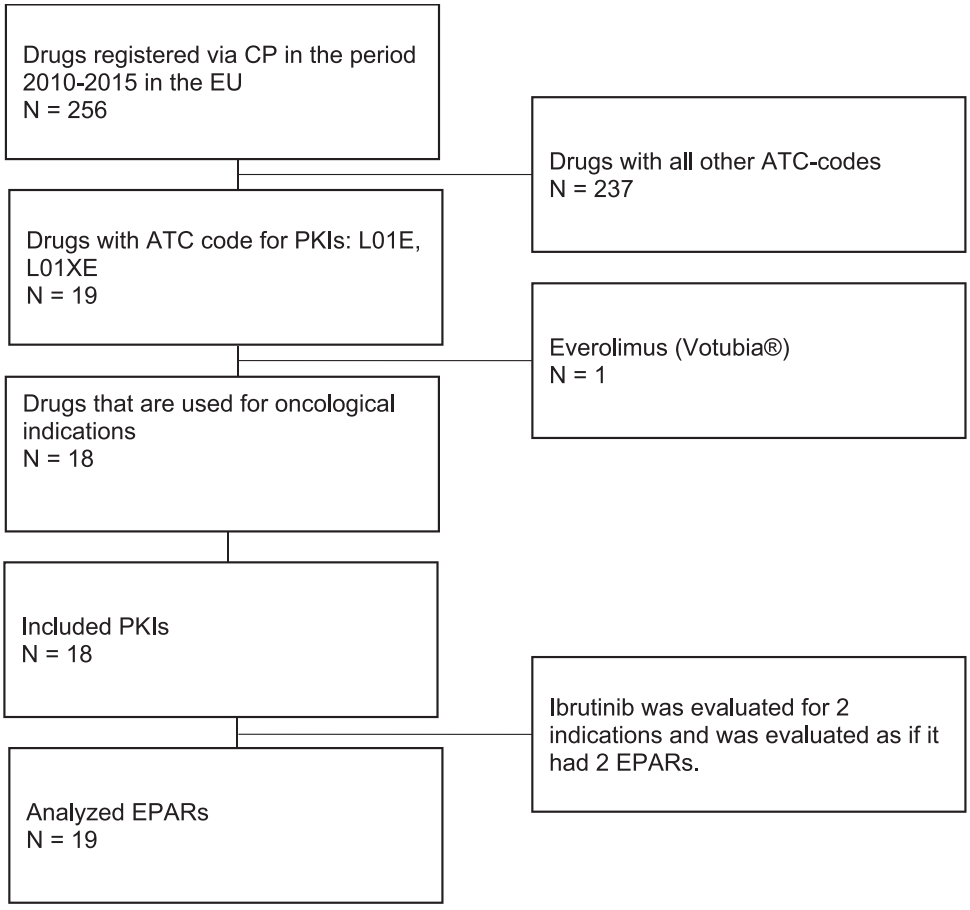

Fig. 1. EPAR selection procedure. There were 256 drugs registered via CP in the EU between 2010 and 2015. Refused and withdrawn drugs, generic drugs, biosimilars and veterinary products were excluded. Of these 256 drugs, 19 drugs met the ATC code L01E and L01XE for PKIs. Votubia® was excluded, because it was initially indicated for subependymal giant cell astrocytoma associated with tuberous sclerosis complex. In total, 18 PKIs were included for evaluation, although ibrutinib was evaluated for 2 indications and it was evaluated as if it had 2 EPARs. Output generated on 1 September 2021 *ATC* Anatomical Therapeutic Chemical classification system, *CP* centralized procedure, *EPAR* European Public Assessment Report, *EU* European Union, *PKIs* Protein kinase inhibitors.

