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Pharmacovigilance study of certain new classes of targeted antineoplastic therapies

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Tese para obtenção do Grau de Doutor em
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(3º ciclo de estudos)

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Declaração de Integridade

Eu, Mafalda Martins de Jesus, que abaixo assino, estudante com o número de inscrição D2927 do curso de 3º grau em Ciências Farmacêuticas da Faculdade de Ciências da Saúde, declaro ter desenvolvido o presente trabalho e elaborado o presente texto em total consonância com o **Código de Integridades da Universidade da Beira Interior**.

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List of Publications

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Carvalho da Silva, S. P.*; **Jesus, M.***; Roque, F.; Herdeiro, M. T.; Costa E Sousa, R.; Duarte, A. P.; Morgado, M. Active Pharmacovigilance Study: A Follow-Up Model of Oral Anti-Cancer Drugs under Additional Monitoring. Current oncology. 2023; 30(4):4139–4152. doi:10.3390/curroncol30040315
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Jesus, M.; Cabral, A.; Monteiro, C.; Duarte, A. P.; Morgado, M. Peripheral Neuropathy Potentially Associated to Poly (ADP-Ribose) Polymerase Inhibitors: An Analysis of the Eudravigilance Database. Current oncology. 2023; 30(7):6533–6545. doi:10.3390/curroncol30070479

Martins, V.*; **Jesus, M.***; Pereira, L.; Monteiro, C.; Duarte, A. P.; Morgado, M. Hematological Events Potentially Associated with CDK4/6 Inhibitors: An Analysis from the European Spontaneous Adverse Event Reporting System. Pharmaceuticals. 2023; 16(10):1340. doi:10.3390/ph16101340
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Available online:
https://www.ordemfarmaceuticos.pt/fotos/editor2/2023/_www/cim/boletim/boletim_jul_set_2023.pdf

- **Scientific Posters:**

Mafalda Jesus; Olímpia Fonseca; Ana Paula Duarte e Manuel Morgado. Inibidores PARP: relevância clínica e o papel do farmacêutico hospitalar na segurança do medicamento. XIV Congresso Nacional da APFH: Um Porto Seguro. Porto, 25-27 Novembro de 2021.

Mafalda Jesus; Olímpia Fonseca; Ana Paula Duarte and Manuel Morgado. PARP Inhibitors: clinical relevance and the role of multidisciplinary cancer teams in drug safety. XVI Annual CICS-UBI Symposium. University of Beira Interior, Health Sciences Faculty, Covilhã, 30th September – 1st October 2021.

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Mafalda Jesus; Olímpia Fonseca; Ana Paula Duarte and Manuel Morgado. PARP inhibitors: Pharmacist's role in the management of adverse effects. VII Scientific Annual Congress of UBIpharma. University of Beira Interior, Health Sciences Faculty, Covilhã, 5th and 6th November 2021. (won the award for best poster)

Mafalda Jesus; Olímpia Fonseca; Ana Paula Duarte e Manuel Morgado. Inibidores da PARP: gestão dos distúrbios do sangue e do sistema linfático. Semana da Investigação do Centro Hospitalar Universitário Cova da Beira. Centro Hospitalar Universitário Cova da Beira, 15 a 19 Novembro de 2021.

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Oral communications related to this thesis:

Mafalda Jesus; Manuel Morgado e Ana Paula Duarte. Inibidores PARP na terapêutica farmacológica. Sessão informativa "CIM à tarde na Sociedade Farmacêutica". Ordem dos Farmacêuticos, Lisboa, 12 Dezembro 2022.
The presentation lasted 1 hour and was given by Mafalda Jesus and moderated by Ana Paula Mendes, from the Drug Information Centre of the Portuguese Pharmaceutical Society.

Resumo Alargado

O cancro é considerado uma das principais causas de morte em todo o mundo. Em 2020, os dados sugerem 19.3 milhões de novos casos de todos os tipos de cancro e cerca de 10 milhões de mortes. Estima-se que a incidência desta doença aumente significativamente nos próximos anos, particularmente em camadas mais jovens da população.

Nas últimas décadas, terapias farmacológicas inovadoras têm emergido em alternativa à quimioterapia convencional, com destaque para as terapias direcionadas. Genericamente, as terapias direcionadas podem incluir como alvos moleculares fatores de crescimento, moléculas de sinalização, proteínas do ciclo celular, moduladores da apoptose, moléculas que promovem a angiogénese, entre outros. São exemplos destas terapias direcionadas as seguintes classes terapêuticas farmacológicas: inibidores da poli(ADP-ribose) polimerase (PARPi), inibidores das cinases dependentes de ciclina (inibidores CDK4/6) e inibidores das tirosinacinases. Estas classes terapêuticas envolvem inúmeras indicações clínicas tais como cancro do ovário, mama, próstata, pulmão, hepático, entre outros. Os PARPi competem com o local de ligação do cofator da enzima PARP, impedindo a reparação do ADN e, consequentemente, induzem a morte celular das células cancerígenas. Quatro inibidores integram esta classe, tais como: olaparib, rucaparib, niraparib e talazoparib. Os inibidores CDK4/6 atuam particularmente na formação do complexo CDK4/6 – ciclina D, impedindo a progressão do ciclo celular, da fase G1 para a fase S. Atualmente, desta classe terapêutica fazem parte três inibidores, palbociclib, ribociclib e abemaciclib. Em adição, os inibidores das tirosinacinases competem com o ATP, impedindo a transferência de grupos fosfato do mesmo para um susbstrato específico. Estes inibidores atuam interrompendo as vias de transdução do sinal das proteínas cinase através da sua inibição. Esta classe é representada por vários inibidores já aprovados, tendo sido abordados no presente trabalho o cabozantinib e o lorlatinib.

Adicionalmente à sua especificidade de atuação que se traduz numa maior eficácia, outro benefício destas terapias reside na minimização de efeitos adversos fora do alvo, causados em tecidos normais, quando comparadas com os fármacos convencionais quimioterápicos. No entanto, a literatura revela que são atribuídos aos mesmos uma lista significativa de efeitos adversos podendo causar alterações no esquema quimioterápico, descontinuação da terapêutica e, em última instância, a morte. Diversos domínios são afetados tais como o domínio hematológico, gastrointestinal, metabólico, cognitivo,

entre outros. Note-se que, muitos destes fármacos são aprovados de forma acelerada, permitindo o seu uso clínico com um benefício clínico mínimo e risco desconhecido de efeitos adversos na população em geral. Desta forma, é de reforçar a importância de estudos clínicos num contexto real de ambulatório e ambiente hospitalar.

Neste contexto, a farmacovigilância destas terapias anticancerígenas é fundamental, permitindo, através da deteção e gestão de reações adversas a medicamentos (RAMs), melhorar a segurança dos doentes oncológicos e auxiliar os profissionais de saúde a identificar possíveis RAMs não documentadas durante o decorrer dos ensaios clínicos. De facto, elevadas incidências para algumas RAMs podem ocorrer, assim como reações adversas raras e de manifestação tardia. Ademais, em oncologia, a subnotificação de RAMs é um fenómeno comum, justificado pelo seu carácter de inevitabilidade.

Esta tese de doutoramento foca essencialmente o estudo da farmacovigilância de terapêuticas direcionadas, incluindo fármacos como: olaparib, niraparib e talazoparib (pertencentes à categoria dos PARPi); palbociclib, ribociclib e abemaciclib (pertencentes à categoria dos inibidores CDK4/6) e, por último, cabozantinib e lorlatinib (integrantes da classe dos inibidores das tirosinacinases). Dados de farmacovigilância provenientes do Sistema Português de Farmacovigilância e da base de dados EudraVigilance foram recolhidos e analisados, segundo uma análise retrospectiva, descritiva e estatística. Variáveis como o género, idade, repórter da RAM, localização geográfica da RAM, sistema afetado pela RAM, *outcome* da RAM, gravidade, critérios de gravidade, RAMs mais reportadas (foram consideradas as 20 RAMs mais reportadas), ação tomada, número de fármacos concomitantes e principal indicação clínica foram consideradas.

Como principais resultados verificou-se que, maioritariamente, as mulheres na idade adulta e idosa são o grupo mais reportado. Distúrbios hematológicos estão muito associados à classe dos PARPi e dos inibidores CDK4/6, tais como anemia, neutropenia, trombocitopenia e leucopenia. Relativamente à classe dos inibidores das tirosinacinases estudados foram reportados com maior frequência distúrbios metabólicos, em particular associados ao lorlatinib, e distúrbios hormonais, associados ao cabozantinib. Pneumonite foi identificada em associação ao olaparib assim como alguns casos de neuropatia periférica foram associados ao palbociclib. Na generalidade, a maioria dos casos foi reportado como grave, traduzindo-se num *outcome* desconhecido. Casos fatais foram identificados nas três classes terapêuticas, em particular nos inibidores CDK4/6.

A participação de todos os profissionais de saúde na notificação de RAMs torna-se, assim, necessária. Novos conhecimentos sobre RAMs dos fármacos pode,

atempadamente, auxiliar na definição de medidas de gestão e prevenção das mesmas, bem como contribuir para a emissão, pelas autoridades de saúde competentes, de *guidelines* relativas a alertas e precauções a ter na utilização destes medicamentos. Realça-se, também, a importância da farmacovigilância na melhoria da qualidade de vida destes doentes, essencial num período tão crítico das suas vidas.

Palavras-chave

Oncologia; Farmacovigilância; Terapias direcionadas; Inibidores da poli(ADP-ribose) polimerase; Inibidores CDK4/6; Inibidores das tirosinacinases; Reações adversas a medicamentos; Segurança do doente.

Abstract

Cancer is considered one of the most devastating causes of death in the world. Innovative and targeted therapies have become urgent in the treatment of cancer. Examples of these therapies include the following therapeutic classes: poly(ADP-ribose) polymerase inhibitors (PARPi), cyclin-dependent kinase inhibitors (CDK4/6 inhibitors) and tyrosine kinase inhibitors (TKIs). These therapies are generally associated with better patient outcomes, with greater specificity and fewer side effects, particularly on healthy tissues. However, the literature reveals a significant list of adverse effects associated with these drugs, which can lead to changes in the chemotherapy regimens, discontinuation of therapy and, ultimately, death. Several domains are affected, including the hematological, gastrointestinal, metabolic, and cognitive domain, among others. In addition, many of these drugs are approved in an accelerated manner, with minimal clinical benefit and an unknown risk of adverse effects in the general population.

Pharmacovigilance of anticancer therapies is fundamental. The detection and management of adverse drug reactions (ADR) can improve the safety of cancer patients and help healthcare professionals identify possible undocumented ADR during clinical trials. In this context, this thesis focuses essentially on the pharmacovigilance of targeted anticancer drugs namely: olaparib, niraparib and talazoparib, which belong to the PARPi class; palbociclib, ribociclib and abemaciclib, which belong to the CDK4/6 inhibitors class; and cabozantinib and lorlatinib, which belong to the TKIs class. Through a retrospective, descriptive and statistical analysis, pharmacovigilance data from the Portuguese Pharmacovigilance System and the EudraVigilance database was collected and analyzed. Variables such as sex, age group, reporter group, geographic origin, individual cases reported by system organ classes, outcome, seriousness, seriousness criteria, most reported preferred terms (PTs) (20 most reported PTs were considered), action taken, number of concomitant medicines per individual case safety report and clinical indications were considered. Hematological disorders were highly associated with PARPi and CDK4/6 inhibitors, particularly anemia, neutropenia, thrombocytopenia, and leukopenia. In addition, metabolic disorders were mainly associated with lorlatinib and hormonal disorders such as hypothyroidism were very common in patients taking cabozantinib. Pneumonitis was associated with olaparib, and some cases of peripheral neuropathy were associated with palbociclib. In general, most cases were reported as serious and were characterized as having an unknown outcome.

Fatal cases were associated with all three therapeutic classes studied, particularly with CDK4/6 inhibitors.

New knowledge about ADR of targeted therapies may help to define timely management and prevention measures and contribute to better develop guidelines on warnings and precautions to be taken when using these drugs. Pharmacovigilance actions become imperative in improving the quality of life of cancer patients at such a critical time in their lives.

Keywords

Oncology; Pharmacovigilance; Targeted therapy; Poly(ADP-Ribose) polymerase inhibitors; CDK4/6 inhibitors; Tyrosine kinase inhibitors; Adverse drug reactions; Patient safety.

