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ORIGINAL ARTICLE

Reported hepatotoxicity and hepatotoxicity guidance in the product information of protein kinase inhibitors in oncology registered at the European Medicines Agency

Marc Maliepaard[1,2] | Yoran S. Faber[1] | Mark T. J. van Bussel[1]

[1]Dutch Medicines Evaluation Board (CBG-MEB), College ter Beoordeling van Geneesmiddelen, Utrecht, The Netherlands

[2]Department of Pharmacology and Toxicology, Radboud University Medical Centre, Nijmegen, The Netherlands

Correspondence
Mark T. J. van Bussel, Dutch Medicines Evaluation Board (CBG-MEB), Graadt van Roggenweg 500, 3531 AH Utrecht, The Netherlands.
Email: m.v.bussel@cbg-meb.nl

Abstract

Protein kinase inhibitors (PKIs) used in oncology can induce severe and even fatal hepatotoxicity. Several PKIs are registered within a certain class to target a specific kinase. No systematic comparison of the reported hepatotoxicity and clinical guidance for monitoring and management of hepatotoxic events between the various PKI summaries of product characteristics (SmPC) is yet available. A systematic analysis of data on 21 hepatotoxicity parameters obtained from the SmPCs and European public assessment reports (EPARs) of European Medicines Agency-approved antineoplastic PKIs ($n = 55$) has been conducted. The median reported incidence (range) of all grades of aspartate aminotransferase (AST) elevations was 16.9% (2.0%–86.4%) for PKI monotherapy, with 2.1% (0.0%–10.3%) being grade 3/4 and for all grades alanine aminotransferase (ALT) elevations 17.6% (2.0%–85.5%), with 3.0% (0.0%–25.0%) being grade 3/4. Fatalities due to hepatotoxicity were reported for 22 out of 47 PKIs (monotherapy) and for 5 out of 8 PKIs (combination therapy). A maximum grade of grade 4 and grade 3 hepatotoxicity was reported for 45% ($n = 25$) and 6% ($n = 3$), respectively. Liver parameter monitoring recommendations were present in 47 of the 55 SmPCs. Dose reductions were recommended for 18 PKIs. Discontinuation was recommended for patients meeting Hy's law criteria (16 out of 55 SmPCs). Severe hepatotoxic events are reported in approximately 50% of the analyzed SmPCs and EPARs. Differences in the degree of hepatotoxicity are apparent. Although liver parameter monitoring recommendations are present in the vast majority of the analyzed PKI SmPCs, the clinical guidance for hepatotoxicity was not standardized.

KEYWORDS
European public assessment report, hepatotoxicity, oncology, protein kinase inhibitors, summary of product characteristics

Abbreviations: ADRs, adverse drug reactions; ALT, alanine aminotransferase; ATC, anatomical therapeutic chemical; AST, aspartate aminotransferase; BCR-ABL, breakpoint cluster region gene-Abelson proto-oncogene; EGFR, epithelial growth factor receptor; EMA, European Medicines Agency; EPARs, European public assessment reports; FDA, Food and Drug Administration; ICH, International Council for Harmonisation; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PKIs, protein kinase inhibitors; SmPC, summary of product characteristics; ULN, upper limit of normal; WHO, World Health Organization.

1 | INTRODUCTION

Protein kinase inhibitors (PKIs) are frequently used in oncology as targeted agents. Targeted agents like PKIs are developed to address an unmet medical need in oncology. The first PKI approved by the European Medicines Agency (EMA) in 2001 was imatinib, targeting the breakpoint cluster region gene-Abelson proto-oncogene (BCR-ABL) protein.[1] Nowadays over 50 PKIs are registered in oncology.[1] Currently, several different PKIs are often registered within a certain class to target a specific kinase. For instance, the epithelial growth factor receptor (EGFR) inhibitors afatinib, erlotinib, dacomitinib, gefitinib, and osimertinib are registered for EGFR-mutated non-small lung cancer. A network meta-analysis on hepatotoxicity with EGFR inhibitors in non–small-cell lung cancer patients indicated that there is some evidence suggesting that gefitinib and erlotinib may be associated with an increased risk of hepatotoxicity.[2] In general, PKIs prevent downstream signaling triggered by growth factors by inhibition of specific oncogenic kinases or by inhibiting specific receptor tyrosine kinases or several receptor-associated kinases. This may ultimately lead to reduced growth of a tumor.

Next to efficacy, safety issues have been reported for PKIs, of which hepatoxicity is of major concern.[3] Around two-thirds of the marketed PKIs had a warning for liver injury in their drug label.[4] Mechanisms of PKI-induced hepatotoxicity may involve the formation of a reactive intermediate due to the metabolism of the PKI via the cytochromes P450 pathway, along with an immune-mediated injury, disruption of hepatic bile acid transport, and mitochondrial malfunction.[4,5] Clinical guidance for monitoring and management of hepatotoxic events per PKI varies between drug labels.[3] A recent review provides dose recommendations for anticancer drugs in patients with renal or hepatic impairment based on EMA, Food and Drug Administration (FDA), or literature data.[6] For some PKIs discontinuation or dose modifications can be required in case of hepatoxicity, whereas for others no dose modification is indicated. Unfortunately, treatment with PKIs can induce severe and even fatal hepatotoxicity.[3,4] A recent systematic comparison of hepatobiliary adverse drug reactions in FDA and EMA drug labeling revealed discrepancies. However, most discrepancies were attributable to less severe hepatic events and low-frequency hepatic adverse drug reactions (ADRs) and had limited implications on clinical outcomes.[7] To the best of our knowledge, an actual and detailed overview of the hepatotoxicity and clinical guidance in case of hepatoxicity, in the summary of product characteristics (SmPC) of PKIs approved by the EMA, has not yet been published. Therefore, a systematic analysis of hepatotoxicity data based on the SmPCs and European public assessment reports (EPARs) of EMA-approved antineoplastic PKIs have been conducted. The SmPC was chosen as the primary data source as SmPCs are a key part of the marketing authorization of all medicines authorized in the European Union and the basis of information for healthcare professionals on how to use a medicine safely and effectively. 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.[8] In addition, for anticancer agents, the standard grading system for AEs is the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) toxicity criteria.[9] Therefore, the data collected from the regulatory sources are standardized, which enables a systematic analysis. This paper aims to provide insight into the hepatotoxicity profile of all approved antineoplastic PKIs until September 2021. Furthermore, the clinical guidance of monitoring and management of hepatotoxicity according to the SmPCs is systematically analyzed.