2.2. Data Extraction

The degree of representation of older patients in the safety analysis presented in the EPARs was evaluated by assessing adherence to the ICH E7 guideline [21] and the ICH E7 Questions and Answers, retrieved from the EMA website [26]. Data was collected by manually reviewing the EPARs based on criteria derived from the ICH E7 guideline, formulated as binary questions ('yes' and 'no', where 'yes' was scored as a positive criterion). The criteria that were abstracted per EPAR are presented in Table 1.

Data was collected in a database using the binary questions from Table 1. The total number of older patients in the pivotal study was extracted from the EPAR. The older population was defined as patients aged 65 years or older, in line with the ICH E7 guideline. Criteria 1, 2, and 3 assess the representation of older patients in the study population. A minimum of 100 older patients in the phase 3 database of the registration dossier would allow for detection of clinically important age-related differences. Novel anticancer agents may be initially evaluated in phase I studies, which also provide safety information [27]. Therefore, the number of older patients in the pivotal studies (regardless of phase) or the safety database combining data from multiple studies were considered for this criterion. For assessment of the inclusion and exclusion criteria (criteria 4 and 5), the pivotal studies were used. The whole database should be evaluated for the presence of age-related safety differences, assessed by criterion 6. Assessment of the presence of age-related pharmacokinetic differences are evaluated by criteria 7, 8, 9, and 10. Criterion 11 evaluates the presence of age-related safety differences.

3. Results

3.1. Data Selection

The selection of PKIs is shown in Fig. 1. Ruxolitinib (Jakavi®) is registered for myeloproliferative disorders and polycythemia vera, which fall under myeloproliferative neoplasms (MPN) in the WHO myeloid neoplasm and acute leukemia classification [28]. This indication fell within the inclusion criteria. Eighteen PKIs were included for analysis (see Table A.1). Since the application of ibrutinib was assessed for two indications (mantle cell lymphoma [MCL] and chronic lymphocytic lymphoma [CLL]) in separate pivotal and safety studies, we evaluated this PKI as if there were two EPARs ($n = 19$).

3.2. Older Patients in Pivotal Studies

The number of older and younger subjects included in the pivotal studies is shown in Fig. 2. The median total number of subjects in the pivotal studies was 246, with a range between 111 (ibrutinib MCL) and 655 (nintedanib). The median number of older patients was 77, with a range between 18 (crizotinib) and 200 (nintedanib). The median percentage of older patients was 31%. The percentage of older patients varied from 14% (crizotinib) to 63% (ibrutinib MCL).

For bosutinib, only a last line indication for patients with CML and "unmet medical need" could be discussed for approval. This last line indication was a post-hoc defined subpopulation of patients with a "high medical need" of pivotal study 3160A4–200-WW. The total number of older patients in this study is not provided in the EPAR. The number of patients in this last line indication was 52 patients, of which 21 patients over 65 years of age.

Assessment of ruxolitinib was based on two pivotal studies, one of which was considered the main study (INC424A2352) for purposes of the application in the EU. This number is shown in Fig. 2. The other pivotal study (INCB18424–351) was considered as supportive, as advised by the CHMP. The total number of subjects exposed to ruxolitinib in the pivotal studies was 301, of which 162 subjects over 65 years of age.

Table 1
Assessment based on ICH E7.

Adherence to ICH E7 guideline
1. Is an estimation of the prevalence of the disease to be treated by age present?
2. Are there >100 subjects present in the pivotal study or safety database?
3. Is safety data presented for various age groups (<65, 65–74, 75–84 and ≥ 85)?
4. Do the inclusion and exclusion criteria of the pivotal studies not have arbitrary upper age cutoffs?
5. Are patients not excluded with concomitant illnesses?
6. Is the overall database evaluated for the presence of age-related differences in adverse events?
7. Is the effect of renal impairment evaluated?
8. Is the effect of hepatic impairment evaluated?
9. Is database evaluated for the presence of age-related differences in pharmacokinetics?
Presence of age-related differences within EPAR
10. Do age-related pharmacokinetic differences exist for that PKI?
11. Do age-related safety differences exist for that PKI?