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List of Abbreviations

AATYK	Apoptosis-associated Tyrosine Kinase
ADR	Adverse Drug Reaction(s)
AE(s)	Adverse Effect(s)
AI	Aromatase Inhibitor
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AXL	From the Greek word anex-elekto, or uncontrolled, a Tyro3 Protein Tyrosine Kinase
BRCA	BReast CAncer Gene
CCK	Colon Carcinoma Kinase
CDK	Cyclin-Dependent Kinase(s)
DDR	Discoidin Domain Receptor
DTC	Differentiated Thyroid Carcinoma
EGF(R)	Epidermal Growth Factor (receptor)
EMA	European Medicines Agency
Eph(R)	Ephrin (receptor)
ER	Estrogen Receptor
ET	Endocrine Therapy
EV	EudraVigilance
FAERS	FDA Adverse Event Reporting System
FDA	U. S. Food and Drug Administration
FGF(R)	Fibroblast Growth Factor (receptor)
GIST	Gastrointestinal Stromal Tumor
HCC	Hepatocellular Carcinoma
HCP	Healthcare Professional(s)
HER2(-)	Human Epidermal Growth Factor Receptor (Negative)
HGF(R)	Hepatocyte Growth Factor (receptor)
HR	Homologous Recombination
HR+	Hormone Receptor-Positive
ICSR(s)	Individual Case Safety Report(s)
IGF(R)	Insulin-like Growth Factor (receptor)
ILD	Interstitial Lung Disease
INFARMED	National Authority of Medicines and Health Products, I.P.
InsR	Insulin Receptor
LMR	Lemur
LTK	Leukocyte Tyrosine Kinase
mCRPC	Metastatic Castration-Resistant Prostate Cancer
M-CSFR	Macrophage Colony-Stimulating Growth Factor
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal-Epithelial Transition
MTC	Medullary Thyroid Cancer
MuSK	Muscle-Specific Kinase
NGF(R)	Nerve Growth Factor (receptor)

NSCLC	Non-Small Cell Lung Cancer
NTRK	Neurotrophic Tyrosine Receptor Kinase
OTC	Over-the-Counter
PAR	Poly(ADP-Ribose)
PARP	Poly(ADP-Ribose) Polymerase(s)
PARPi	Poly(ADP-Ribose) Polymerase Inhibitor(s)
PDGF(R)	Platelet-derived Growth Factor (receptor)
PFS	Progression-Free Survival
PhV	Pharmacovigilance
PPES	Palmar-Plantar Erythrodysesthesia Syndrome
PPS	Portuguese Pharmacovigilance System
PT(s)	Preferred Term(s)
RB	Retinoblastoma
RCC	Renal Cell Carcinoma
RET	Rearranged during Transfection
ROR	Receptor Orphan
ROS	RTK expressed in some epithelial cell types
RTK	Receptor Tyrosine Kinase(s)
RYK	Receptor Related to Tyrosine Kinases
Rx	Medical Prescription
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
TIE	Tyrosine Kinase Receptor in Endothelial Cells
TK	Tyrosine Kinase
TKI	Tyrosine Kinase Inhibitor(s)
TRK	Tropomyosin Receptor Kinase
ULN	Upper Limit of Normal
VEGF(R)	Vascular Endothelial Growth Factor (Receptor)

Chapter 1
Introduction

Chapter 1

General Introduction

Cancer is considered one of the most devastating causes of death in the world. Globally, 17 million new cancer diagnoses are estimated each year [1]. For instance, in 2020, 19.3 million new cases were estimated, and 10 million cancer deaths were reported [2]. By 2040, it is expected that the number of new cancer cases reported will increase to 27.5 million [3]. In this context, investment in early detection methods and, in particular, the development of new anticancer agents has become urgent to treat this large subset of diseases.

Over the last years, cancer therapy has undergone a drastic evolution with the introduction of targeted therapy [4]. The literature reports several already approved clinical indications including lung cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, melanoma, leukemia, among others [5]. In fact, over the past decade, the U.S. Food and Drug Administration (FDA) has approved approximately 40 new targeted therapies for 12 different types of cancer [6]. Targeted therapy interferes with specific molecules to block the growth and spread of cancer cells. Depending on the target, targeted therapy can act on cell surface antigens, growth factors, receptors or signal transduction pathways that are involved in the regulation of cell cycle progression, cell death, metastasis, and angiogenesis [7]. Examples of targeted therapies include the following therapeutic classes: tyrosine kinase inhibitors (TKIs), monoclonal antibodies, immune checkpoint inhibitors, cyclin-dependent kinase (CDK) inhibitors and poly(ADP-ribose) polymerase inhibitors (PARPi) [8–12]. The effectiveness of these classes lies in the targeted action of the therapy to the disease site. In addition, another beneficial role of these therapies is to minimize off-target side effects caused to normal tissues compared to conventional chemotherapeutic agents [13]. However, according to the literature, targeted therapies are associated with a wide range of adverse effects (AEs) that may cause changes in chemotherapy regimens, discontinuation of therapy and, ultimately, death [6,14–16]. Several studies and case reports have highlighted the toxicity associated with these anticancer agents. Wang *et al.* reported a study regarding the lethal toxic effects associated with immune checkpoint inhibitors. This study reported a total of 613 lethal events related to immune checkpoint inhibitors from 2009 to early 2018 [17]. A real-world study using the FDA Adverse Event Reporting System (FAERS) database described hospitalization as the most serious outcome event in hematological toxicities related to PARPi [18]. Concerning TKIs, Lim *et al.* described a case report in

which patients experienced serious life-threatening complications after starting treatment with sunitinib, a TKI used in the treatment of metastatic renal cell carcinoma (RCC) [19]. In addition, an analysis by Kassem *et al.* provided evidence that the use of CDK4/6 inhibitors is associated with an increased risk of all-grade and high-grade hematological adverse events [20].

Pharmacovigilance (PhV) of anticancer therapies is fundamental, allowing through the detection and management of adverse drug reactions (ADR), to improve the safety of cancer patients and to help healthcare professionals (HCP) to identify possible undocumented ADR during clinical trials [21,22]. Targeted therapies are a new recent generation of anticancer drugs and, therefore the specific safety profile of many of these drugs has been based on the results provided by clinical trials [21,23,24]. Moreover, in oncology, under-reporting of ADR is a common phenomenon, justified by its unavoidable nature [21,22]. Data provided by the National Authority of Medicines and Health Products, I.P. (INFARMED, I.P.) highlight the importance of PhV, through the number of tablets dispensed in the hospital setting. **Table 1.1.** shows the number of tablets dispensed (in units) in 2020, 2021 and 2022 for some approved antineoplastic targeted substances in Portugal.

Table 1.1. Consumption of targeted therapies in Portugal in 2020, 2021 and 2022.
Source: Information Centre of Medicines and Health Products (CIMI), INFARMED, I.P.

Active Substance	Quantity (number of pills in units)		
	2020	**2021**	**2022**
Olaparib	158 412	127 609	103 699
Niraparib	27 953	30 305	44 482
Talazoparib	-	750	3 150
Palbociclib	118 858	124 782	136 405
Ribociclib	144 756	238 052	343 099
Abemaciclib	11 866	45 085	84 311
Cabozantinib	8 696	13 800	19 261
Lorlatinib	7 081	12 284	17 330
Total	**477 622**	**592 667**	**751 737**

New knowledge about ADR of targeted therapies may help to define timely management and prevention measures and contribute to better develop guidelines on warnings and precautions to be taken when using these drugs. It should be noted that the accelerated approval of these drugs often allows their clinical use with a minimal clinical benefit and unknown risk in terms of safety profile in the general population [24]. PhV actions

become imperative in improving the quality of life of cancer patients at such a critical time in their lives.

1.1. Thesis overview and aim

The aim of this doctoral thesis encompasses two main goals, namely:

1) to establish, in a precise and detailed manner, the safety profile of the medicines under study, considering that they have recently been approved on the market and that most safety studies are based on the results of clinical trials in controlled conditions;

2) provide better support to HCP in managing ADR using real-world data. Through this, adequate counseling and supportive care with pharmacological and non-pharmacological measures can be provided before starting treatment to help more and more patients benefit from these innovative agents. Furthermore, this knowledge can contribute to support a better choice in terms of therapeutic agents/maximum benefit from targeted drugs.

This doctoral thesis essentially focuses on the PhV study of targeted antineoplastic drugs, namely: olaparib, niraparib and talazoparib, which belong to the PARPi class; palbociclib, ribociclib and abemaciclib, which belong to the CDK4/6 inhibitors class; and cabozantinib and lorlatinib, which belong to the TKIs class. In order to organize the different aspects, this thesis has been divided into **5 chapters**.

In chapter 1, an introduction to the topic is given. Firstly, an overview of cancer and targeted therapies is presented, followed by a literature review concerning the targeted drugs and their therapeutic classes. In addition, a comprehensive description of the most common AEs associated with the targeted drugs studied and their management is also described.

In chapter 2, we describe the methods of this work. Data from the Portuguese Pharmacovigilance System (PPS) and EudraVigilance (EV) database were collected and evaluated through a retrospective, descriptive and statistical analysis. Variables such as sex, age group, reporter group, geographic origin, individual cases reported by system organ classes (SOC), outcome, seriousness, seriousness criteria, most reported preferred terms (PTs) (20 most reported PTs were considered), action taken, number of concomitant medicines per individual case safety report (ICSR), and clinical indications were considered.

Chapter 3 presents the main findings of this study. The results are presented by therapeutic class and by data source involved in the study.

In chapter 4, the results are discussed in accordance with other PhV studies published in the literature. The discussion is presented by therapeutic class, and both national and European results were discussed.

Finally, chapter 5 focuses on the overall conclusions of the thesis, the main limitations of the study as well as a brief overview of the future perspectives reserved for the PhV field in targeted therapies and in oncology in general.

1.2. PARP inhibitors

This subchapter was adapted from the published review article:

Jesus M, Morgado M, Duarte AP. PARP inhibitors: clinical relevance and the role of multidisciplinary cancer teams on drug safety. Expert Opin Drug Saf. 2022; 21(4):541-551. doi:10.1080/14740338.2022.1996561

1.2.1. PARP – Description and mechanism of action

Described more than 50 years ago, poly(ADP-Ribose) polymerases (PARP) constitute a superfamily of 18 proteins, categorized into three groups, according to their catalytic activity [25].

PARP1 was the first family member identified, being the most characterized in the literature [26]. Considered the most abundant isoform, it is responsible for more than 90% of the catalytic activity of PARP in the cell nucleus [27]. This member was initially identified for its role in the detection and repair of single-strand DNA breaks and in base excision repair [26]. PARP1 is also activated by double-strand breaks [26] and selectively regulates E2F1-mediated induction of DNA repair factors involved in homologous recombination (HR) [28]. Recent evidence suggested that PARP1 is involved in a variety of cellular processes ranging from cell proliferation to cell death. In fact, PARP1 has nuclear proteins as substrates that are involved in transcriptional regulation, apoptosis, inflammation, chromatin descondensation and cell cycle regulation [28–30]. PARP2 is the isoform most closely related to PARP1, sharing a similarity of 69% of its catalytic domain [31]. Although PARP1 and PARP2 are better known for their involvement in DNA repair processes, it is known that other PARPs also play an important role in several cellular processes [32]. For example, PARP3 shares some of the functions of PARP1, particularly its involvement in the DNA repair process [33]. In addition to sharing several structural similarities, these family members are known to be activated in a similar manner by DNA-dependent catalytic activation through local destabilization of the catalytic domain [32]. PARP3 has also been shown to interact with and regulate tankyrase 1, actions that may be potentially important in cancer therapy [33]. PARP5a and PARP5b are also involved in the synthesis of poly(ADP-ribose) (PAR) in humans [34]. In addition, PARP10, like PARP1 and PARP2, has been implicated in DNA repair. Conversely, PARP7 activity is not directly linked to DNA repair [35].

In this context, when DNA damage occurs, it is rapidly recognized by the DNA-binding domain of PARP1. Consequently, this binding activates PARP1 which, by increasing its catalytic activity, cleaves NAD+ into nicotinamide (β-NAD+) and PAR polymers [36,37]. More specifically, it is known that the binding of PARP1 to DNA induces a conformational change in the protein, allowing β-NAD+, the PARP1 co-factor, to bind to the active site of the enzyme. Subsequently, PARP1 uses β-NAD+ hydrolysis to promote the transfer of PAR fractions to the target proteins [38]. This parylation activity leads to the addition of PAR to nuclear proteins, such as histones, and PARP1 (autoPARylation) itself, through the formation of covalent bonds [39,40]. The addition of these PAR chains mediates DNA repair by modifying the chromatin structure (e.g., via histone-PARylation) [40] and by recruiting other DNA repair proteins, such as the repair protein XRCC1 (also known as X-ray repair cross-complementing protein 1) [39]. The reduction in the affinity of the bond between PARP1 and DNA due to its autoPARylation allows other proteins in the repair complex to access the site of damage [38].

1.2.2. PARP inhibitors – Mechanism of action

The observation of small nicotinamide analogue molecules (β-NAD+) involved in the PARlylation process led to the development of PARPi [41]. This class of anticancer drugs competes with nicotinamide (β-NAD+) for the catalytic active site of the PARP molecules. The first demonstration of PARP inhibition activity dates back to 1971, after the treatment of HeLa cells with thymidine and nicotinamide [42]. Several benzamides have also been identified as inhibitors of PARP activity. However, their low potency and specificity have proven to be clinically unviable compounds [43,44].

In the literature, the precise mechanism of PARPi is not completely clearly described, in particular how these inhibitors kill tumor cells. Several theories have emerged. Rose *et al.* reviewed different mechanisms of action by which PARPi induce their anti-cancer activity. However, it is unclear whether one or several of these mechanisms mediate the activity of PARPi [45]. This review describes two methods of cytotoxicity induced by PARPi. Since some studies have shown that PAR recruits DNA repair proteins to the site of damage, the first method relies on inhibition of the PARP enzyme. The inhibition of its catalytic activity occurs through interaction of PARPi with the binding site of the PARP enzyme cofactor, β-NAD+, in its catalytic domain. In this way, it becomes possible to prevent DNA repair, and consequently, by increasing repair errors, cancer cell death is induced. The second method involves the concept of "PARP trapping". In this case, the prevention of autoPARylation and the release of PARP1/PARP2 from damaged DNA by

the inhibitors mediates their cytotoxic activity, preventing the recruitment of additional DNA repair proteins [38,46,47]. As a result, the cell is unable to properly repair its DNA during replication, which can lead to mitotic catastrophe and subsequent cell death [48].

In the two methods described above, PARP1 is considered the main target of PARPi. The activity of other members of the PARP family, including PARP2 and PARP3 can be inhibited by PARPi [46,49]. In fact, all PARPi that have been developed provide effective and affordable inhibition of PARP1 and PARP2. However, there are differences in their ability to induce PARP trapping [38,46]. For example, niraparib is more potent at PARP1 trapping when compared to olaparib and rucaparib. On the other hand, talazoparib is more potent at PARP1 trapping compared to niraparib [38] and has demonstrated 100 times greater potency at trapping PARP-DNA complexes in preclinical studies if compared to olaparib [50]. Studies showed that veliparib is the least efficient PARP trapper [38,46]. This difference is understood to be one of the reasons for the variation in recommended doses and the different levels of cytotoxicity of the different PARPi [51].