2 | METHODS

2.1 | Selection of protein kinase inhibitors

PKIs were selected based on anatomical therapeutic chemical (ATC) codes from the EMA database.[1,10] The World Health Organization (WHO) updated ATC codes for PKIs were also taken into account.[11] PKIs registered for an antineoplastic indication by EMA until September 2021 were included. Generic and biosimilar products were excluded. An overview of the PKI selection criteria is presented in Table S1. The selection process of the PKIs from the EMA Excel database is shown in Figure S1. An overview of the selected PKIs including their protein kinase targets and therapeutic indications is shown in Table S2.

2.2 | Data collection of hepatic parameters

The SmPC of the selected PKIs was systematically screened for data on 21 hepatotoxicity parameters (Table 1). The SmPCs and EPARS were collected from the EMA webpage of the specific PKIs. The URL to the different PKI EMA pages was found in the Excel database in column AD "URL".[1] The SmPCs and EPARs were extracted in the period between September 7 and October 18, 2021. If the numeric data for these parameters was not present in the SmPC the initial EPAR was analyzed. A schematic overview of the data collection process is shown in Figure S2. The hepatotoxicity parameters were selected based on the articles of Hoofnagle et al. and Shah et al.[3,12] Hepatotoxicity is a preferred term name in the medical dictionary for regulatory activities in the system organ class hepatobiliary disorders. The CTCAE criteria for aspartate aminotransferase (AST)/alanine aminotransferase (ALT) increase contain a cross-reference to hepatobiliary disorders: hepatic failure. Hepatic failure is defined as a disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, alkaline phosphatase, aminotransferase, and/or prolongation of prothrombin time. Hy's law criteria are defined as ALT or AST $>3\times$ upper limit of normal (ULN) and bilirubin $>2\times$ ULN AST, ALT, and transaminase elevations were collected separately if available, as AST and ALT data provide more specific information on the degree of hepatotoxicity than the combined transaminases.[13]

TABLE 1 Schematic representation of used parameters.

	Hepatic parameter
1	Incidence hepatotoxicity
2	Prevalence hepatotoxicity
3	AST elevations
4	ALT elevations
5	GGT elevations
6	Bilirubin elevations
7	Elevated transaminases
8	Maximum severity hepatotoxicity
9	Latency to onset hepatotoxicity
10	Time to recovery after hepatotoxicity
11	Other forms of drug-induced liver damage
12	Liver function test abnormalities
13	Monitoring schedule liver parameters
14	Cases of hepatic failure
15	Fatalities due to hepatotoxicity
16	Dose modifications and alterations due to hepatotoxicity
17	Primary route of elimination
18	Patients with hepatic impairment
19	Use in patients with severe hepatic impairment
20	Liver metastases
21	Combinational therapy leading to hepatotoxicity

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

2.3 | Clinical guidance

The posology section (4.2), the special warnings and precautions for use section (4.4), the undesirable effects section (4.8), and the pharmacokinetic properties section (5.2) of the SmPCs were systematically screened and analyzed for information on hepatoxicity and treatment guidance for the selected PKIs.

2.4 | Collecting monotherapy data

If PKI monotherapy data were available, the safety population data in which patients received monotherapy as presented in the EPAR were analyzed for the hepatotoxicity data missing in the SmPC. If available, the safety data for patients receiving monotherapy and the registered dose as given in section 4.2 of the SmPC was used. When such safety population data were not sufficient or present, data from pivotal phase III studies as reported in the EPAR were analyzed. Phase II studies were only used when pivotal phase III studies were not present or lacked the needed data.

2.5 | Collecting combination therapy data

PKI combination therapy data were used when an analyzed PKI was registered as combination therapy and safety population data with monotherapy were not available.

3 | RESULTS

3.1 | Hepatotoxicity parameters monotherapy ($n = 47$)

The incidence of AST and ALT elevations in PKI monotherapy is shown in Table 2. The median incidence (range) of all grades AST elevations was 16.9% (2.0–86.4). The median incidence (range) of grade 3/4 AST elevations was 2.1% (0.0–10.3). The median incidence (range) of all grades ALT elevations was 17.6% (2.0–85.5). The median incidence (range) of ALT grade 3/4 elevations was 3.0% (0.0%–25.0%). The data on GGT elevations, bilirubin elevations, and elevated transaminases are shown in Table S3. The median (range) of all grades of incidences were 4.0% (0.4–62), 7.7% (0.0–84), and 6.5% (0.4–48.8), respectively.

3.2 | Latency to onset/time to recovery monotherapy data

The median latency to onset of hepatotoxicity was 7.5 (4.0–52.0) weeks after PKI dosing and was reported for eight out of 47 PKIs. Six out of the 47 PKIs mentioned a time to recover after some form of hepatotoxicity. The median time to recovery was 1.8 (1.5–10) weeks.

3.3 | Fatal cases due to hepatotoxicity monotherapy

Fatalities due to hepatotoxicity have been reported in the SmPC or the EPAR of 22 out of 47 PKIs (Table 2). These cases were rare and most often reported due to hepatitis reactivation.

3.4 | Hepatotoxicity parameters protein kinase inhibitor combination therapy ($n = 8$)

The incidence of all grades of AST elevations for combination therapy PKIs is shown in Table 3. The median (range) AST incidence elevation was 22.8% (4.8–71). The median incidence (range) of grade 3/4 elevations was 4.6% (2.8–7.0). The median ALT incidence (range) elevation was 41.4% (9.7–67). The median (range) ALT grade 3/4 elevation was 6.1% (2.5–11.0).