ICH International Council for Harmonization of Technical Requirements for Pharmaceuticals, PKI protein kinase inhibitor.

3.3. Age-Related Differences

An overview of the adherence to the ICH E7 criteria (Table 1) is shown in Fig. 3. In all EPARs, except the one for pazopanib, an evaluation of the effect of age on pharmacokinetics was described (criterion 11). Only the EPAR of axitinib stated that age over 60 had a statistically significant influence on axitinib clearance, which resulted in correspondingly higher axitinib exposure. For the other PKIs, the evaluation of age-related pharmacokinetic differences revealed no effects of age.

An evaluation of age-related safety differences was included in all EPARs (criterion 8). Numerical age-related safety differences were found in 15 out of 19 EPARs (79%). These differences included higher incidence of AEs, AEs of higher grades, or different AEs between age-groups. No numerical differences were found for bosutinib, ceritinib, dabrafenib, and pazopanib. The EPARs of bosutinib and crizotinib both stated that the number of older patients was low; 28 and 21, respectively.

3.4. Adherence to ICH E7 Guideline

An estimation of age distribution of the target population was included in 8 out of 19 EPARs (42%). This varied from stating a median age at diagnosis to a statement about trends in incidence regarding age. More than 100 older patients were included in the pivotal study or safety database in 11 out of 19 EPARs (58%). The number of older patients in the safety database was not reported in 6 out of 19 EPARs (32%), while all EPARs showed the number of older patients in the pivotal study (see Fig. 2). Five out of 19 EPARs (26%) included fewer than 100 subjects in both the pivotal study and safety database. In 10 out of 19 EPARs (53%), safety data was presented for various age groups: as a table with age-stratified safety data, as a discussion, or both.

Although some eligibility criteria for the pivotal trial for bosutinib could be extracted from the EPAR text, it could not be determined whether patients were excluded by age or comorbidities. Assessment of ruxolitinib was based on two pivotal studies, one of which was the main study (INC424A2352) for the purposes of the application in the EU and the other one was considered supportive (INCB18424–351). The main pivotal study is presented in Fig. 3. Except for the supportive study INCB18424–351 of ruxolitinib, no upper age cutoffs were stated. On the other hand, all pivotal studies for which the eligibility criteria were explicitly provided excluded subjects with comorbidities. The most frequent reasons for exclusion were clinically significant cardiovascular disease or impaired organ function.

The effect of renal and hepatic impairment was evaluated in 17 and 15 out of 19 EPARs (89% and 79%), respectively. In the EPARs of