Figure 1.1. describes the PARP activity in the DNA repair process and its prevention by PARPi activity. **Table 1.2.** summarizes the different PARPi that have been approved by the drug regulatory authorities and are available on the pharmaceutical market. In the following sections, a summary of the approval history, mechanism of action, indications and AEs are discussed in detail.

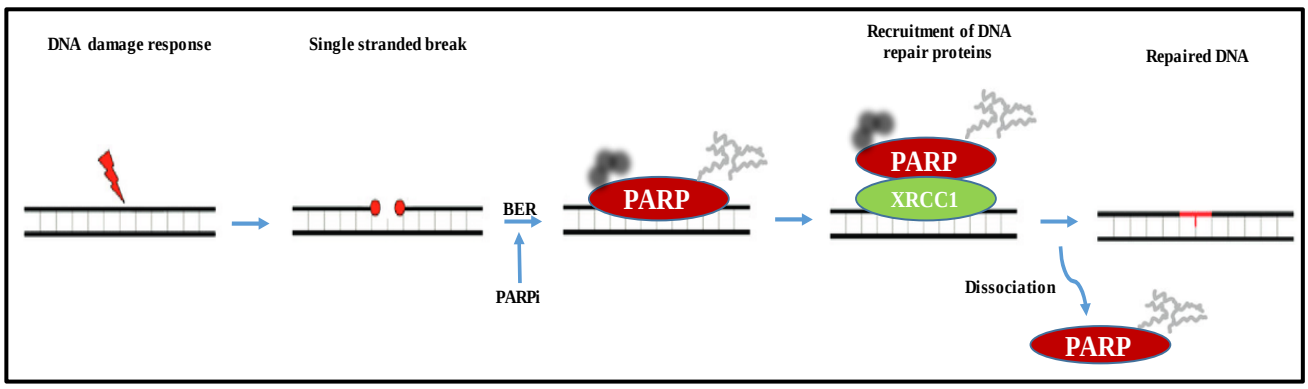

Figure 1.1. Schematic representation of PARP1 activity in the DNA repair process and its inhibition by PARPi [11].

Abbreviations: BER, Base excision repair; PARP(i), Poly(ADP-Ribose) polymerase (inhibitor); XRCC1, X-ray repair cross-complementing protein 1.

Table 1.2. Profile of approved PARPi.

PARP Inhibitor	First Approval Year FDA/EMA	Mechanism of Action	Approved Clinical Indications						References
			Ovarian cancer 1st line maintenance (after platinum)	Recurrent ovarian cancer 2nd line maintenance (after platinum)	Recurrent/metastatic ovarian cancer	Recurrent, metastatic breast cancer	Metastatic pancreatic cancer maintenance after chemotherapy	Recurrent, metastatic castration-resistant prostate cancer	
Niraparib	2017/2017	PARP 1/2 inhibitor	✓	✓	✓				[52,53]
Olaparib	2014/2014	PARP 1/2/3 inhibitor	✓	✓	✓	✓	✓	✓	[54–58]
Rucaparib	2016/2018	PARP 1/2/3 inhibitor		✓	✓			✓	[59,60]
Talazoparib	2018/2019	PARP 1/2 inhibitor				✓			[50,61]

Abbreviations: FDA, U.S. Food and Drug Agency; EMA, European Medicines Agency.

1.2.3. PARP inhibitors – Characterization and clinical development

As a class of drugs, PARPi have had an excellent impact in the treatment of oncological diseases. In fact, the antitumor activity of these drugs is highlighted by the numerous clinical trials carried out over the last decade [62].

As a result, the FDA and the European Medicines Agency (EMA) have already approved four PARPi with several clinical indications, namely: olaparib, rucaparib, niraparib and talazoparib [63–66]. Within the approved clinical indications, it is important to distinguish between two groups: PARPi that are prescribed for treatment and PARPi that are prescribed for maintenance. PARPi, prescribed for treatment, are understood as the drugs initially used in an attempt to shrink the current tumor. Otherwise, maintenance therapy is the continuation of treatment, after the use of the drug that is considered the standard treatment of a particular tumor. Other PARPi are under investigation, such as veliparib and pamiparib, but have not yet been approved by drug regulatory authorities.

1.2.3.1. Olaparib

Olaparib was the first PARPi to be developed for the treatment of solid tumors. It is approved as maintenance therapy for adult patients with recurrence, high-grade platinum-sensitive serous epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer with positive BReast CAncer gene (BRCA) mutation (germline and/or somatic) and who are in response to platinum-based chemotherapy [54,55,63]. These therapeutic indications have been approved based on a few highly successful clinical trial studies. Study 19 (NCT00753545), a randomized, double-blind, placebo-controlled, phase 2 study and SOLO-2 (NCT01874353), a randomized, double-blind, placebo-controlled, phase 3 trial revealed clinical results that led to the approval of olaparib in the previously described indications [54,55].

Olaparib was approved for the treatment of germline BRCA-1 and/or BRCA-2 mutated, human epidermal growth factor receptor-negative (HER2-) breast cancer and for metastatic pancreatic cancer, in 2018 and 2019, respectively [56,57]. More recently, in 2020, olaparib was associated with longer progression-free survival (PFS) in men with metastatic castration-resistant prostate cancer (mCRPC) who had disease progression while receiving enzalutamide or abiraterone and who had alterations in genes involved in HR repair [67].

1.2.3.2. Rucaparib

In 2016, rucaparib was approved for the maintenance treatment of patients with deleterious BRCA mutation (germline or somatic)-associated advanced ovarian carcinomas, following multiple chemotherapy regimens. This approval was based on the results of the clinical trials Study10 (NCT01482715) and ARIEL2 (NCT01891344) [68]. In this context, the subsequent ARIEL3 trial (NCT01968213) showed excellent results in improving PFS in patients with BRCA mutation-associated ovarian carcinoma and also in patients with BRCA wild-type ovarian cancer [69].

Similar to olaparib, the inhibitor rucaparib was also approved by the FDA in 2020 for the treatment of mCRPC. Both inhibitors are approved for tumors with BRCA1/2 alterations. Rucaparib has been approved for patients who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy [60]. However, as mentioned above, the indications for olaparib are extended to patients who had alterations in genes with a role in HR repair, including proteins such as ataxia telangiectasia mutated kinase and PALB2 [70]. New PARPi are being investigated for the treatment of prostate cancer [71].

1.2.3.3. Niraparib

Based on the results of the randomized phase III ENGOT-OV16/NOVA (NOVA) trial (NCT01847274), niraparib was approved by the FDA in 2017. This PARP1/2 inhibitor was the first to be approved for the maintenance treatment of women with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy [52]. Based on the results of the OCEANS trial (NCT00434642), bevacizumab was the only agent approved for the maintenance therapy. This drug was administered in combination with chemotherapy and continued as a single agent in patients after six to eight cycles of combined chemotherapy. In this context, niraparib appears as a therapeutic alternative with specific advantages, namely a different mechanism of action and an oral administration convenience once a day [72,73].

1.2.3.4. Talazoparib

Talazoparib, approved by the FDA in 2018, is approved for the treatment of adults with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative, locally advanced or metastatic breast cancer [61,74]. The approval of this agent resulted from a phase III clinical trial, EMBRACA trial (NCT01945775), which compared this PARPi with chemotherapy in patients with advanced breast cancer and a germline BRCA1/2

mutation. The results showed a 46% reduction in the risk of disease progression or death compared with the standard-therapy group [74]. Although talazoparib has mainly been studied in breast cancer, its effectiveness in ovarian cancer is being investigated. However, compared with other PARPi, the evidence supports that the use of talazoparib in epithelial ovarian cancer is limited.

1.2.4. Adverse effects of PARP inhibitors

In this section, a comprehensive description of the most common AEs of approved PARPi is presented. The frequency of AEs is also discussed.

1.2.4.1. Gastrointestinal disorders

Table 1.3. presents the most common adverse reactions at the gastrointestinal level, according to information collected from the summary of product characteristics (SmPC) of each approved PARPi.

Table 1.3. Main adverse reactions in the gastrointestinal system.

PARPi	Main Adverse Reactions (Very common, ≥ 1/10)					
	Nausea	**Vomiting**	**Diarrhea**	**Dyspepsia**	**Constipation**	**Abdominal pain**
Niraparib	✓	✓	✓	✓	✓	✓
Olaparib	✓	✓	✓	✓		
Rucaparib	✓	✓	✓	✓		✓
Talazoparib	✓	✓	✓			✓

Gastrointestinal AEs such as nausea, vomiting and diarrhea are common with all PARPi. Data from clinical trials showed that nausea was the most reported AE. In the SOLO-2 trial, nausea was reported by 148 (76%) out of 195 patients treated with olaparib [54]; in the ARIEL3 study, 280 (75%) out of 372 patients treated with rucaparib [69] and in the ENGOT-OV16/NOVA study, 270 (74%) out of 367 patients treated with niraparib [53]. On the other hand, talazoparib demonstrated a less pronounced AE. The safety profile of this drug, based on pooled data from 494 patients, reported that 44.3% of patients experienced nausea [66].

Other common symptoms include dyspepsia, constipation, and abdominal pain. Constipation is described as very common with niraparib only, having been reported in 146 (39.8%) out of 367 patients treated with this inhibitor [54]. Dyspepsia is considered to be more common in patients taking rucaparib. This symptom was reported by 54 out

of 372 patients. Abdominal pain is also a verified effect in this class of drugs [69]. However, it is only described as a common AE with olaparib (≥ 1/100 to < 1/10) [63].

1.2.4.2. Hematological disorders

Table 1.4. presents the most common adverse reactions in the hematological system, according to the information collected from the SmPC of each approved PARPi.

Table 1.4. Main adverse reactions in the hematological system.

PARPi	Main Adverse Reactions (Very common, ≥ 1/10)			
	Anemia	**Neutropenia**	**Leukopenia**	**Thrombocytopenia**
Niraparib	✓	✓	✓	✓
Olaparib	✓	✓	✓	✓
Rucaparib	✓	✓		✓
Talazoparib	✓	✓	✓	✓

Hematological reactions are common to all PARPi, especially anemia, neutropenia, leukopenia, and thrombocytopenia. Their manifestations, particularly reactions such as thrombocytopenia, anemia, and neutropenia, tend to occur at the beginning of treatment, with the frequency decreasing over time. For example, in their analysis, Berek *et al.* (2018) reported that these grade≥3 hematologic effects only occurred during the first three months of niraparib administration at a daily dose of 300mg. After dose reduction, the incidence of hematological effects decreased considerably, except for anemia, which persisted after the third month of administration [75].

The SmPC reports anemia as the most common AE among PARPi. In SOLO-2 trial, anemia was reported in 85 (43.6%) out of 195 patients treated with olaparib [54]; in the ARIEL3 study, in 139 (37%) out of 372 patients treated with rucaparib [69] and in the ENGOT-OV16/NOVA study, in 184 (50%) out of 367 patients treated with niraparib [53]. Talazoparib showed that 49.6% of patients developed anemia, based on pooled data from 494 patients [66].

Thrombocytopenia and neutropenia are two other reactions that are considered very common with PARPi. In the ENGOT-OV16/NOVA study, approximately 60% and 30% of patients experienced thrombocytopenia and neutropenia of any-grade, respectively [65]. Similar to anemia, niraparib has a more pronounced effect in inducing thrombocytopenia of any-grade compared to olaparib and rucaparib. Olaparib and rucaparib induced thrombocytopenia of any-grade in only 14% and 28% of patients,

respectively [54,69]. Leukopenia is classified as a common AE ($\geq 1/100$ to $< 1/10$) within rucaparib, in contrast to other inhibitors [64].

1.2.4.3. Nervous disorders

Table 1.5. shows the most common adverse reactions in the nervous system, according to the information collected from the SmPC of each approved PARPi.

Table 1.5. Main adverse reactions in the nervous system.

PARPi	Main Adverse Reactions (Very common, ≥ 1/10)		
	Headache	**Dizziness**	**Dysgeusia**
Niraparib	✓	✓	
Olaparib	✓	✓	✓
Rucaparib		✓	✓
Talazoparib	✓	✓	

Dizziness is common to all PARPi. In the SOLO-2 trial, dizziness was reported in 26 (13%) out of 195 patients treated with olaparib [54]; in the ARIEL3 study, 54 (15%) out of 372 patients treated with rucaparib [69] and in the ENGOT-OV16/NOVA study, 61 (17%) out of 367 patients treated with niraparib [53]. In relation to the talazoparib inhibitor, dizziness was reported in 69 (14%) out of 494 patients [66]. This suggests that dizziness is more common in patients taking niraparib.

Headache is also considered to be very common with PARPi. However, in the ARIEL3 study, only 67 (18%) out of 372 patients experienced this effect [69]. In this case, headache is not considered to be a very common AE in patients taking rucaparib. Furthermore, the incidence of headache is similar for the inhibitors niraparib, talazoparib and olaparib. In the ENGOT-OV16 / NOVA study, headache was reported in 95 (26%) out of 367 patients treated with niraparib [53]; in 131 (26.5%) out of 494 patients reported this effect using talazoparib [66], as well as in 49 (25%) out of 195 patients treated with olaparib [54]. Dysgeusia was more common with rucaparib and olaparib [63,64].

1.2.4.4. Metabolism and nutrition disorders

PARPi also caused some metabolic and nutritional disorders. Decreased appetite is a very common AE of all PARPi, affecting approximately 20-25% of patients enrolled in clinical trials of these drugs. In this context, decreased appetite was reported in 43 (22%) out of 195 patients treated with olaparib in the SOLO-2 trial [54]; in 87 (23%) out of 372 patients treated with rucaparib in the ARIEL3 trial [69] and in 93 (25%) out of 367 patients treated with niraparib in the ENGOT-OV16/NOVA trial [53]. With talazoparib, decreased appetite was observed in 100 (20.2%) out of 494 patients [66].