TABLE 2 Overview of hepatotoxicity parameters in analyzed PKIs monotherapy. Total number of PKIs monotherapy $N = 47$.

PKI	Incidence of AST elevations (%)		Incidence of ALT elevations (%)		Latency to onset of hepatotoxicity (weeks)	Time to recovery (weeks)	Cases of hepatitis or hepatic failure	Fatal cases due to hepatotoxicity
	All grades	Grade 3–4	All grades	Grade 3–4				
Acalabrutinib	–	–	2.0[a]	–	–	–	Yes	–
Afatinib	8.3[a]	–	11.3	0.0	–	–	Yes	Yes
Alectinib	17.0	3.7	16.0	3.7	12.0	–	Yes[a]	–
Avapritinib	10.9[a]	0.5[a]	–	0.5[a]	–	–	Yes[a]	Yes[a]
Axitinib	6.1	1.0[a]	6.5	1.2[a]	–	–	–	Yes[a,c]
Binimetinib	13.8[a]	2.1[a]	9.6[a]	2.3[a]	–	–	Yes[a]	–
Bosutinib	22.3	6.7	27.7	14.4	4.0	2.0	Yes	Yes[d]
Brigatinib	68.0	3.6	49.0	4.7	–	–	–	–
Cabozantinib (Cabometyx®)	–	3.3	–	3.6	5.9[f]	–	Yes	Yes[e]
Cabozantinib (Cometriq®)	86.4[a]	3.3[a]	85.5[a]	6.1[a]	–	–	Yes[a]	Yes[a]
Ceritinib	29.1[a]	6.9[a]	–	25.0	–	–	–	No[a]
Crizotinib	–	6.0	–	11.0	6.0	–	Yes	Yes
Dabrafenib	8.0[a]	0.5[a,b]	11.0[a]	1.0[a,b]	–	–	–	–
Dacomitinib	34.5[a]	0.5[a]	39.5[a]	1.4[a]	12.0	1.0	Yes	Yes
Dasatinib	–	–	–	–	–	–	Yes	Yes[d]
Duvelisib	9.2[a]	–	9.2[a]	–	8.0	4.0	Yes[a]	–
Encorafenib	12.6[a]	0.5[a,b]	16.4[a]	1.4[a,b]	–	–	Yes[b,g]	–
Entrectinib	17.5	3.6	16.1	3.4	–	–	–	–
Erlotinib	5.0[a]	0.0[a]	83.0[a]	0.0[a]	–	–	Yes	Yes
Everolimus	–	–	–	–	–	–	–	–
Fedratinib	59.0	2.0	52.0	3.0	4.0	–	Yes	–
Gefitinib	7.9[a]	–	10.1[a]	–	–	–	Yes	Yes
Gilteritinib	80.6	10.3	82.1	12.9	–	–	–	–
Ibrutinib	5.6[a]	0.0[a]	11.8[a]	0.0[a]	–	–	Yes	Yes
Idelalisib	16.8[a]	8.0[a]	17.6[a]	11.4[a]	12.0	–	Yes	–
Imatinib	–	4.8	–	6.8	20.1[a]	1.0	Yes	Yes
Lapatinib	2.0[a]	0.3[a]	2.2[a]	0.3[a]	7.0[a]	–	–	Yes
Larotrectinib	26.5	1.5	32.0	3.0	6.0	10.0	–	–
Lenvatinib (Lenvima®)	13.7	–	11.1	–	6.4	–	Yes	Yes

TABLE 2 (Continued)

PKI	Incidence of AST elevations (%)		Incidence of ALT elevations (%)		Latency to onset of hepatotoxicity (weeks)	Time to recovery (weeks)	Cases of hepatitis or hepatic failure	Fatal cases due to hepatotoxicity
	All grades	Grade 3–4	All grades	Grade 3–4				
Lorlatinib	48.6[a]	2.1[a]	38.7[a]	2.1[a]	–	–	–	–
Midostaurin	33.8	2.8	33.1	3.5	–	–	–	–
Neratinib	7.4	0.7	8.5	1.3	–	–	–	–
Nilotinib	12.0	1.0	24.0	4.0	–	–	Yes	Yes[d]
Osimertinib	6.3[a]	0.2[a,b]	6.6[a]	1.2[a,b]	–	–	–	–
Pazopanib	18.0	4.9	21.0	8.0	–	–	Yes	Yes
Pemigatinib	42.5[a]	6.2[a,b]	43.2[a]	4.1[a,b]	–	–	–	–
Ponatinib	–	4.0	–	6.0	52.0	–	Yes	Yes[d]
Regorafenib	65.0	5.9	45.2	5.5	8.0	–	Yes	Yes
Ruxolitinib	31.5	0.0	40.7	0.0[h]	–	–	Yes	–
Selpercatinib	55.0	9.0	49.5	10.6	4.1	–	–	–
Sorafenib	53.6	2.0	58.9	4.4	–	–	Yes	Yes[d]
Sunitinib	–	–	–	–	–	–	Yes	Yes
Temsirolimus	8.4	1.6	5.3	0.6	–	–	–	–
Tivozanib	–	1.9[a]	–	0.8[a]	–	–	–	–
Trametinib	63.0[a]	4.0[a]	36.0[a]	3.0[a]	24.0	–	Yes[a]	Yes[a]
Vandetanib	4.3[a]	–	3.9[a]	1.7[a]	12.0[a]	1.5	–	–
Vemurafenib	4.0[a]	0.6[a,b]	5.0[a]	0.9[a,b]	6.5[a]	–	–	–

[a]Not sufficient data in SmPC, data extracted from EPAR.
[b]Only grade 3 no grade 4.
[c]Due to hepatorenal syndrome.
[d]Due to hepatitis B reactivation.
[e]Due to hepatic encephalopathy.
[f]Latency to onset hepatic encephalopathy.
[g]Present for combination therapy with binimetinib.
[h]Unknown for grade 3 elevations, no grade 4 elevations.