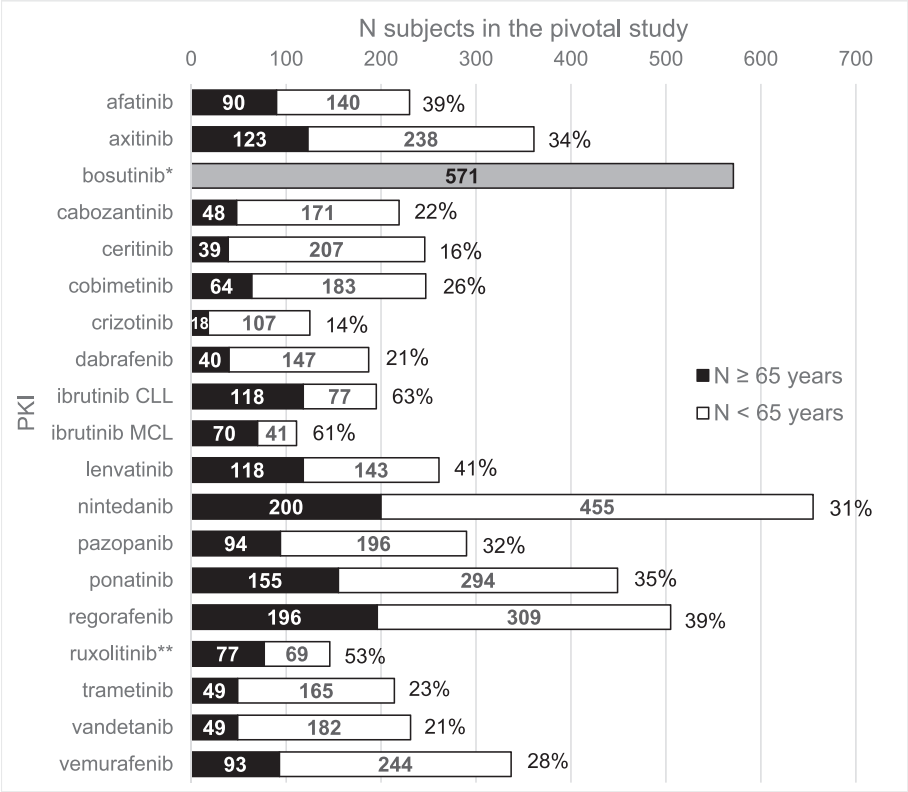

Fig. 2. Number of older adults and younger subjects in the pivotal study. The older adults (black) and younger (white) subjects in the pivotal study and percentage elderly subjects are shown. *CLL*, Chronic Lymphocytic Leukemia, *MCL*, Mantle Cell Lymphoma. *Approval of bosutinib is based on a post-hoc defined subpopulation of patients with a high medical need from this population. **The EPAR of ruxolitinib describes two pivotal studies. The number of subjects in the main pivotal study is shown.

bosutinib and cabozantinib, the effect of renal impairment was not evaluated; only phase I data was available for bosutinib and the effect of renal impairment on cabozantinib pharmacokinetics and safety had not been studied. The effect of hepatic impairment was not evaluated for cabozantinib, cobimetinib, crizotinib, and ponatinib. The EPAR of cobimetinib stated that no data were available. The EPAR of ponatinib stated that the effect of hepatic impairment on safety was not evaluated, due to paucity of data.

4. Discussion

4.1. Age-Related Differences

The primary aim of the study was to evaluate whether age-related safety differences were evaluated and present for PKIs. In all EPARs, an evaluation of presence of age-related safety differences was included. Age-related safety differences are described in the EPARs of most PKIs, even in the highly selected study population. These age-related differences include more AEs, AEs of higher grades, or a different safety profile compared to younger patients. Other studies have shown similar frequencies of PKI-related AEs between older and younger subjects, although there may be an increase in specific AEs in older patients [29,30]. The toxicities may also have greater impact on the quality of life in older patients compared to younger patients [31,32], which subsequently can influence the efficacy and tolerability of treatment. Confirmation by larger observational or prospective studies is needed [29,30]. Due to different disease setting and different targets of the kinase inhibitors, pooling of available safety data for the different PKIs is not considered adequate to analyze the age dependent safety results. It was therefore not our intention to perform a pooled analysis of specific types of adverse events across studies.

The ICH E7 guideline states that pharmacokinetics should be evaluated, since older patients are known to have altered pharmacokinetic properties and a reduced homeostatic capacity [7,10]. The effect of age on pharmacokinetics has been discussed in all EPARs, except for the EPAR of pazopanib. However, only for axitinib age-related pharmacokinetic differences were described. In the other EPARs it is stated that age did not have a significant effect on pharmacokinetics. Most PKIs are metabolized by cytochrome *P450* (CYP) enzymes and predominantly excreted with feces. A minor fraction is eliminated with urine [33]. Hepatic clearance may be slightly decreased in older patients [11,34,35], since aging is associated with decreased liver mass and reduced hepatic blood flow. However, unlike for renally cleared drugs, slightly reduced hepatic capacity usually does not lead to a clinically relevant increase in exposure and the need for dose reductions. Aging is associated with decreased liver mass and reduced hepatic blood flow. Unlike for renally cleared drugs, reduced metabolic clearance in older patients is usually not a limiting factor.