The increase in creatinine levels in blood is classified as very common with the inhibitor rucaparib only. In the ARIEL3 study, the results showed that 15% of patients had an increase in blood creatinine of any-grade. However, increases stabilized over time [69]. It is known that rucaparib inhibits two renal transport proteins, MATE1 and MATE2-K, which are involved in the secretion of creatinine [69]. Olaparib also caused an increase in creatinine levels in blood. However, with olaparib, this reaction was only classified as common, as indicated in the SmPC [63].

1.2.4.5. Fatigue

Fatigue is common to all PARPi and is one of the most common AEs observed in patients. Approximately 59-69% of patients experienced fatigue of any-grade. The results were as follows: in the SOLO-2 trial, fatigue was reported in 128 (66%) out of 195 patients treated with olaparib [54]; in the ARIEL3 study, the same occurred to 258 (69%) out of 372 patients treated with rucaparib [69] and in the ENGOT-OV16/NOVA study, 218 (59%) out of 367 patients treated with niraparib reported fatigue [53]. Talazoparib caused fatigue in 282 (57.1%) out of 494 patients [66].

1.2.4.6. Others

Respiratory AEs are more commonly associated with the inhibitors niraparib and olaparib, according to the SmPC. Cough and dyspnea are mentioned. In this context, in the SOLO-2 and ENGOT-OV16/NOVA trials, 17% and 15% of patients had coughing of any-grade using olaparib and niraparib, respectively. Dyspnea of any-grade increased by 12% and 19% with olaparib and niraparib, respectively [53,54]. Nasopharyngitis was also considered to be a very common adverse reaction in patients using niraparib [65].

Increases in the transaminase enzymes, aspartate, and alanine aminotransferase (AST and ALT), are also seen as very common, particularly in patients taking rucaparib. Results from ARIEL3 study showed that 34% of patients had an increase in either ALT

or AST of any-grade. However, increases in the concentrations of these enzymes were generally transient, self-limiting, and not associated with other signs of liver toxicity [69].

In addition, cardiac disorders are more often associated with the inhibitor niraparib. These disorders mainly include palpitations and hypertension. In the ENGOT-OV16/NOVA study, 10% and 19% of 367 patients treated with niraparib had palpitations and hypertension of any-grade, respectively [53]. According to the FDA label, these effects may be related to pharmacological inhibition of the dopamine, norepinephrine, and serotonin transporters [76].

Cutaneous toxicities were also reported to be very common with rucaparib and talazoparib, according to the SmPC. Photosensitivity reactions and rash are more common with rucaparib. In the ARIEL3 trial, the authors reported 17% of any-grade photosensitivity reactions and 12% of any-grade rash [69]. Alopecia is usually observed with the inhibitor talazoparib. Results showed that 22.3% of the patients had alopecia of any-grade [66].

1.2.5. Management of adverse effects

The previous section reported the most common AEs of the four PARPi approved by the FDA and the EMA. This section aims to focus on the management of AEs, which is essential to ensure pharmacological success. **Table 1.6.** presents suggestions for pharmacological and non-pharmacological measures for the management of AEs. Depending on the grade, dose interruption and/or dose reduction may be considered in addition to treatment recommendations for symptom control. In general, grade 1/2 recommends continuation of the PARPi therapy with possible consideration of dose interruption [76–78]. Grade 3/4 suggests maintaining PARPi and considering dose reduction [53,54,69].

Table 1.6. Pharmacological and non-pharmacological measures for the management of AEs of PARPi [65,75,79–86]**.**

Disorders	Adverse effect	Suggested management
Gastrointestinal	Nausea/Vomiting	✓ Antiemetic Rx only: 5-HT_3 antagonists, metoclopramide, prochlorperazine, dexamethasone, olanzapine or lorazepam; ✓ Light meal/snack.
	Diarrhea	✓ OTC's: Loperamide.
	Constipation	✓ OTC's: Senna or polyethylene glycol.
	Dyspepsia/Abdominal Pain	✓ OTC's: Proton pump inhibitor.
Hematological	Anemia	✓ As symptoms occur mostly at the beginning of treatment, general management consists of holding dose, lab reassessment and dose reduction if needed; ✓ Symptomatic anemia and for hemoglobin values of less than 7g/dL, transfusions should be discussed.
	Neutropenia	
	Leukopenia	
	Thrombocytopenia	
Neurological	Headache	✓ OTC treatment should be referenced.
	Dysgeusia	✓ Diet changes, cooler temperature of foods, improvement in oral hygiene and maintain hydration.
Metabolism	Creatinine elevations	✓ Namely with rucaparib: do not require dose adjustment.
	ALT and AST elevations	✓ As mentioned above, increases in the levels of these enzymes are temporary and tend to stabilize over time.
Fatigue		✓ Exercise, massage therapy, good sleep hygiene, stress reduction/psychosocial interventions; ✓ Pharmacological options: psychostimulants, such as ginseng and methylphenidate.
	Palpitations	✓ Monitor blood pressure and heart rate, particularly if history of cardiovascular disease;

Cardiovascular	Hypertension	✓ Antihypertensive medication and dose reduction, if necessary.
Cutaneous	Photosensitivity reaction	✓ Sun protection, hats, skin moisturizers when initiating PARPi therapy.
	Rash	
	Alopecia	✓ Redirect to dermatology.

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; OTC, Over-the-counter; Rx, Medical prescription.

1.3. CDK 4/6 inhibitors

1.3.1. Cyclin-dependent kinases – Description and mechanism of action

CDKs are protein kinases that play an important role in the regulation of the cell cycle, transcription, and splicing [87,88]. Originally, CDKs were discovered in model organisms such as grogs and yeasts [89], having been characterized as regulators of the eukaryotic cell cycle [90]. Since these pioneering studies in the 1980s, the importance of this family in the cell cycle and how their catalytic activity works has been clearly demonstrated [89–91].

The CDK family represents a distinct branch within the CMGC group (cyclin-dependent protein kinases, mitogen-activated protein kinases or MAP kinases, glycogen synthase kinases, and CDK-like kinases) [92], of which 20 are classified as CDKs and the other 5 forms compose a more distant group of CDK-like (CDKL) kinases [92,93]. CDKs belong to the class of serine/threonine kinases, whose activity is regulated by a regulatory component – a cyclin [89]. Humans have 13 cyclin groups (A, B, C, D, E, F, G, H, J, K, L, T, and Y). In fact, cyclins and their cognate CDKs are required components of the cell division cycle [92].

Several functions of this family have been established and are well described in the literature [94]. In this context, CDK1 has been implicated in the control of the M phase of the cell cycle in complex with cyclin A and cyclin B. In addition, CDK2 is also involved in cell cycle control, namely in the G1-S phase, in complex with cyclin E and cyclin A. In contrast, the role of CDK5 is associated with neuronal function, more precisely in complex with p35 and p39 [91]. CDKs 7, 8, 9, 11 and 20 have been implicated in the regulation of mRNA synthesis [95]. The functions developed by members of the CDK family impact several hallmarks of cancer treatment, with the most successful clinical approach being related to CDK4 and CDK6 [96]. CDK4/6 are involved in the pathway that allows DNA to be duplicated and divided evenly between the two daughter cells [88,89], more specifically in regulating of cell cycle progression from G1 phase to S phase [97,98]. During DNA synthesis, in the presence of mitogenic signals, CDK4/6 bind to the D-type cyclins (cyclin D1, cyclin D2 and cyclin D3) and form catalytically active complexes [97,99]. According to the literature, cyclin D1 is the best characterized, however CDK4 and CDK6 can form complexes with all three types of cyclin D [100]. A key function of these complexes is associated with the phosphorylation of the retinoblastoma (RB) tumor suppressor protein. It should be noted that kinases are

enzymes that catalyze the transfer of a phosphate group from adenosine triphosphate (ATP) to a specific target substrate to regulate various activities such as proliferation, survival, metabolism, apoptosis transcription and other cellular processes [99].

RB acts as a negative regulator of the cell cycle, preventing premature cell division by biding to E2F transcription factors [101,102]. When not phosphorylated, the protein is fully active, particularly in G1 phase or when cells are quiescent in G0 phase. The non-phosphorylated form of RB binds to E2F transcription factors and represses the transcription of genes regulated by E2F. However, the addition of phosphate groups by CDK4/6 promotes the desactivation of RB function, releasing E2F transcription factors and allowing the expression of genes required for S phase entry and consequently cell cycle progression [101,103]. CDK2 has a similar function to CDK4/6; however, RB phosphorylation occurs through binding to E-type cyclins [104].

Following these activities in the cell cycle, hyperactivation of the CDK4/6-cyclin D complex is indeed commonly associated with cancerous conditions [105]. In this context, CDK4/6 inhibitors have become relevant therapeutic agents [106].

1.3.2. CDK4/6 inhibitors – Mechanism of action

Tissue homeostasis is ensured by two physiological processes that include cell division and cell death. These two mechanisms, in balance, prevent overproliferation and limit the potential for cancer [107]. Cyclins and CDKs play an important role in the Gap phases, G1 and G2, determining whether cells progress through the cell cycle. As mentioned above, CDK4 and CDK6 regulate the mid-G1 phase through the complex formed with D-type cyclins [108]. This complex represents an attractive target and has attracted particular interest as an anticancer therapy, leading to the development of a new class of drugs: CDK4/6 inhibitors [109,110]. The approved CDK4/6 inhibitors are classified as ATP-competitive agents. These agents block the cellular transition from G1 to S phase of the cell cycle by selectively targeting the ATP binding site of CDK4/6 kinases, via hydrogen bonds [98,107,109]. **Figure 1.2.** describes the activity of the CDK4/6-cyclin D complex in cell cycle progression and its inhibition by CDK4/6 inhibitors.

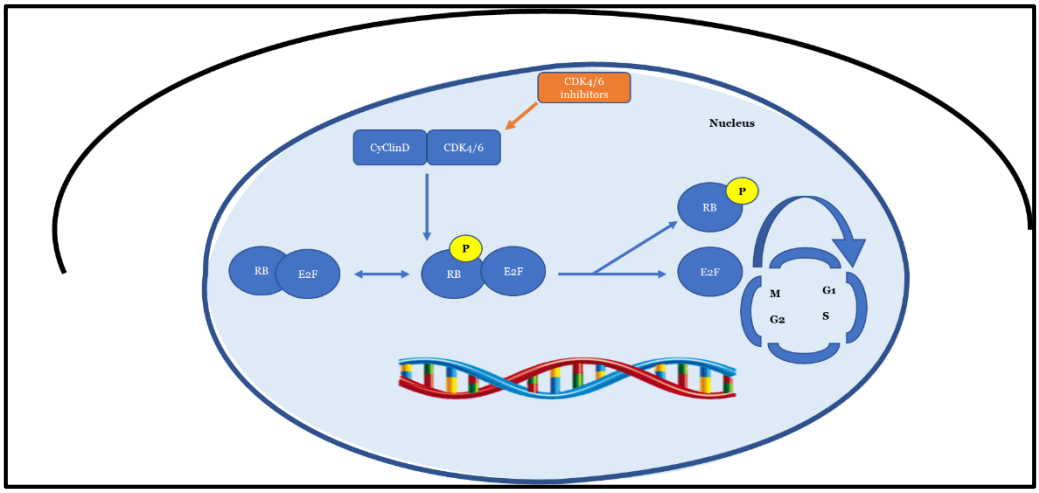

Figure 1.2. Schematic representation of the activity of the CDK4/6-cyclin D complex in cell cycle progression and its inhibition by CDK4/6 inhibitors.
Abbreviations: CDK, Cyclin-dependent kinase; P, Phosphate group; RB, Retinoblastoma protein.

1.3.3. CDK4/6 inhibitors – Characterization and clinical development

Over the last decade, several data have described the regulation of CDK4/6 activity in proliferating cells and revealed the clinical impact of CDK4/6 inhibitors. In this context, three generations of CDK inhibitors have been developed and tested in different types of cancer [102]. The first generation of inhibitors was characterized by a lack of selectivity and an inadequate balance between efficacy and toxicity. This generation consisted of flavopiridol and roscovitine [111,112]. Later, a second generation of inhibitors emerged with a focus on increasing selectivity and potency. Dinaciclib was part of this generation. However, in clinical trials (phase I/II) it was also reported to have limited efficacy and significant toxicity, mainly related to multi-target activity against other isoforms such as CDK1 and CDK9 [113,114]. A third generation was developed, which proved to be selective towards CDK4/6 kinases with potent efficacy and reduced toxicity. As a result, the FDA and the EMA have already approved three CDK4/6 inhibitors, namely: palbociclib, ribociclib and abemaciclib [115–117]. These substances are orally bioavailable and highly selective CDK4/6 inhibitors [107] and have been approved for the treatment of breast cancer in various settings and combination regimens [118,119].

Breast cancer is the most common malignancy in women, affecting millions of women each year according to the World Health Organization [1,120]. Hormone receptor-positive (HR+) and HER2- is the most common molecular subtype of breast cancer in many countries [121,122]. In fact, approximately 75% of all patients with stage IV breast

cancer have this subtype and have often been treated with single-agent endocrine therapy (ET) [118]. Despite the significant results of this therapy, the poor prognosis of patients with advanced HR+/HER2- breast cancer may be related to the acquired resistance to the ET therapy [123]. Loss or mutation of the estrogen receptor (ER), alteration of the ER pathway and deregulation of cell cycle signaling molecules are proposed mechanisms responsible for ET resistance [124]. In this context, CDK4/6 inhibitors have been introduced as a treatment option for patients with HR+, HER2- advanced breast cancer, either as first-line therapy in combination with an aromatase inhibitor (AI) or as a second-line therapy in combination with fulvestrant, particularly in women who have received prior ET [125–127].