TABLE 3 Overview of hepatotoxicity in PKIs (combination) therapy. Total number of PKIs combination therapy $N = 8$.

PKI	Incidence of AST elevations (%)		Incidence of ALT elevations (%)		Latency to onset of hepatotoxicity (weeks)	Time to recovery (weeks)	Cases of hepatitis or hepatic failure?	Fatal cases due to hepatotoxicity
	All grades	Grade 3–4	All grades	Grade 3–4				
Abemaciclib + endocrine therapy	14.2	4.2	15.1	6.1	8.5	2.0	Yes[a]	Yes[a]
Alpelisib + fulvestrant	10.9[a]	2.8[a]	44.0	4.2[b]	–	–	–	–
Cobimetinib + vemurafenib	71.0	7.0	67.0	11.0	–	–	–	–
Lenvatinib (Kisplyx®) + everolimus	4.8	–	9.7	–	12.1	–	Yes	Yes
Nintedanib + docetaxel	31.3[a]	–	38.8[a]	–	2.0[a]	2.0[a]	Yes[a]	Yes
Palbociclib + letrozole or fulvestrant	55.5	3.9[b]	46.1	2.5	–	–	Yes[a]	Yes[a]
Ribociclib + endocrine therapy	–	6.7	–	9.7	12.1	3.1	Yes[a]	Yes[a]
Tucatinib + trastuzumab and capecitabine	–	5.0	–	6.0	5.2	3.0	–	–

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a]Not sufficient data in SmPC, data extracted from EPAR.

[b]Only grade 3 no grade 4.

3.5 | Latency to onset/time to recovery combination therapy data

The median latency to onset was 8.5 weeks (2.0–12.1). The median time to recovery was 2.5 weeks (2.0–3.0).

3.6 | Fatal cases of hepatotoxicity combination therapy

Fatalities due to hepatotoxicity were reported in five out of the eight PKIs with combination therapy data (Table 3). Cases of hepatitis or hepatic failure were also reported in the SmPC or EPAR of these PKIs.

3.7 | Incidence and severity of hepatotoxicity

Fatal cases of hepatotoxicity were reported in 49% ($n = 27$ out of 55) of the reviewed PKI SmPCs and EPARs. Grade 4 hepatotoxicity as a maximum grade has been reported in 45% ($n = 25$) of the analyzed PKI SmPCs and EPARs. Grade 3 hepatotoxicity as a maximum grade has been reported in 6% ($n = 3$) of the analyzed PKI SmPCs and EPARs.

3.8 | Hepatitis B reactivation

Cases of hepatitis or hepatic failure were reported for 60% ($n = 28$ out of 47) of monotherapy PKIs (Table 2) and for 63% (5 out of 8) of the combination therapy PKIs (Table 3). Five PKIs with BCR-ABL as the main target (i.e., imatinib, bosutinib, dasatinib, nilotinib, and ponatinib) contain a general warning of hepatitis B reactivation due to PKI use in the SmPC.

3.8.1 | SmPC liver parameter monitoring recommendations

All PKIs were mainly eliminated through hepatic metabolism. Liver parameter monitoring recommendations were present in 47 of the 55 SmPCs. Twenty-seven out of 55 analyzed SmPCs recommend a liver parameter test before the initiation of treatment. Twenty-six out of 55 analyzed SmPCs recommend liver parameters monitoring as clinically indicated in patients. The actual clinical guidance in the product information can be accessed via the EMA website.[14]

3.8.2 | SmPC treatment recommendations in case of severe hepatic impairment

No dose adjustment or precautions were needed in case of severe hepatic impairment for 3 PKIs (alpelisib, cobimetinib, and duvelisib). Use

TABLE 4 Treatment recommendations per CTC grade in analyzed SmPCs when hepatotoxicity occurs. Total number of PKIs $N = 55$.

PKI	Grade 1	Grade 2	Grade 3	Grade 4
Abemaciclib	No dose adjustment.	No dose adjustment. Persistent or recurrent, suspend dose until toxicity resolves to baseline or grade 1. Resume at next lower dose.	Suspend dose until baseline or grade 1. Resume at next lower dose.	Discontinue treatment. Elevation in AST and/or ALT > 3 × ULN WITH total bilirubin >2 × ULN, in the absence of cholestasis (*Hy's law*), discontinue.
Acalabrutinib[a]	–	–	First and second Interrupt. once resolved to grade 1 or baseline. resume at lower dose. Third Interrupt. Once resolved to grade 1 or baseline, resume at a reduced frequency. Fourth Discontinue.	First and second interrupt. Once resolved to grade 1 or baseline, resume at lower dose. Third interrupt. Once resolved to grade 1 or baseline, resume at a reduced frequency. Fourth, discontinue.
Afatinib	No dose adjustment.	No dose adjustment. Prolonged or intolerable, interrupt until grade ≤1. Resume with dose reduction by 10 mg decrements.	Interrupt until grade ≤1. Resume with dose reduction by 10 mg decrements.	Discontinue treatment.
Alectinib	–	–	Withhold until baseline or grade ≤1. Resume at a reduced dose.	Withhold until baseline or grade ≤1, resume at a reduced dose. ALT or AST elevation of grade = 2 (>3 times ULN) with total bilirubin elevation >2 times ULN in the absence of cholestasis or hemolysis (*Hy's law*), permanently discontinue.
Alpelisib[a]	No dose adjustment. Initiate appropriate medical therapy and monitor as clinically indicated.	No dose adjustment. Initiate appropriate medical therapy and monitor as clinically indicated. For grade 2 total bilirubin elevation, interrupt Piqray dose until recovery to grade ≤1 and resume at the same dose if resolved in ≤14 days or resume at the next lower dose level if resolved in >14 days.	Grade 3 Interrupt until improvement to grade ≤1, then resume at the next lower dose level.	Permanently discontinue.
Avapritinib[a]	–	–	Interrupt until ≤ grade 2. Resume at the same dose or at a reduced dose, if warranted.	Interrupt until ≤ grade 2. Resume at the same dose or at a reduced dose, if warranted.
Axitinib	Dose increase or reduction is recommended based on individual safety and tolerability.	Dose increase or reduction is recommended based on individual safety and tolerability.	Dose increase or reduction is recommended based on individual safety and tolerability.	Dose increase or reduction is recommended based on individual safety and tolerability.
Binimetinib	–	No dose adjustment. If no improvement within 2 weeks, withheld until improved to grade ≤1 or baseline, than resume at the same dose	First occurrence withheld for up to 4 weeks. If improved to grade ≤1 or baseline, resume at reduced dose. If not improved, permanently discontinue. Recurrent, consider permanently discontinuing.	First occurrence withheld for up to 4 weeks. If improved to grade ≤1 or baseline level, resume at a reduced dose level. If not improved, permanently discontinue. Recurrent, permanently discontinue. AST or ALT > 5× ULN and blood bilirubin >2× ULN (*Hy's law*), consider permanent discontinuation.