The older patients in the heavily selected study population, due to inclusion criteria, are possibly the fitter and younger older patients, who may not differ substantially from younger patients. The real-world older patient population, on the other hand, may be older, less fit, and may have altered pharmacokinetics and pharmacodynamics that make them more prone to develop AEs [7,10,11]. Exposure-safety analysis in older versus younger subjects should be evaluated in order to determine whether pharmacokinetic imparities might explain age-related safety differences. A real-world study comparing exposure of seven protein kinase inhibitors found comparable exposures between older and younger patients, except for dabrafenib [36]. A general trend towards increased drug sensitivity in older patients, similar to anesthetics,

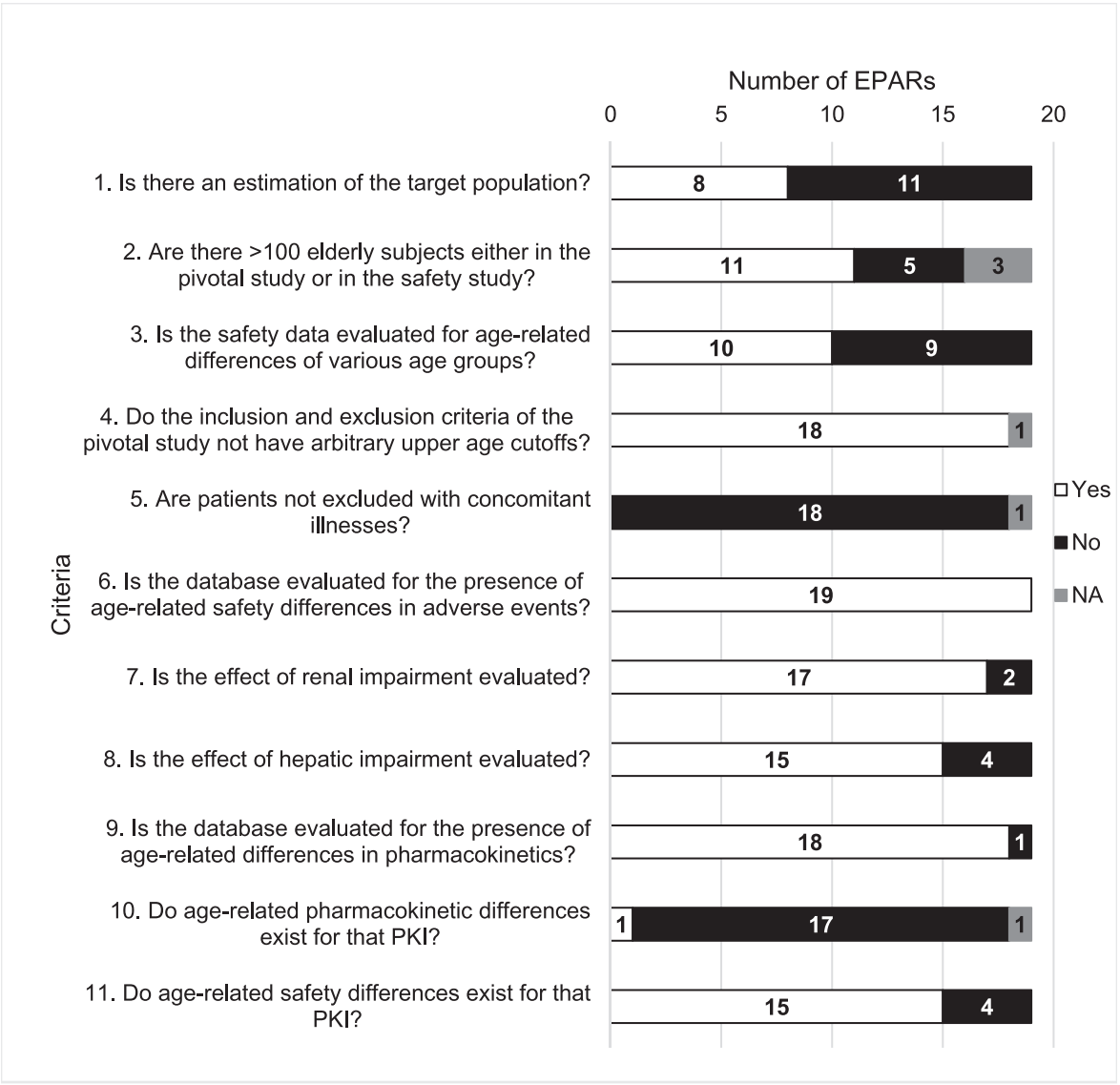

Fig. 3. Adherence to ICH E7 criteria from Table 1. The bars show the number of EPARs that adhere, do not adhere, and adherence that could not be determined from the EPAR, to the criteria from Table 1. The EPAR of ibrutinib was considered as two separate EPARs ($n = 19$). *EPAR* European Public Assessment Report, *ICH* International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, *NA* not available.

anticoagulants, cardiovascular, and respiratory drugs [10] might also apply to PKIs, which could result in a different safety profile at similar exposure.

Evaluation of age-related safety and pharmacokinetic differences is expected in EPARs, since this is included in the EMA template for assessment of the registration dossier. The number of older patients in pharmacokinetic, controlled, and uncontrolled clinical studies should be filled out as well as a table with AEs stratified by age [37]. Seven out of 19 (37%) EPARs included a table with age-stratified AEs. Only 3 out of 19 (16%) EPARs included a table in which AEs of patients <65 and ≥ 65 years were compared.

4.2. Adherence to ICH E7 Guideline