1.3.3.1. Palbociclib

Palbociclib was the first CDK4/6 inhibitor to be approved by drug regulatory agencies in 2015. Considering the therapeutic indication mentioned in the previous section, some successful clinical trials have contributed to the approval of this drug [128]. In this context, PALOMA-2 (NCT01740427), a randomized, double-blind, placebo-controlled, phase 2 study showed a significantly longer PFS in patients treated with palbociclib in combination with letrozole than in patients treated with letrozole alone. PFS was 24.8 months in the palbociclib-letrozole group and 14.5 months in the placebo-letrozole group [129]. Encouraging results were also seen in PALOMA-3 (NCT01942135), a randomized, double-blind, placebo-controlled, phase 3 study. In this study, patients with HR+, HER2- metastatic breast cancer whose disease had progressed during prior ET that were treated with palbociclib plus fulvestrant had a longer PFS, 9.2 months, than fulvestrant alone, 3.8 months [125].

1.3.3.2. Ribociclib

Based on the results of MONALEESA-2 (NCT01958021) study, ribociclib was approved by the FDA and the EMA in 2017. This randomized, double-blind, placebo-controlled, phase 3 trial conducted in 29 countries described that patients treated with ribociclib plus letrozole had a significantly longer PFS, 25.3 months, than those who received placebo plus letrozole, 16 months. Most patients involved in the study had stage IV breast cancer [127,130].

Later, in 2018, based on the MONALEESA-3 (NCT02422615) trial, the therapeutic indication was expanded to include combination treatment with fulvestrant. According to the results, median PFS was significantly improved in patients treated with ribociclib plus fulvestrant compared to patients treated with placebo plus fulvestrant (20.5 months

versus 12.8 months, respectively) [131,132]. These significant results were also seen in other clinical trials involving ribociclib [133].

1.3.3.3. Abemaciclib

To date, the last CDK4/6 inhibitor to be approved was abemaciclib in 2018. As with the other inhibitors, the results described in the clinical trials that led to the approval of abemaciclib were very promising. Between 2014 and 2015, MONARCH-2 (NCT02107703), a phase III, randomized, double-blind, placebo-controlled trial was conducted in women with HR+/HER2- advanced breast cancer whose disease had progressed while receiving prior ET. Abemaciclib plus fulvestrant significantly prolonged PFS compared to fulvestrant alone (median, 16.4 months versus 9.3 months, respectively) [126]. In addition, MONARCH-3, a phase 3, randomized, double-blind study of abemaciclib or placebo plus a nonsteroidal AI (anastrozole or letrozole at physician's choice) showed that median PFS was significantly prolonged in the abemaciclib arm. This clinical trial enrolled postmenopausal women with HR+/HER2- advanced breast cancer who had not received prior systemic therapy in the advanced setting. Abemaciclib showed significant antitumor activity as initial therapy for women with metastatic cancer in MONARCH-3 study and in patients who had progressed on ET in MONARCH-2 study [134].

1.3.4. Adverse effects of CDK4/6 inhibitors

In the following sections, a comprehensive description of the most relevant AEs of the approved CDK4/6 inhibitors is presented. The frequency of some AEs is also discussed.

1.3.4.1. Hematological disorders

Although the mechanism of action and efficacy of CDK4/6 inhibitors are similar, some differences in their toxicity profiles have been reported [135]. Onesti *et al.* explored the safety profile of CDK4/6 inhibitors in a systematic review and a meta-analysis study. The most common toxicities reported were hematological disorders such as neutropenia, leukopenia, anemia, and thrombocytopenia for both palbociclib and ribociclib. However, gastrointestinal toxicities were the most reported with abemaciclib [135].

In light of the information described above, in the PALOMA-2 trial, neutropenia was the most commonly reported AE, followed by leukopenia. In this context, any-grade of neutropenia was reported in 353 (79.5%) out of 444 patients in the palbociclib-letrozole arm, of whom 249 (56.1%) reported grade 3 neutropenia and 46 (10.4%) reported grade 4 neutropenia. In the placebo-letrozole group, only 14 (6.3%) out of 222 patients

experienced neutropenia, regardless of grade. Leukopenia was less reported, with 39% of patients experiencing leukopenia of any-grade and 24.1% and 0.7% experiencing grade 3 or 4 leukopenia, respectively. Anemia and thrombocytopenia of any-grade were also reported with percentages of 24.1% and 15.5%, respectively [129]. In PALOMA-3 trial, hematological toxicities were also the most common in the palbociclib-fulvestrant arm, including neutropenia, leukopenia, anemia, and thrombocytopenia. Out of a total of 345 patients treated with palbociclib-fulvestrant, neutropenia of any-grade was reported in 272 patients (78.8%), leukopenia of any-grade was reported in 157 patients (45.5%); anemia of any-grade was reported in 90 patients (26.1%) and thrombocytopenia in 67 patients (19.4%) [125]. According to the SmPC of palbociclib, neutropenia of any-grade is one of the most common reactions, and dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop grade 3 or grade 4 neutropenia [117]. Leukopenia, anemia, and thrombocytopenia are also classified as very common AEs [117]. In the MONALEESA trials, neutropenia was the most common AE observed in the ribociclib group. In fact, the most common grade 3 or 4 AEs were hematological disorders such as neutropenia and leukopenia [122,132]. In MONALEESA-3 trial, grade 3-4 neutropenia and leukopenia were observed in 57.1% and 15.5% of patients in the ribociclib group, respectively [132]. Anemia was also seen but in a smaller number of patients compared to neutropenia. The SmPC of ribociclib characterizes neutropenia, leukopenia and anemia as very common reactions and thrombocytopenia as a common reaction [116]. In terms of AEs that occurred during treatment with abemaciclib, neutropenia was also the most reported AE. According to MONARCH-2, in a total of 441 patients, 203 (46.0%) experienced neutropenia of any-grade, of whom 104 patients (23.6%) reported grade 3 neutropenia and only 13 patients (2.9%) reported grade 4 neutropenia. Anemia and leukopenia were also seen in approximately 120 patients. Thrombocytopenia was also reported but to a lesser extent than neutropenia [126,134]. The abemaciclib SmPC states that neutropenia, leukopenia, anemia, and thrombocytopenia are very common AEs in patients taking this medicine.

Hematological toxicity is considered the most common toxicity observed with CDK4/6 inhibitors and is related to their action on CDK6, which is a key regulator of hematopoietic proliferation [136]. Palbociclib and ribociclib are administered for three consecutive weeks, followed by a one-week break to allow recovery of hematopoietic progenitors. In contrast, abemaciclib is given continuously. In fact, abemaciclib has a higher affinity for CDK4 and, consequently, this CDK4/6 inhibitor shows lower hematological toxicity compared to palbociclib and ribociclib [102]. Additionally, ribociclib has a more favorable hematological toxicity profile than palbociclib [137].

Table 1.7. presents the most common hematological adverse reactions, according to the information in the SmPC for each CDK4/6 inhibitor.

Table 1.7. Main adverse reactions in the hematological system.

	Main Adverse Reactions (Very common, ≥ 1/10)			
CDK4/6 inhibitor	**Neutropenia**	**Leukopenia**	**Thrombocytopenia**	**Anemia**
Palbociclib	✓	✓	✓	✓
Ribociclib	✓	✓		✓
Abemaciclib	✓	✓	✓	✓

1.3.4.2. Gastrointestinal disorders

Gastrointestinal disorders are transversal to the majority of anticancer drugs and therefore it is essential to analyze the additional burden of CDK4/6 inhibitors in patients taking these drugs. Shohdy *et al.* performed a systematic review and a meta-analysis study that highlighted the gastrointestinal toxicities and their impact on patients' quality of life. According to their research, the incidence of all-grade gastrointestinal toxicities ranged from nausea, followed by vomiting, diarrhea, and decreased appetite for both palbociclib and ribociclib. The addition of a CDK4/6 inhibitor to hormone therapy slightly increased the incidence of gastrointestinal AEs of any-grade. However, there was no significant increase in the risk of high-grade (3-4) gastrointestinal toxicity [138]. In fact, in the PALOMA-3 study, nausea (29.0%) of any-grade was the most reported AE in the palbociclib-fulvestrant group, followed by diarrhea, constipation and vomiting. None of the patients experienced grade 3-4 nausea, diarrhea, and constipation [125]. Nausea, diarrhea, and vomiting are considered very common AEs in palbociclib SmPC. Also, in MONALEESA-3 study, nausea of any-grade (45.3%) was the most common AE reported in the ribociclib plus fulvestrant group [131]. Diarrhea, vomiting, and constipation were also reported. In general, gastrointestinal toxicities of all grades were slightly more common in the ribociclib plus fulvestrant group than in the palbociclib plus fulvestrant group [125,131]. However, as mentioned above, gastrointestinal toxicity is more predominant with abemaciclib [139]. In MONARCH-3 trial, diarrhea of all grades was the most reported AE, occurring in 81.3% of patients taking abemaciclib. Grade 2-3 diarrhea was experienced by a small percentage of patients (27.2% and 9.5%, respectively). Other GI toxicities have been reported, such as nausea, abdominal pain, vomiting, decreased appetite and constipation, but with a lower frequency compared to diarrhea [134]. In this context, according to the SmPC of abemaciclib, diarrhea, vomiting and nausea are considered the most common reactions among gastrointestinal disorders [115]. These symptoms can be explained by the inactivation of the RB protein and the consequent arrest of the cell cycle in quiescent phases of both cancerous and normal

cells. One of the most vulnerable tissues to this antiproliferative action is the gastrointestinal epithelium [138].

Other frequently AEs that have a direct impact on patients' quality of life have been mentioned. Palbociclib, ribociclib and abemaciclib have a high risk of causing stomatitis. In fact, patients receiving ET alone rarely experience this AE. A meta-analysis performed by Long *et al.* observed that in a total of 1849 patients receiving CDK4/6 inhibitors plus ET, stomatitis events were reported by 378 patients (20.4%) compared to 105 patients (9.3%) in the control group [140]. According to the SmPC information, stomatitis is considered a very common reaction in patients taking palbociclib, ribociclib and abemaciclib. [115-117]. Dysgeusia is a common reaction in patients taking ribociclib and dyspepsia is a common reaction experienced in patients taking abemaciclib [115,116]. **Table 1.8**. presents the most common gastrointestinal toxicities according to the information collected from the SmPC of each CDK4/6 inhibitor.

Table 1.8. Main adverse reactions in the gastrointestinal system.

	Main Adverse Reactions (Very common, ≥ 1/10)			
CDK4/6 inhibitor	**Nausea**	**Vomiting**	**Diarrhea**	**Stomatitis**
Palbociclib	✓	✓	✓	✓
Ribociclib	✓	✓	✓	✓
Abemaciclib	✓	✓	✓	✓

1.3.4.3. Fatigue

Fatigue is one of the most common non-hematological AEs of all grades [141]. Based on the pooled data from 3 randomised trials, PALOMA-1, PALOMA-2 and PALOMA-3, fatigue of any-grade was reported in 362 (41.5%) out of a total of 872 patients receiving palbociclib. In addition, grade 3 and grade 4 fatigue was experienced by only a few patients: 23 (2.6%) and 2 (0.2%) patients, respectively [117]. Fatigue is also a very common reaction reported in the ribociclib SmPC [116]. In fact, in MONALEESA-2 trial, fatigue of any-grade was experienced by 122 (36.5%) out of a total of 334 patients in the ribociclib group. Grade 3-4 were experienced by only 8 patients [127]. In patients treated with abemaciclib, fatigue is also reported in a large proportion of patients, being classified as a very common reaction [115]. In this context, a study developed by Takada *et al.* reported the AEs that led to dose reductions. Fatigue was one of the AEs that contributed to two-levels of dose reductions [142]. Diarrhea, neutropenia, and fatigue were the most common AEs of abemaciclib leading to dose reductions [134].

1.3.4.4. Other disorders

Other AEs have been associated with CDK4/6 inhibitors. Ribociclib has been reported to cause a higher rate of hepatic and respiratory toxicity as well as QTc prolongation, compared with palbociclib and abemaciclib [101]. In this context, elevations in transaminases such as ALT and AST are mentioned as very common reactions and may imply discontinuation of ribociclib in grade 2 [139]. Considering the respiratory disorders, cough and dyspnea are classified as very common reactions in the ribociclib SmPC [116]. In addition, a few case reports have described the possible occurrence of pneumonitis and interstitial lung disease (ILD). These cases were considered serious and some of them had a fatal outcome [143]. In fact, ILD/pneumonitis are classified as common reactions in the SmPC of palbociclib, ribociclib and abemaciclib [115–117].

QTc prolongation is usually dose-dependent and reversible. According to Hotobagyi *et al.*, most of patients who experienced QTc prolongation were able to continue treatment with ribociclib 600 mg without intervention [127]. In addition, abemaciclib is more commonly associated with increased blood creatinine levels [142], which may be related to the inhibition of renal tubular secretion of creatinine without affecting glomerular function [144]. Arthralgia of any-grade was also more frequently observed in patients taking ribociclib [135]. Alopecia, typically grade 1, is associated with all three inhibitors [137] and it is considered a very common reaction among them [115–117]. Regarding nervous system disorders, headache and dizziness are very common reactions in patients taking ribociclib and abemaciclib [115,116]. On the contrary, these reactions are not mentioned in the SmPC of palbociclib [117]. **Table 1.9**. shows the classification of some AEs, according to the information collected from the SmPC of each CDK4/6 inhibitor.

Table 1.9. Main adverse reactions in several affected systems.