TABLE 4 (Continued)

PKI	Grade 1	Grade 2	Grade 3	Grade 4
Bosutinib	–	–	Interrupt until grade ≤1 resume at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, consider discontinuation.	Interrupt until grade ≤1 resume at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, consider discontinuation. If transaminase elevations = 3 × ULN occur concurrently with bilirubin elevations >2 × ULN and alkaline phosphatase <2 × ULN (*Hy's law*), discontinue.
Brigatinib	–	–	Withheld until baseline or less than or equal to 3 × ULN. then resumed at next lower dose.	Withhold until baseline or less than or equal to 3 × ULN, then resumed at next lower dose. Grade ≥2 elevation (>3 × ULN) of ALT or AST with concurrent total bilirubin elevation >2 × ULN in the absence of cholestasis or hemolysis (*Hy's law*), permanently discontinue.
Cabozantinib (Cabometyx®)	–	Interrupt treatment until the adverse reaction resolves to grade ≤1. Consider re-initiating at a reduced dose.	Interrupt treatment until the adverse reaction resolves to grade ≤1. Re-initiating at a reduced dose.	If adverse reaction resolves to grade ≤1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue.
Cabozantinib (Cometriq®)	–	If intolerable, dose interruptions are recommended.	Dose interruptions are recommended, dose reduction if AE persists.	Dose interruptions are recommended, dose reduction if AE persists.
Ceritinib	–	–	Withhold until baseline or ≤3 times ULN, then reinitiate with dose reduction.	Permanently discontinue. ALT or AST elevation >3 times ULN with concurrent total bilirubin elevation >2 times ULN (in the absence of cholestasis or hemolysis) (*Hy's law*), permanently discontinue.
Cobimetinib	Continue at the prescribed dose.	Continue at the prescribed dose.	Continue at the prescribed dose.	Interrupted. If improved to grade ≤1 within 4 weeks, restart at a dose reduced by 20 mg and vemurafenib at a clinically appropriate dose. per its SmPC. Treatment should be discontinued if liver laboratory abnormalities do not resolve to grade ≤1 within 4 weeks or if grade 4 liver laboratory abnormalities recur after initial improvement.
Crizotinib	–	–	Withhold until grade 1 or baseline, then resume at 250 mg once daily and escalate to 200 mg twice.	Withhold until grade 1 or baseline, then resume at 250 mg once daily and escalate to 200 mg twice. Grade 2, 3, or 4 ALT or AST elevation with concurrent grade 2, 3, or 4 total bilirubin elevation (in the absence of cholestasis or hemolysis) (*Hy's law*), permanently discontinue.
Dabrafenib[a]	Continue treatment and monitor as clinically indicated.	Continue treatment and monitor as clinically indicated. Intolerable, interrupt until toxicity is grade ≤1 and reduce by one dose level when resuming.	Grade 3 interrupt until toxicity is grade ≤1 and reduce by one dose level when resuming therapy.	Discontinue permanently, or interrupt therapy until grade ≤1 and reduce by one dose level when resuming therapy.

TABLE 4 (Continued)

PKI	Grade 1	Grade 2	Grade 3	Grade 4
Dacomitinib	No dose modification	No dose modification	Severe elevations in transaminases, interrupt treatment.	Severe elevations in transaminases, interrupt treatment.
Dasatinib[a]	–	Interrupt until the AE has resolved or returned to baseline. The same dose should be resumed if this is the first occurrence, and the dose should be reduced if this is a recurrent AE.	Treatment must be withheld until the AE has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the AE.	Treatment must be withheld until the AE has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the AE.
Duvelisib	–	Maintain dose. Monitor at least weekly until return to <3× ULN.	Withhold and monitor at least weekly until return to <3× ULN. Resume at the same dose (25 mg twice daily) for the first occurrence or at a reduced dose (15 mg twice daily) for subsequent occurrences.	Discontinue.
Encorafenib	–	Maintain. If no improvement within 4 weeks. Withheld until improved to grade ≤1 or to pre-treatment/baseline levels, and then resumed at the same dose.	First occurrence of grade 3. Withheld for up to 4 weeks. If improved to grade ≤1 or baseline levels, resume at reduced dose. If not improved, permanently discontinue. Recurrent grade 3 considers permanent discontinuation.	First occurrence withheld for up to 4 weeks. If improved to grade ≤1 or baseline levels, then resume at reduced dose level. If not improved, permanently discontinue. Recurrent, permanently discontinue. AST or ALT > 5× ULN and blood bilirubin >2× ULN (*Hy's law*), permanently discontinue.
Entrectinib	–	–	Withhold until grade ≤1 or to baseline. Resume at the same dose if resolution occurs within 4 weeks. Permanently discontinue if adverse reaction does not resolve within 4 weeks.	Withhold until ≤1 or to baseline. Resume at reduced dose if resolution occurs within 4 weeks Permanently discontinue if adverse reaction does not resolve within 4 weeks. Permanently discontinue for recurrent events. ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the absence of cholestasis or hemolysis) (*Hy's law*), permanently discontinue.
Erlotinib	–	–	Interrupt.	Interrupt.
Everolimus[a]	–	Tolerable, no dose adjustment required. Intolerable, temporary dose interruption until grade ≤1. Re-initiate treatment at the same dose. If toxicity recurs at grade 2, interrupt treatment until grade ≤1. Re-initiate 5 mg daily.	Temporary dose interruption until grade ≤1. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at grade 3, consider discontinuation.	Discontinue treatment.
Fedratinib	–	–	Interrupt until ≤ grade 1 or baseline. Restart dose at 100 mg daily below the last given dose. Monitor ALT, AST, and bilirubin (total and direct) every 2 weeks for at least 3 months following the dose reduction. If re-occurrence of grade 3 or higher elevation, discontinue.	Interrupt until resolved to ≤ grade 1 or baseline. Restart dose at 100 mg daily below the last given dose. Monitor ALT, AST, and bilirubin (total and direct) every 2 weeks for at least 3 months following the dose reduction. If re-occurrence of grade 3 or higher elevation, discontinue.