For PKIs registered between 2010 and 2015, representation of older patients in the (pivotal) studies was highly variable. None of the PKIs meet every criterion (see Table B.1). The study population should be reasonably representative of the target population, and criteria 3, 4, and 5 from Table 1 should be considered to estimate the representation of older patients [26]. First, the majority of the EPARs do not include descriptions of the demographics of the real-world older target population for the intended indication. Secondly, and perhaps the most objective criterion, there should be at least 100 older patients included in the phase II and III database [21]. The number of older patients in the phase II and III database could not be extracted from the EPAR, therefore the number of patients in the pivotal study or in the safety database were considered. In most EPARs >100 subjects were included in the pivotal study or safety database, but only 7 out of 19 pivotal studies included >100 older patients. The arbitrary cutoff at 100 subjects may not be realistic for every drug included. For example, the number of 100 older patients may not be necessary for drugs used in a younger population, such as cabozantinib and vandetanib used in thyroid cancer. Crizotinib and ceritinib are used in patients with anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC). These patients tend to be younger than the general population with lung cancer, as shown by real-world experience studies [2,38].

Third, in only about half of the EPARs data is presented for various age groups. None of the PKIs comply with all three criteria (see Table B.1), indicating that the older population is not well represented in the EPARs.

Underrepresentation of older patients in clinical studies is a widely known problem [4,6,14,39]. The median percentage of older patients in the pivotal study across all PKIs included in this study was 32% (see Fig. 2), while more than half of new cancer diagnoses are in older patients [2,25]. A US Food and Drug Administration (FDA) study that analyzed demographic data of 224,766 patients with cancer enrolled onto trials supporting registration from 2005 to 2015 found that only 24% of patients enrolled in trials for oncological drugs were 70 years or older, while this population makes up 42% of the target population. The rates of enrollment were compared to corresponding incidence rates in the US cancer population [4].