	Main Adverse Reactions (Very common, ≥ 1/10)			
CDK4/6 inhibitor	**AST/ALT elevation**	**Cough**	**Pneumonitis/Interstitial lung disease**	**Alopecia**
Palbociclib	✓			✓
Ribociclib	✓	✓		✓
Abemaciclib	✓			✓

1.3.5. Management of adverse effects

The previous section reported on the AEs associated with the three approved CDK4/6 inhibitors. As mentioned, the correct management of AEs is essential to ensure the success of the therapy and, consequently, provide a better quality of life for cancer patients. **Table 1.10.** describes several pharmacological and non-pharmacological measures reported in the literature for the management of CDK4/6 inhibitors AEs.

Hematological AEs are very common with CDK4/6 inhibitors and can be adequately managed with standard supportive care [126]. For non-hematological toxicities, namely for grade 1 and grade 2, no dose hold or dose adjustment is required. For grade 3 or higher toxicities, dose hold and, subsequently, dose reduction is considered [139].

Table 1.10. Pharmacological and non-pharmacological measures for the management of CDK4/6 inhibitors AEs [139,145–147].

Disorders	Adverse effect	Suggested management
Hematological	Neutropenia	✓ <u>Complete blood count:</u> - Palbociclib: prior to the start of each cycle, mid-cycle for the first two cycles, and as clinically indicated. - Ribociclib: prior to the start of the first two cycles, mid-cycle for the first two cycles, at the start of each subsequent 4 cycles, and as clinically indicated.
	Thrombocytopenia	✓ Grade 3 (<50,000–25,000/mm^3) and grade 4 (<25,000 mm3): treatment is held until recovery to 50,000/mm^3 and resumed at one dose level lower. ✓ If recurrent grade 3 or 4, two dose reductions are instituted.
	Anemia	✓ Grade 3 (hemoglobin < 8.0 g/dL) and grade 4 (life-threatening consequences): treatment should be held until improvement to grade 2 (hemoglobin < 10.0–8.0 g/dL) or better and resumed at one dose level lower. ✓ Red blood cells transfusion should follow the institutional protocol.
Gastrointestinal	Nausea/Vomiting	✓ Routine antiemetics: metoclopramide, prochlorperazine, haloperidol and serotonin 5-HT_3.
	Diarrhea	✓ Non-pharmacological measures such as hydration, dietary changes and avoidance of other offending agents; ✓ Anti-diarrheal agents such as loperamide, deodorized tincture of opium, diphenoxylate/atropine and octreotide; ✓ If significant diarrhea, prophylactic treatment should be considered.

Hepatobiliary	AST and/or ALT elevations	✓ Grade 1: no dose adjustment is required; ✓ Grade 2: dose interruption until recovery and resume at the same dose level. If recurrent, resume at next lower dose level; ✓ Grade 3: dose interruption until recovery and resume at next lower dose level. If recurrence, discontinue ribociclib; ✓ Grade 4: discontinue ribociclib.
Cardiac	QTc prolongation	✓ Avoidance of agents that prolong the QT interval; ✓ Supplementation for electrolyte abnormalities.

Abreviations: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase.

1.4. Tyrosine kinase inhibitors

1.4.1. Tyrosine Kinase – Description and mechanism of action

Kinases have emerged as one of the most intensively pursued targets, particularly in cancer research, due to their role in cellular signaling. As mentioned above, kinases are enzymes that catalyze the transfer of a phosphate group from ATP to a specific target substrate [148]. In this context, a tyrosine kinase (TK) can transfer a phosphate group from ATP to the tyrosine residues of specific proteins inside the cell.

Receptor tyrosine kinases (RTKs) are a subclass of TKs [149], of which there are nearly 60 RTKs in the human genome [150]. These proteins act as signal transducers that mediate cell-to-cell communication by phosphorylating tyrosine residues on key intracellular substrate proteins [151] and are therefore critical for maintaining cellular homeostasis [152]. RTKs consist of 3 main structures: an N-terminal extracellular ligand-binding domain, a transmembrane domain, and a C-terminal intracellular domain with TK activity. The extracellular domain has different structures and sequences, depending on the class of receptor and the ligand involved. The C-terminal region, the kinase domain, consists of an ATP-binding cleft located between the N-terminal and C-terminal lobes [153].

Considering their mechanism of activation, RTKs have two characteristics in common: (1) dimerization after binding to their ligands and (2) autophosphorylation of tyrosine residues. In normal cells, RTKs can be activated by binding of a ligand to the extracellular regions of the receptor. This binding induces receptor dimerization, and the resulting conformational change allows the TK domain to adopt an active conformation through autophosphorylation, leading to the activation of downstream signaling molecules and, consequently, biological responses [149,154]. Alterations or abnormal activation of RTKs (e.g., mutations, translocations) have been observed and described as a contributing factor in several cancers [155-157].

RTKs can be classified into 20 families, according to their structure and ligand [150]. **Table 1.11**. presents the classes of RTKs and their associated members.

Table 1.11. RTK classes and their receptive members. Adapted from [158].

RTK classes	Members
EGF	EGFR, ERBB2 (HER2), ERBB3 (HER3), ERBB4 (HER4)
Insulin	INSR IGFR
PDGF	PDGFRα, PDGFRβ, M-CSFR, KIT, FLT3L
VEGF	VEGFR1, VEGFR2, VEGFR3
FGF	FGFR1, FGFR2, FGFR3, FGFR4
CCK	CCK4
NGF	TRKA, TRKB, TRKC
HGF	MET, RON
EphR	EPHA1–6, EPHB1–6
AXL	AXL, MER, TYRO3
TIE	TIE, TEK
RYK	RYK
DDR	DDR1, DDR2
RET	RET
ROS	ROS
LTK	LTK, ALK
ROR	ROR1, ROR2
MUSK	MUSK
LMR	AATYK1, AATYK2, AATYK3
Undetermined	RTK106

Abbreviations: EGF(R), Epidermal growth factor (receptor); InsR, Insulin receptor; IGFR, Insulin-like growth factor receptor; PDGF(R), Platelet-derived growth factor (receptor); M-CSFR, Macrophage colony-stimulating growth factor; VEGF(R), Vascular endothelial growth factor (receptor); FGF(R), Fibroblast growth factor (receptor); CCK, Colon carcinoma kinase; MET, Mesenchymal-epithelial transition; NGF(R), Nerve growth factor (receptor); TRK, Tropomyosin receptor kinase; HGF(R), Hepatocyte growth factor (receptor); Eph(R), Ephrin (receptor); AXL, from the Greek word anex-elekto, or uncontrolled, a Tyro3 protein tyrosine kinase; TIE, Tyrosine kinase receptor in endothelial cells; RYK, Receptor related to tyrosine kinases; DDR, Discoidin domain receptor; RET, Rearranged during transfection; ROS, RTK expressed in some epithelial cell types; LTK, Leukocyte tyrosine kinase; ALK, Anaplastic lymphoma kinase; ROR, Receptor orphan; MuSK, Muscle-specific kinase; LMR, Lemur; AATYK, Apoptosis-associated tyrosine kinase.

1.4.2. Tyrosine kinase inhibitors – Mechanism of action

As targeted therapies, TKIs are used to interfere with the cellular pathways that regulate malignant cell growth. As a result, this class of drugs is an important option in the treatment of several types of cancer [159,160].

The majority of TKIs discovered to date compete with ATP. ATP consists of adenosine, which contains a ribose sugar and an adenine ring, and three phosphate groups. Because

of their chemical structure, small-molecules kinase inhibitors can target the ATP binding site of a kinase [153]. **Figure 1.3**. shows the mechanism of action of TKIs through competition with ATP.

According to the literature, TKIs can be divided into different categories. Initially, three types of inhibitors were identified based on their mechanisms of action and target binding modes. Type I TKIs bind to the ATP-binding site in the kinase domain through hydrogen bonds that mimic the hydrogen bonds normally formed by ATP [161]. Examples of FDA approved type I TKIs are crizotinib, dasatinib and erlotinib. Type II TKIs compete in an indirectly way with ATP by occupying the hydrophobic pocket adjacent to the ATP-binding site. In this context, the inactive conformation of the RTKs is emphasized [153]. Imatinib and sorafenib are examples of type II TKIs. In addition, the third class of TKIs bind away from the catalytic ATP-binding site and thereby modulate the activity of the kinase in an allosteric manner [162]. Trametinib and cobimetinib are classified as type III TKIs. Later, other categories of TKIs have emerged. Type IV to type VII have also been characterized as allosteric inhibitors. Type IV and type V have been described to form reversible bounds, whereas type VI and type VII have been described to form generally irreversible bonds [163].

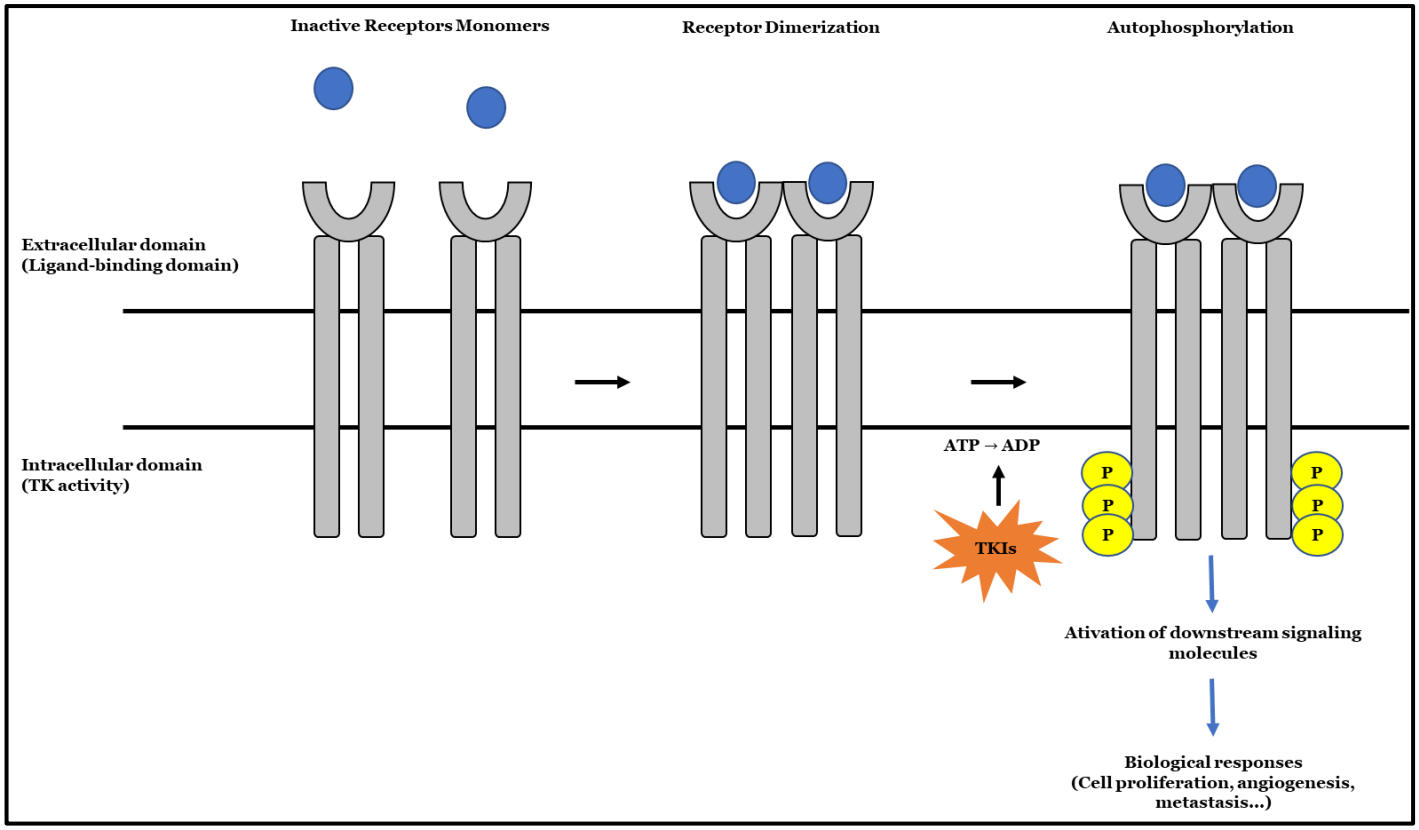

Figure 1.3. Schematic representation of the mechanism of action of TKIs.
Abbreviations: P, Phosphate group; TKIs, Tyrosine kinase inhibitors.

1.4.3. Tyrosine kinase inhibitors – Characterization and clinical development

In 2001, following the successful FDA approval of imatinib for the treatment of chronic myeloid leukemia, several potent and well-tolerated TKIs —targets including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1, HER2, neurotrophic tyrosine receptor kinase (NTRK), vascular endothelial growth factor receptor (VEGFR), rearranged during transfection (RET), MET, fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and KIT— have emerged and play an important role in cancer treatment [157,163]. According to the literature, there are 68 TKIs approved by the FDA, and several are used in the treatment of various diseases in addition to cancer, such as Crohn's disease, idiopathic pulmonary fibrosis, and ulcerative colitis [163,164]. **Table 1.12.** lists the TKIs that have been approved over the last years and their main approved clinical indications according to the FDA. All TKIs listed in the table interact with RTKs.

Table 1.12. Summary of TKIs approved by the FDA. Adapted from [163].