(Continues)

TABLE 4 (Continued)

PKI	Grade 1	Grade 2	Grade 3	Grade 4
Gefitinib	–	Use with caution.	Consider discontinuation.	Consider discontinuation.
Gilteritinib[a]	–	–	Interrupt until toxicity resolves or improves to grade 1. Resume at a reduced dose.	Interrupt until toxicity resolves or improves to grade 1. Resume at a reduced dose.
Ibrutinib[a]	–	–	Withheld until grade ≤1 or baseline, reinitiate at starting dose. If AE persists or recurs following two dose reductions, discontinue.	Withheld until grade ≤1 or baseline, reinitiate at starting dose. If AE persists or recurs following two dose reductions, discontinue.
Idelalisib	–	–	Withheld until values have returned to grade ≤1, resume at 100 mg twice daily. If the event does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician. If the event recurs, treatment must be withheld until the values return to grade 1 or less, after which re-initiation at 100 mg twice daily may be considered at the discretion of the physician.	Withheld until values have returned to grade ≤1, resume at 100 mg twice daily. If the event does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician. If the event recurs, treatment must be withheld until the values return to grade 1 or less, after which re-initiation at 100 mg twice daily may be considered at the discretion of the physician.
Imatinib	–	–	Treatment should be withheld until bilirubin levels have returned to <1.5 × IULN and transaminase levels to <2.5 × IULN. Continue at a reduced daily dose.	Treatment should be withheld until bilirubin levels have returned to <1.5 × ULN and transaminase levels to <2.5 × ULN. Continue at a reduced daily dose.
Lapatinib	–	–	Discontinue. Patients should not be retreated.	Discontinue. Patients should not be retreated.
Larotrectinib	–	Continued dosing may be appropriate, though close monitoring to ensure no worsening of the toxicity is advised.	Withheld until the AE resolves or improves to baseline or grade 1. Resume at the next dose modification if resolution occurs within 4 weeks. Permanently discontinued if an adverse reaction does not resolve within 4 weeks.	Withheld until the AE resolve or improves to baseline or grade 1. Resume at the next dose modification if resolution occurs within 4 weeks. Treatment should be permanently discontinued if an adverse reaction does not resolve within 4 weeks.
Lenvatinib (Kisplyx®)	–	–	Interrupt until grade ≤1 or baseline. Resume with dose reduction.	Discontinue.
Lenvatinib (Lenvima®)	–	–	Interrupt until grade ≤1 or baseline. Interrupt until grade ≤1 or baseline. Resume with dose reduction.	Discontinue Do not resume (grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as grade 3)
Lorlatinib[a]	No dose modification or reduce by 1 dose level, as clinically indicated.	Consider no dose modification or reduce by 1 dose level, as clinically indicated.	Withhold until symptoms resolve to grade ≤ 2 or baseline, then resume at 1 reduced dose level.	Withhold until symptoms resolve to grade ≤2 or baseline, then resume at 1 reduced dose level.
Midostaurin[a]	–	–	Interrupt until toxicities considered at least possibly related have resolved to grade ≤2, then resume.	Interrupt until toxicities considered at least possibly related have resolved to grade ≤2, then resume.

TABLE 4 (Continued)

PKI	Grade 1	Grade 2	Grade 3	Grade 4
Neratinib	–	–	Stop until grade ≤1. Evaluate alternative causes. Resume at the next lower dose level if grade ≤1 occurs within 3 weeks. If grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue. If grade 3 hepatotoxicity persists longer than 3 weeks, discontinue permanently	Permanently discontinue. Evaluate alternative causes.
Nilotinib	–	–	Doses should be reduced to 400 mg once daily or interrupted	Doses should be reduced to 400 mg once daily or interrupted
Nintedanib	–	–	After treatment interruption and recovery of transaminase-values to ≤2.5 × ULN in conjunction with bilirubin to normal, dose reduction from 200 mg twice daily to 150 mg twice daily and – if a 2nd dose reduction is considered necessary – from 150 mg twice daily to 100 mg twice daily.	After treatment interruption and recovery of transaminase-values to ≤2.5 × ULN in conjunction with bilirubin to normal, dose reduction from 200 mg twice daily to 150 mg twice daily and – if a 2nd dose reduction is considered necessary – from 150 mg twice daily to 100 mg twice daily. AST and/or ALT values to >3 × ULN in conjunction with an increase of total bilirubin to ≥2 × ULN and ALKP < 2 × ULN (*Hy's law*). Unless there is an alternative cause established, permanently discontinue.
Osimertinib[a]	–	–	If adverse reaction improves to grade 0–2 after withholding for up to 3 weeks restart at the same dose (80 mg) or a lower dose (40 mg). AE that does not improve to grade 0–2 after withholding for up to 3 weeks, permanently discontinue.	AE improves to grade 0–2 after withholding for up to 3 weeks restart at the same dose (80 mg) or a lower dose (40 mg). AE that does not improve to grade 0–2 after withholding for up to 3 weeks, permanently discontinue.
Palbociclib[a]	No dose adjustment is required.	No dose adjustment is required.	Withhold until symptoms resolve to grade ≤1; grade ≤2 (if not considered a safety risk for the patient). Resume at the next lower dose.	Withhold until symptoms resolve to grade ≤1; grade ≤2 (if not considered a safety risk for the patient). Resume at the next lower dose.
Pazopanib	–	Continue pazopanib with weekly monitoring of liver function until transaminases return to grade 1 or baseline.	Interrupt until transaminases return to grade 1 or baseline. If the potential benefit of reinitiating treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce at a reduced dose of 400 mg daily and perform serum liver tests weekly for 8 weeks. If transaminase elevations >3 × ULN recur, then permanently discontinue.	Interrupt until transaminases return to grade 1 or baseline. If the potential benefit of reinitiating treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce at a reduced dose of 400 mg daily and perform serum liver tests weekly for 8 weeks. Transaminase elevations >3 × ULN recur, then permanently discontinue. Transaminase elevations >3 × ULN concurrently with bilirubin elevations >2 × ULN (*Hy's law*) Permanently discontinue.