Underrepresentation of older patients can be due to the inclusion and exclusion criteria for the pivotal studies. While only one pivotal study excluded patients by age, every pivotal study excluded patients by comorbidities. The ICH E7 guideline states that patients should not 'unnecessarily' be excluded by comorbidities, which leaves room for interpretation. The comorbidities by which patients are excluded are most often significant cardiovascular disease or impaired organ function. Since these comorbidities are most common among older adults, these entry criteria lead to inclusion of younger patients [12]. Preferential inclusion of younger patients causes study populations to be less representative of the real-world cancer population. Patients that are excluded in clinical studies may well be treated with that PKI in clinical practice after authorization, unless it is a contraindication mentioned in the summary of product characteristics.

4.3. Future Perspectives

Active pharmacovigilance programs may detect unknown adverse drug reactions in a real-world setting that do not always correspond to the known adverse drug reactions described in the summary of product characteristics [40]. This study only includes EPARs, therefore only data from clinical trials are described. Although spontaneous reporting elucidates AEs in the real world, AEs are not systematically collected. In addition, the more serious adverse drug reactions are more likely to be reported compared to non-serious adverse drug reactions [41,42].

The current ICH E7 guideline considers patients aged 65 years or older to be older adults, which may not be as appropriate anymore for the current clinical setting. People have been living longer and longer disease-free since the adaptation of the guideline in 1993 [43,44]. Physicians particularly need information on the age group 75 years and older, because pharmacokinetic and pharmacodynamic differences become clinically relevant in this age group [13]. The FDA recently updated its guideline on inclusion of older adults in cancer clinical trials [45]. This update emphasizes inclusion of older patients in earlier phases of development and inclusion of adults 75 years of age and older. Recommendations on increasing older adults in existing trials have been described elsewhere [46].

4.4. Research Limitations

EPARs are the only data source for this study, therefore no original study reports or data from scientific publications are included. For example, the full inclusion and exclusion criteria of the pivotal study of bosutinib were not included in the EPAR. It could not be determined whether there was an upper-age cutoff, while this information is available in original study reports and on ClinicalTrials.gov [47]. There is a selection bias in drafting the EPAR, because the level of description of safety data per age group is dependent on the assessor. Pooled analysis on an adverse event-specific level is not possible [48].

Another limitation of this study is that all adverse events are equally valued for older and younger patients in the EPAR. Older patients may experience practical problems that should be considered [13]. Persistent AEs of a lower grade may have a greater impact on the quality of life for older patients compared to younger patients, for example diarrhea in combination with slow walking speed. In addition, some AEs, such as falls, may be more hazardous for older patients [47].

Assessing adherence to the ICH E7 guideline is subjective. Identifying and valuing the EPARs is sensitive to interpretation bias. Additionally, the criteria were equally valued, while there are some criteria that are undisputable, such as the presence of evaluation of age-related safety differences.

5. Conclusion

For the majority of the 18 PKIs registered by the EMA in the period 2010–2015, age-related safety differences exist. Pharmacokinetic differences between older and younger patients were present only for axitinib, while this was not the case for the other PKIs. The proportion of older patients in the pivotal studies indicates that this population is underrepresented. About half of the studies in the EPARs did not include sufficient number of older patients to detect clinically important differences. Eligibility criteria of the pivotal studies negatively influenced enrollment of the real-world older population, resulting in a fit study population. Adherence to the ICH E7 guideline differs substantially: none of the PKIs meet all criteria. Adequate representation of older patients in clinical trials for PKIs is vital, since they make up the majority of the cancer population.

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Author Contributions

Emma van Kampen: Data Collection; Analysis and Interpretation of Data, Manuscript Writing.

Mark T.J. van Bussel: Conception and Design, Analysis and Interpretation of Data, Approval of Final Article.

Thijs H. Oude Munnink: Conception and Design, Analysis and Interpretation of Data, Approval of Final Article.

Daan J. Touw: Conception and Design, Analysis and Interpretation of Data, Approval of Final Article.

K. Esther Broekman: Conception and Design, Analysis and Interpretation of Data, Approval of Final Article.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2023.101636.

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