Drug	First approval year FDA/EMA	Main therapeutic area
Afatinib	2013/2013	NSCLC
Alectinib	2015/2017	NSCLC
Avapritinib	2020/2020	Gastrointestinal stromal tumors
Axitinib	2012/2012	RCC
Brigatinib	2017/2018	NSCLC
Cabozantinib	2012/2014 (capsules), 2016 (tablets)	R.CC; HCC; DTC; MTC
Capmatinib	2020/2022	NSCLC
Ceritinib	2014/2015	NSCLC resistant to crizotinib
Crizotinib	2011/2012	NSCLC
Dacomitinib	2018/2019	NSCLC
Entrectinib	2019/2020	Solid tumors expressing NTRK gene fusion; NSCLC
Erlotinib	2004/2005	NSCLC, pancreatic neoplasms
Fostamatinib	2018/2020	Thrombocytopenia
Gefitinib	2003/2009	NSCLC
Gilteritinib	2018/2019	Acute myeloid leukemia
Lapatinib	2007/2008	Breast Neoplasms
Larotrectinib	2018/2019	Solid tumors expressing NTRK gene fusion
Lenvatinib	2015/2015	Thyroid Neoplasms
Lorlatinib	2018/2019	NSCLC
Midostaurin	2017/2017	Acute myeloid leukemia, Mastocytosis
Neratinib	2017/2018	Breast Neoplasms
Nintedanib	2014/2015	Idiopathic Pulmonary Fibrosis

Osimertinib	2015/2016	NSCLC
Pazopanib	2009/2010	RCC
Pemigatinib	2020/2021	Cholangiocarcinoma
Pralsetinib	2020/2021	NSCLC
Regorafenib	2012/2013	Colorectal Neoplasms; HCC
Ripretinib	2020/2021	Gastrointestinal stromal tumors
Selpercatinib	2020/2021	NSCLC; thyroid neoplasms
Sorafenib	2005/2006	HCC; RCC
Sunitinib	2006/2021	Gastrointestinal stromal tumors; RCC; neuroendocrine tumors
Tepotinib	2021/2022	NSCLC
Tivozanib	2021/2017	RCC
Tucatinib	2020/2021	Breast neoplasms
Vandetanib	2011/2012	Thyroid neoplasms

Abbreviations: NSCLC, Non-small cell lung cancer; RCC, Renal cell carcinoma; HCC, Hepatocellular carcinoma; DTC, Differentiated thyroid carcinoma; MTC, Medullary thyroid cancer; NTRK, Neurotrophic tyrosine receptor kinase.

In the following sections, two TKIs widely used in oncology are discussed in more detail, as well as the AEs associated with these inhibitors.

1.4.3.1. Cabozantinib

Cabozantinib is an oral multiple RTK inhibitor with activity against VEGFR 1, 2, 3, HGF (MET), AXL, the angiopoietin receptor TIE-2, RET, KIT, and FLT-3 in vitro and in vivo [165]. This drug is approved by the EMA in several therapeutic indications. Cabozantinib, in tablet pharmaceutical form, is indicated for advanced RCC: (1) as a first-line treatment of adult patients with intermediate or poor risk in terms of prognosis and (2) in adults who have received prior VEGF-targeted therapy. Considering the RCC treatment, cabozantinib can also be used in combination with nivolumab, a monoclonal antibody, as a first-line treatment. In addition, cabozantinib in tablet pharmaceutical form is approved as a monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib and in adults with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine who have progressed during or after prior systemic therapy [166,167]. Several clinical trials have reported the efficacy and effectiveness of cabozantinib as monotherapy. The phase III METEOR trial (NCT01865747) and the phase II CABOSUN trial (NCT01835158) are examples of trials evaluating cabozantinib in patients with RCC [168,169]. The phase III CELESTIAL trial (NCT01908426) reported significant results in patients with HCC who had been treated with sorafenib [170]. In addition, the phase III COSMIC-311 trial (NCT03690388) showed a significant

prolonged PFS in patients taking cabozantinib with progressive radioiodine-refractory DTC who had previously received a VEGFR-targeted therapy such as sorafenib and lenvatinib [171]. Studies in other types of solid tumors have also been developed, particularly in patients diagnosed with mCRPC and in non-small cell lung cancer (NSCLC) [172,173].

In addition, cabozantinib, in capsule pharmaceutical form, is approved for adults with progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC). In fact, cabozantinib showed a manageable AE profile and significantly improved PFS and response rates in patients with progressive metastatic MTC, including those previously treated with other TKIs [174]. Note that, tablets and capsules are not bioequivalent and should not be used interchangeably [175].

1.4.3.2. Lorlatinib

Lorlatinib was approved for the treatment in patients with ALK-positive advanced NSCLC who have not received prior treatment with an ALK inhibitor and whose disease has progressed after receiving (1) alectinib or ceritinib as the first ALK TKI therapy or (2) crizotinib and at least one other ALK TKI [176]. In fact, the approval of this drug appeared to address drug resistance and improve brain penetration in patients [177].

The efficacy of lorlatinib was confirmed in the global phase II portion of a phase I/II study (NCT03052608). In this context, this trial highlighted the promising antitumor activity in treatment-naïve patients with ALK-positive advanced NSCLC and demonstrated that lorlatinib was a treatment option for patients whose disease has progressed after treatment with crizotinib, alectinib, ceritinib and brigatinib [178]. Other clinical trials have shown good results with lorlatinib. The phase III CROWN trial (NTC03052608) described the durable benefit of lorlatinib over crizotinib in patients with treatment-naïve ALK-positive NSCLC and supported the use of lorlatinib as first-line therapy in patients with and without baseline brain metastases [179]. Indeed, lorlatinib has excellent central nervous system penetration and has been shown to be effective in patients with intracranial metastases [180].

1.4.4. Adverse effects of tyrosine kinase inhibitors

With the widespread use of TKIs, an increasing frequency of TKI-induced AEs has been highlighted. These effects can be classified as mild to life-threatening, affecting multiple organ systems. The following sections describe the most common AEs associated with

TKIs. The frequency of several AEs associated with cabozantinib and lorlatinib is also discussed.

1.4.4.1. Cardiovascular disorders

Cardiotoxicity has been reported as a notable ADR of TKIs, ranging from hypertension, atrial fibrillation, reduced cardiac function, and heart failure to sudden death [160]. In the METEOR and CABOSUN clinical trials, hypertension was one of the AEs reported associated with cabozantinib. In METEOR trial, 73 (22%) out of 331 patients reported grade 1-2 hypertension [168]. In the CABOSUN study, 63 (80.8%) out of 78 patients reported hypertension of any-grade [169]. In CELESTIAL trial, one of the most common grade 3 or 4 AE in the cabozantinib group was hypertension [170]. According to the SmPC of cabozantinib and lorlatinib, hypertension is classified as a very common reaction [166,176]. In addition, according to the results of a phase 3 study reported by Shaw *et al.*, patients taking lorlatinib experienced more grade 3-4 hypertension than grade 1 hypertension [181]. Cirmi *et al.* performed an analysis using the FAERS database, which reported several cardiovascular toxicities such as heart failure, embolic and thrombotic events, hypertension, ischemic heart disease and QT prolongation. In fact, most reports resulted in initial or prolonged hospitalization, death, and other serious events [182].

1.4.4.2. Hematological disorders

Hematological disorders such as anemia have also been associated with patients taking TKIs. According to the lorlatinib SmPC, anemia is considered a very common reaction in patients taking this drug [176]. Anemia is considered a common AE of ALK-TKIs. Tao *et al.* performed a systematic review and meta-analysis of patients with ALK-positive NSCLC. Although anemia was more commonly associated with other ALK-TKIs such as alectinib, ceritinib and crizotinib, this AE was reported in lorlatinib patients with a pooled incidence of 9.5% [183]. In patients taking cabozantinib, anemia and thrombocytopenia are considered very common AEs. In fact, both AEs have been reported in the cabozantinib clinical trials. In the CABOSUN clinical trial, anemia and thrombocytopenia of any-grade occurred in 33.3% and 39.7% of patients taking this drug, respectively [169]. In real-world studies, anemia and thrombocytopenia were also reported as hematological disorders in patients taking cabozantinib. However, grade 3-4 anemia and thrombocytopenia were not commonly associated with cabozantinib [184].

1.4.4.3. Gastrointestinal disorders

TKIs are often associated with gastrointestinal AEs, particularly diarrhea. Studies have shown that diarrhea can occur in 30-90% of patients treated with TKIs, depending on the specific TKI used [185]. Other gastrointestinal AEs reported include nausea, vomiting, dyspepsia, and constipation [8]. According to the SmPC, diarrhea, nausea and constipation are very common reactions associated with cabozantinib and lorlatinib [166], [176]. In METEOR trial, grade 1-2 diarrhea was the most reported AE in patients taking cabozantinib. In a total of 331 patients, 206 (62%) experienced diarrhea, 158 (48%) experienced nausea, 106 (32%) experienced vomiting and 89 (27%) experienced constipation [168]. The results of CELESTIAL trial also highlighted diarrhea of any-grade in patients taking cabozantinib. More than half of the patients in this trial experienced diarrhea, followed by nausea, vomiting and constipation [170]. In addition, Solomon *et al.* reported diarrhea in 10% of patients, followed by vomiting in patients taking lorlatinib [178]. The mechanisms of TKI-induced diarrhea are not well described [185]. However, in patients taking cabozantinib, gastrointestinal AEs may be related to cabozantinib's inhibition of VEGFR, which is highly expressed in the intestine [186].

1.4.4.4. Others

Other AEs have been associated with TKIs. Hypercholesterolemia and hypertriglyceridemia are very common reactions in patients taking lorlatinib. These reactions usually occur within the first few weeks of treatment [187]. Solomon *et al.* reported that hypercholesterolemia (66%) and hypertriglyceridemia (45%) were the most reported AEs associated with lorlatinib [178]. However, these AEs rarely led to dose delay or dose reduction [187]. In contrast, cabozantinib is highly associated with AST/ALT and bilirubin elevations. These reactions are classified as very common in the SmPC [166]. In CELESTIAL trial, an AST increase of any-grade was observed in 105 (22%) out of 467 patients. This AE was considered one of the most common grade 3 or 4 AE in the cabozantinib group and one of the most common AE of any-grade leading to dose reduction [170].

Cabozantinib is also strongly associated with cutaneous toxicities. Hand-foot skin reaction, also known as palmar-plantar erythrodysesthesia syndrome (PPES), is classified as a very common AE in patients taking cabozantinib [166]. In METEOR study, 115 (35%) out of 331 patients experienced PPES [168]. This was also observed in the CELESTIAL trial. PPES was considered the most common high-grade event (17% with cabozantinib versus 0% with placebo) [170]. Rash has also been reported with VEGFR-TKIs [186], [188].

According to pivot trials, approximately 20% of patients receiving lorlatinib experienced cognitive effects and behavioral changes. Sisi *et al.* reported on a study of spontaneous reports submitted to the FAERS database. Among the ALK inhibitors studied, lorlatinib showed a higher frequency of reports of psychiatric disorders, with mood disorders, psychotic disorders, anxiety, agitation, and irritability being highlighted [189]. Cognitive effects included memory impairment, cognitive dysfunction, and amnesia [187]. According to lorlatinib SmPC, mood effects are classified as a very common reaction in patients taking this drug. Psychotic effects and changes in mental status are listed as common reactions [176]. Cognitive effects are also reported to be very common in the SmPC [176]. These AEs usually occur within the first 2 months of treatment and are usually grade≤2 in terms of seriousness [187]. The mechanism underlying psychiatric disorders with ALK inhibitors is still unclear. However, ALK may play a role in the internalization and regulation of the dopamine D2 receptor, which is involved in cognition and controls motor function and motivation [190]. As with other anticancer drugs, fatigue is a very common AE of TKIs [8,166,176].

1.4.5. Management of adverse effects

The previous section reported on AEs associated with TKIs, with a particular focus on patients taking cabozantinib and lorlatinib. EGFR-TKIs are typically associated with a variety of serious dermatological reactions, diarrhea, and hepatotoxicity [191]. In addition, patients taking ALK inhibitors commonly report gastrointestinal disturbances such as diarrhea, nausea and vomiting, and cardiac toxicity [192]. **Table 1.13.** and **Table 1.14.** describe several pharmacological and non-pharmacological measures reported in the literature for the management of TKIs, especially for cabozantinib and lorlatinib.

Table 1.13. Pharmacological and non-pharmacological measures for the management of the most common AEs associated with cabozantinib [193-195].

Disorders	Adverse effect	Suggested management
Vascular	Hypertension	✓ Blood pressure should be monitored regularly; ✓ Follow hypertension management guidelines: the antihypertensive agent should be carefully considered due to potential inhibition of CYP3A4.
Gastrointestinal	Diarrhea	✓ Dietary adjustments may be used to relieve diarrhea including probiotics, continuous oral hydration, small and frequent meals; avoid foods and drinks containing lactose; ✓ Loperamide may be considered in appropriate patients.
	Nausea/vomiting	✓ Consider metoclopramide and ondansetron, although there are no evidence-based recommendations.
Cutaneous	PPES	✓ Prophylactic measures such as removal of hyperkeratosis and protection of pressure sensitive areas should be considered. Recommendations include the use of thick cotton gloves and socks, padded insoles in shoes, and avoidance of heat or friction on the hands and feet; ✓ Urea cream and clobetasol cream can be used as treatments.
Hepatobiliary	AST, ALT, and bilirubin elevations	✓ Laboratory tests should be performed prior to treatment and closely monitored: (1) every 2 weeks for the first 8 weeks of treatment and (2) every 4 weeks thereafter; ✓ Patients whose baseline ALT, AST, and total bilirubin are ≤ 3 times the upper limit of normal (ULN) and who develop a grade 3 or higher increase in any of these parameters during cabozantinib treatment should have their treatment interrupted; ✓ Cabozantinib should be permanently discontinued if ALT or AST are elevated > 3 times ULN with concomitant elevation of total bilirubin > 2 times ULN or if hepatic dysfunction does not resolved after treatment interruption.
General disorders	Fatigue	✓ Aerobic exercise reduces fatigue in fit patients ; ✓ Testosterone monitoring should be considered in male patients; ✓ Consider psychostimulants such as methylphenidate and corticosteroids; ✓ If hypothyroidism is present, consider correcting this condition.

Abreviations: PPES, Palmar-plantar erythrodysaesthesia syndrome; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ULN, Upper limit of normal.