(Continues)

TABLE 4 (Continued)

PKI	Grade 1	Grade 2	Grade 3	Grade 4
Pemigatinib	No dose adjustment.	No dose adjustment.	Dose of patients who are taking 13.5 mg once daily reduce to 9 mg once daily. Dose of patients who are taking 9 mg once daily reduce to 4.5 mg once daily.	Dose of patients who are taking 13.5 mg once daily reduce to 9 mg once daily. Dose of patients who are taking 9 mg once daily reduce to 4.5 mg once daily.
Ponatinib	–	Occurrence at 45 mg: interrupted, monitor hepatic function. Resume at 30 mg after grade ≤1, or baseline. Occurrence at 30 mg: Interrupted, resumed at 15 mg after grade ≤1, or baseline. Occurrence at 15 mg: discontinue.	Occurrence at 45 mg: interrupt, monitor hepatic function. Resume at 30 mg after grade ≤1, or baseline. Occurrence at 30 mg: Interrupt, resume at 15 mg after grade ≤1, or baseline. Occurrence at 15 mg: discontinue.	Occurrence at 45 mg: interrupted. monitor hepatic function. resume at 30 mg after grade ≤1. or baseline. Occurrence at 30 mg: interrupt, resume at 15 mg after grade ≤1, or baseline. Occurrence at 15 mg: discontinue. Elevation of AST or ALT ≥ 3 × ULN concurrent with an elevation of bilirubin >2 × ULN and alkaline phosphatase <2 × ULN (*Hy's law*) discontinue.
Regorafenib	Continue treatment.	Continue treatment. Monitor liver function weekly until grade ≤1 or baseline.	1st occurrence Interrupt. Monitor weekly until return to <3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start treatment, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks. Re-occurrence, discontinue treatment permanently.	Any occurrence, discontinue treatment permanently. >3 times ULN (grade 2 or higher) with concurrent bilirubin >2 times ULN (*Hy's law*). Discontinue. Monitor liver function weekly until resolution or return to baseline.
Ribociclib	No dose adjustment is required.	Dose interruption until ≤ baseline grade, then resume at same dose level. If grade 2 recurs, resume at next lower dose level.	Dose interruption until ≤ baseline grade, then resume at next lower dose level. If grade 3 recurs, discontinue.	Discontinue. If patients develop ALT and/or AST > 3 × ULN along with total bilirubin >2 × ULN irrespective of baseline grade (*Hy's law*), discontinue.
Ruxolitinib	Dose reduction (50%)	Dose reduction (50%)	Dose reduction(50%)	Dose reduction(50%)
Selpercatinib	–	–	Suspend dose until toxicity resolves to baseline. Resume at dose reduced by 2 levels. After at least 2 weeks tolerated without recurrent increased ALT or AST, increase dosing by 1 dose level. Tolerated without recurrence for at least 4 weeks, increase to dose taken prior to the onset of grade 3 or 4 increased AST or ALT. Permanently discontinue if grade 3 or 4 ALT or AST increases if grade 3 or 4 ALT or AST increases recur despite dose modifications.	Suspend dose until toxicity resolves to baseline. Resume at dose reduced by 2 levels. After at least 2 weeks tolerated without recurrent increased ALT or AST, increase dosing by 1 dose level. Tolerated without recurrence for at least 4 weeks, increase to dose taken prior to the onset of grade 3 or 4 increased AST or ALT. Permanently discontinue if grade 3 or 4 ALT or AST increases if grade 3 or 4 ALT or AST increases recur despite dose modifications.

TABLE 4 (Continued)

PKI	Grade 1	Grade 2	Grade 3	Grade 4
Sorafenib[a]	Management may require temporary interruption or dose reduction. After improvement of non-hematological adverse reactions, the dose may be increased.	Management may require temporary interruption or dose reduction. After improvement of non-hematological adverse reactions, the dose may be increased.	Management may require temporary interruption or dose reduction. After improvement of non-hematological adverse reactions, the dose may be increased.	Management may require temporary interruption or dose reduction. After improvement of non-hematological adverse reactions, the dose may be increased.
Sunitinib	–	–	–	Discontinue and appropriate supportive care should be provided.
Temsirolimus	No dose adjustment.	No dose adjustment.	Dose adjustment. The recommended dose for patients who have baseline platelets[3] 100×10^9/L is 10 mg intravenous once a week infused over a 30–60 min period.	Dose adjustment. The recommended dose for patients who have baseline platelets 100×10^9/L is 10 mg intravenous once a week infused over a 30–60 min period.
Tivozanib[a]	–	–	Dose reduction, reduce to 890 μg once daily with the normal treatment schedule of 21 days of dosing, followed by a 7-day rest period.	Interrupt treatment.
Trametinib[a]	Continue and monitor as clinically indicated.	Grade 2 (Tolerable) Continue treatment and monitor as clinically indicated. Grade 2 (Intolerable), interrupt until toxicity is grade ≤1 and reduce by one dose level when resuming therapy.	Interrupt therapy until toxicity is grade ≤1 and reduce by one dose level when resuming therapy.	Discontinue permanently, or interrupt until grade ≤1 and reduce by one dose level when resuming therapy.
Tucatinib	No dose modification is required.	Hold until grade ≤1, then resume at the same dose level.	Hold until grade ≤1, then resume at the next lower dose level.	Permanently discontinue. ALT or AST > 3 × ULN and bilirubin >2 × ULN (*Hy's law*), permanently discontinue.
Vandetanib[a]	–	–	Temporarily stop and resume at a reduced dose when toxicity has resolved or improved to grade 1.	Temporarily stop and resume at a reduced dose when toxicity has resolved or improved to grade 1.
Vemurafenib[a]	No dose reduction.	Tolerable no dose reduction. Intolerable, interrupt until grade ≤1. Resume at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered). 2nd or persistence after treatment interruption. Interrupt until grade ≤1. Resume at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily). Third occurrence or persistence after second dose reduction discontinue permanently.	1st Interrupt treatment until grade ≤1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered). 2nd occurrence of any grade 3 AE or persistence after treatment interruption. Interrupt until grade ≤1. Resume at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily). 3rd occurrence of any grade 3 AE or persistence after 2nd dose reduction, discontinue permanently.	1st occurrence. Discontinue permanently or interrupt vemurafenib treatment until grade ≤1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily). 2nd occurrence or persistence of any grade 4 AE after 1st dose reduction, discontinue permanently.

Abbreviations: –, no data; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTC, common toxicity criteria; ULN, upper limit of normal.

[a]Data presented recommendation in SmPC for general AEs per CTC grade.

with caution was recommended for 13 PKIs, and a dose reduction was recommended for 18 PKIs. The other PKIs ($n = 21$) were recommended not to be used in patients with severe hepatic impairment.

3.8.3 | Treatment modifications and alteration recommendations per common toxicity criteria grade

When hepatotoxicity occurs upon treatment with PKIs, different treatment recommendations per CTC grade were provided in the SmPCs (Table 4). When no specific guidance for hepatotoxicity was given the general treatment modification per CTC grade is displayed. This was the case for 17 out of 55 analyzed SmPCs.

3.8.4 | Hy's Law

A recommendation for treating patients meeting Hy's law criteria (ALT or AST > 3 × upper limit of normal (ULN) and bilirubin > 2 × ULN) was mentioned in 15 out of 55 analyzed SmPCs CTC grade 4 in parentheses in Table 4. In all cases of Hy's law, treatment discontinuation was recommended.

4 | DISCUSSION

This review provides an overview of the hepatotoxicity data and treatment guidance across SmPCs of antineoplastic PKIs approved by EMA until September 2021. Up to that time, EMA has approved 55 antineoplastic PKIs, of which over 40 antineoplastic PKIs since Shah et al. published their article on FDA-registered PKIs in 2013.[1] This indicates the rapid development and the progress made in the field of antineoplastic PKIs in the previous years. Severe hepatotoxicity was reported in most of the analyzed PKI SmPCs and EPARs. AST and ALT were the most reported liver parameter. However, the incidence range of elevation for these parameters was wide. Events of ≥grade 4 hepatotoxicity were mentioned for 94% (52 out of 55) of the analyzed PKIs in the SmPC or EPAR. Some form of grade 3 or 4 hepatotoxicity is present in the SmPC or EPAR for all assessed PKIs. The aim of this review was to create an overview of the hepatotoxicity and resulting treatment recommendations for PKIs reported in their SmPCs. Missing, semiquantitative, or insufficient SmPC data were complemented with EPAR data. No data from the original clinical study reports or scientific publications were used. A limitation of this review is the descriptive indirect comparison of the PKIs. Data from the assessed PKIs were extracted from studies that vary in study population and confounding hepatotoxicity factors such as liver metastasis, age, or underlying disease. Therefore, comparing the quantitative data based on indirect study comparisons cannot be justified from both a clinical and scientific perspective. The clinical guidance was restricted to the SmPC guidance only as defined in the method section. Therefore, off-label guidance has not been taken into account. As only EMA-approved PKIs have been included we did not analyze PKIs which have been withdrawn or refused and were not granted a marketing authorization. This systematic analysis revealed that the clinical guidance for hepatotoxicity was not standardized due to differences in study design. These findings can contribute to the design of future registration studies in which the clinical guidance in the study protocol for hepatotoxicity has been aligned with previously authorized PKIs.

5 | CONCLUSION

Based on our overview, we found widespread incidence numbers for hepatotoxicity parameters for PKIs based on the data from the SmPC and EPAR. Differences in the degree of hepatotoxicity for different PKIs are apparent and in approximately 50% of SmPCs and EPARs of the analyzed PKIs, severe hepatotoxic events following treatment are reported. Furthermore, although liver parameter monitoring recommendations are present in the vast majority of SmPCs of the analyzed PKIs, the actual clinical guidance for hepatotoxicity in the SmPC is not standardized.[15–98]

AUTHOR CONTRIBUTIONS

M. Maliepaard: conception and design, analysis and interpretation of data, revising the manuscript critically. Y.S. Faber: acquisition of data, analysis, and interpretation of data, revising the manuscript critically. M. T.J. van Bussel: conception and design, analysis and interpretation of data, drafting the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Download medicine data at https://www.ema.europa.eu/en/medicines/download-medicine-data#european-public-assessment-reports-(epar)-section reference number 1.

ORCID

Marc Maliepaard https://orcid.org/0000-0002-2351-6814
Mark T. J. van Bussel https://orcid.org/0000-0003-0048-6314

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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