Table 1.14. Pharmacological and non-pharmacological measures for the management of the most common AEs associated with lorlatinib [187,196,197].

Disorders	Adverse effects	Suggested management
Hematological	Anemia	✓ Iron supplementation, erythropoietin therapy and blood transfusion should be considered; ✓ Consider blood transfusion if hemoglobin<6 g/dL
Gastrointestinal	Diarrhea	✓ Management with standard medical therapy such as loperamide and probiotics; ✓ Dietary modification: avoid dairy products, light diet and eat several small meals; ✓ Suspend use of lorlatinib until resolution to grade≤1, if grade 3-4.
	Constipation	✓ Increase fluid intake, eat a high-fibre diet and take regular exercise; ✓ Laxatives such as lactulose and polyethylene glycol should be considered.
Metabolism and nutrition	Hyperlipidemia (Hypercholesterolemia and hypertriglyceridemia)	✓ Patients should have their lipid profile analyzed 1-3 months after starting lorlatinib treatment. Thereafter, annual monitoring is recommended for those with adequate lipid levels. Others should be assessed 1-3 months after initiation or adjustment of lipid-lowering medication; ✓ Appropriate medical therapy (lipid-lowering agents) and dose interruption; ✓ Consider dose modification for more severe (grade≥3) and difficult-to-treat AEs.
Mood	Anxiety, irritability, and depression	✓ Benzodiazepines and antidepressants may be considered for the relief and treatment of anxiety and/or depression; ✓ Treatment should be interrupted if symptoms are perceived to be moderate to severe (grade 2 or higher) and resumed f symptoms improve to grade 1.
Cognitive	Memory impairment, cognitive disorders, and amnesia	✓ Dose modification or dose reduction should be considered if patients' usual activities or relationships are affected by cognitive effects; ✓ Referral for neurological consultation.

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Chapter 2
Materials and Methods

Chapter 2

Materials and Methods

2.1. Data source and data extraction

Two data sources were used to analyze the safety profile of the targeted drugs considered in this study:

- A national database, provided by the PPS, and a European database, provided by the EV. The PPS is coordinated by the INFARMED, I.P. and it is responsible for monitoring the safety of medicines with marketing authorization through the collection and evaluation of ADR reports, the identification of risks associated with medicines in use, the implementation of risk minimization measures and the communication of these results to HCP, patients, caregivers, and citizens in general [1]. Also, the PPS is composed by 9 Regional Pharmacovigilance Units located in several different parts of Portugal [2]. The request for access to the ICSRs was made through the Pharmacovigilance Unit of Beira Interior and addressed to INFARMED, I.P. by filling a specific form for the purpose and signing a confidentiality agreement, during July and August 2023.

- In addition, concerning the European database, data on ICSRs were retrieved from the website of suspected ADR of the EV database by accessing www.adrreports.eu (accessed on 2 August 2023). The EV is a system for managing and analyzing ICSRs of suspected ADR related to medicines which have been authorized or are being studied in clinical trials in the European Economic Area [3,4].

The targeted drugs considered for this study were selected based on some points namely: their recent marketing authorization date in Portugal and their approved clinical indications, which cover a wide range of therapeutic actions. In this context, we analyzed the safety data for the following targeted drugs: olaparib, niraparib and talazoparib, which belong to the PARPi class; palbociclib, ribociclib and abemaciclib, which belong to the CDK4/6 inhibitors class and cabozantinib and lorlatinib, which are classified as TKIs.

2.2. Individual Case Safety Reports selection

- The PPS provided the information on ICSRs via Office® Excel® files considering the years 2020, 2021 and 2022 for the following suspected drugs: olaparib,

niraparib, palbociclib, ribociclib, abemaciclib, cabozantinib and lorlatinib. Talazoparib was not included in the analysis due to a lack of reports in the years considered. Only one ICSR was provided for the year 2021. All suspected ADR reports in which the above drugs were not described as the only suspected drug were excluded. Information was collected on sex, age group, reporter group, individual cases reported by SOC, outcome, seriousness, seriousness criteria, most reported PTs (20 most reported PTs were considered), number of concomitant medicines per ICSR, and clinical indications.

- In the EV database, by using the line listing function, we selected all ICSRs with olaparib, niraparib, talazoparib, palbociclib, ribociclib, abemaciclib, cabozantinib and lorlatinib as the suspected drug, considering the year 2022. All suspected ADR reports in which the above drugs were not described as the only suspected drug were excluded. Information was collected on sex, age group, reporter group, geographic origin, individual cases reported by SOC, and seriousness. Taking into account the last point, a more detailed analysis was carried out from 1 November 2022 to 31 December 2022. Information was collected on sex, age group, outcome, seriousness, seriousness criteria, most reported PTs (20 most reported PTs were considered), action taken, number of concomitant medicines per ICSR, and clinical indications.

- Categorical variables were described by their absolute and relative frequencies using Office® Excel® 365 software, version 2208 (Microsoft Corporation, Redmond, WA, USA). Pearson's Chi-Square test was used to verify a possible relationship between the variables with a statistical significance level of 5% ($p < 0.05$). In this case, IBM SPSS Statistics 28 (IBM, Armonk, NY, USA) was used.

- Each ICSR may include one or more suspected ADR. The ADR included in each ICSR were analyzed according to the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a rich and highly specific standardized medical terminology to facilitate the international sharing of regulatory information for medical products used by humans ((https://www.meddra.org, accessed on 2 August 2023).

- According to the International Council on Harmonization E2D (Post Approval Safety Data Management: Definition and Standards for Expedited Reporting E2D) guideline, a case is classified as "serious" if it results in death, is considered

life threatening, requires or prolongs hospitalization, results in disability/incapacity, determines a congenital anomaly/birth defect, or results in other medically important event or reaction [5]. For the ICSRs that described two or more seriousness criteria, we considered the most serious seriousness criteria. In addition, in case of two or more ADR with a different outcome reported in a single ICSR, the outcome with the lower level of resolution was considered. The suspected ADR described in each ICSR were grouped according to the SOC.

2.3. References

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Chapter 3
Results

Chapter 3

Results

3.1. PARP inhibitors

3.1.1. National Database Results

3.1.1.1. Main Characteristics of ICSRs

A total of 53 ICSRs with olaparib and niraparib as the suspected drug were reported to the PPS database in 2020, 2021 and 2022. More specifically, 39 ICSRs related to olaparib and 14 ICSRs related to niraparib. The majority of cases were associated with female patients (N = 47, 88.7%) and only 1 case was described as "not specified" (N = 1, 1.9%) in terms of gender. Many of the ICSRs involved patients aged 18-64 years (N = 20, 37.7%) and 65-85 (N = 10, 18.9%) years. Almost 45% of ICSRs were classified as "not specified" in terms of age group. Many cases were reported by HCP (N = 49, 92.5%).

Considering the individual cases reported by SOC, "Blood and lymphatic disorders" was the most reported SOC in the ICSRs analyzed. The SOCs "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" and "General disorders and administration site conditions" were also found to have a similar number of reported ICSRs (17 and 16 ICSRs, respectively), followed by "Gastrointestinal disorders" (12 ICSRs). Concerning the seriousness of reported cases, almost 70% of cases were classified as serious (N = 37, 69.8%). In this sense, no statistically significance difference (p = 0.2287) was found between the seriousness and the drugs studied. For concomitant medicines, most ICSRs did not provide this information (N = 39, 73.5%). Ovarian cancer was highlighted as the main clinical indication treated in the ICSRs (N = 22, 41.5%), although in a good percentage of cases the clinical indication was not described (N = 18, 34.0%). These results are presented in detail in **Table 3.1.**

Table 3.1. Demographic characteristics of ICSRs involving olaparib and niraparib as the suspected drug in 2020, 2021 and 2022, according to the PPS database.

	Individual Case Safety reports (%)		
	Olaparib N=39	Niraparib N=14	Total N=53
Sex			
Male	5 (12.8)	0	5 (9.4)

Female	34 (87.2)	13 (92.9)	47 (88.7)
Not specified	0	1 (7.1)	1 (1.9)
Age group			
Pediatrics (<18 years)	0	0	0
Adult (18-64 years)	14 (35.9)	6 (42.8)	20 (37.7)
Elderly (65-85 years)	6 (15.4)	4 (28.6)	10 (18.9)
Very Elderly (>85 years)	0	0	0
Not Specified	19 (48.7)	4 (28.6)	23 (43.4)
Reporter group			
HCP	36 (92.3)	13 (92.9)	49 (92.5)
Non-HCP	3 (7.7)	1 (7.1)	4 (7.5)
Individual cases reported by SOC			
Total number of individual cases	**71**	**29**	**100**
Blood and lymphatic disorders	20 (28.2)	9 (31.0)	29 (29.0)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	16 (22.6)	1 (3.4)	17 (17.0)
General disorders and administration site conditions	11 (15.5)	5 (17.3)	16 (16.0)
Gastrointestinal disorders	9 (12.7)	3 (10.4)	12 (12.0)
Injury, poisoning and procedural complications	4 (5.6)	6 (20.7)	10 (10.0)
Skin and subcutaneous tissue disorders	2 (2.8)	2 (7.0)	4 (4.0)
Nervous system disorders	3 (4.2)	0	3 (3.0)
Respiratory, thoracic, and mediastinal disorders	2 (2.8)	0	2 (2.0)
Psychiatric disorders	1 (1.4)	1 (3.4)	2 (2.0)
Investigations	0	1 (3.4)	1 (1.0)
Renal and urinary disorders	1 (1.4)	0	1 (1.0)
Hepatobiliary disorders	1 (1.4)	0	1 (1.0)
Immune system disorders	1 (1.4)	0	1 (1.0)
Musculoskeletal and connective tissue disorders	0	1 (3.4)	1 (1.0)
Number of individual cases [a]			
Serious	29 (74.4)	8 (57.1)	37 (69.8)
Non-serious	10 (25.6)	6 (42.9)	16 (30.2)
Concomitant medicines per ICSR			
1	0	0	0
2	1 (2.6)	1 (7.1)	2 (3.8)
3	1 (2.6)	1 (7.1)	2 (3.8)
4	1 (2.6)	1 (7.1)	2 (3.8)
5 or more	3 (7.6)	5 (35.8)	8 (15.1)
Not reported	33 (84.6)	6 (42.9)	39 (73.5)
Clinical indications			
Ovarian cancer	13 (33.3)	9 (64.3)	22 (41.5)
Breast cancer	6 (15.4)	0	6 (11.3)
Prostate cancer	4 (10.3)	0	4 (7.5)
Pancreatic cancer	3 (7.7)	0	3 (5.7)

Unknown	13 (33.3)	5 (35.7)	18 (34.0)

[a] Pearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).

Abbreviations: HCP, Healthcare professionals; SOC, System Organ Class.

3.1.1.2. Characteristics of Adverse Events

A detailed analysis of the ADR of ICSRs reported above was performed considering olaparib and niraparib as the suspected drug in the years 2020, 2021 and 2022. According to the outcome of the reported ADR, most cases were not clear about it (N = 36, 68.0%). "Recovered/Resolved" resolution was noted in both olaparib and niraparib cases. The majority of serious cases were classified as "other medically important information" criteria (N = 26, 70.3%). A total of 4 fatal cases were reported.

Anemia was the most reported ADR in patients taking olaparib and niraparib, followed by disease progression, particularly associated with olaparib. Thrombocytopenia was associated with both PARPi analyzed. On the other hand, neutropenia and nausea were more reported in patients taking olaparib. These results are shown in detail in **Table 3.2.**

Table 3.2. Characteristics of reported ADR involving olaparib and niraparib as the suspected drug in 2020, 2021 and 2022, according to the PPS database.

	Individual Case Safety reports (%)		
	Olaparib N=39	Niraparib N=14	Total N=53
Outcome [a]			
Recovered/Resolved	4 (10.3)	4 (28.6)	8 (15.1)
Recovered/Resolved with Sequelae	0	0	0
Recovering/Resolving	4 (10.3)	0	4 (7.5)
Not recovered/Not resolved	0	1 (7.1)	1 (1.9)
Fatal	4 (10.3)	0	4 (7.5)
Unknown	27 (69.1)	9 (64.3)	36 (68.0)
Seriousness criteria [b]			
Total number of serious cases	**29**	**8**	**37**
Other (other medically important information)	20 (69.0)	6 (75.0)	26 (70.3)
Congenital	0	0	0
Disability	1 (3.4)	0	1 (2.7)
Hospitalization	3 (10.4)	1 (12.5)	4 (10.8)
Life threatening	1 (3.4)	1 (12.5)	2 (5.4)
Death	4 (13.8)	0	4 (10.8)
Most reported symptoms [c]			
Total number of symptoms reported	**83**	**38**	**121**
Anemia	12 (14.5)	6 (15.8)	18 (14.9)
Disease progression [d]	10 (12.0)	2 (5.2)	12 (9.9)

Thrombocytopenia	5 (6.0)	4 (10.5)	9 (7.4)
Fatigue [e]	7 (8.4)	2 (5.2)	9 (7.4)
Neutropenia	7 (8.4)	0	7 (5.8)
Nausea	5 (6.0)	1 (2.6)	6 (5.0)
Toxicity to various agents	0	6 (15.8)	6 (5.0)
Hematotoxicity	3 (3.6)	2 (5.2)	5 (4.1)
Ovarian cancer recurrent	3 (3.6)	0	3 (2.5)
Oedema peripheral	1 (1.2)	1 (2.6)	2 (1.7)
Pneumonitis	2 (2.4)	0	2 (1.7)
Rash	2 (2.4)	0	2 (1.7)
Vomiting	2 (2.4)	0	2 (1.7)
Abdominal discomfort	1 (1.2)	0	1 (0.8)
Abdominal distension	0	1 (2.6)	1 (0.8)
Abdominal pain upper	1 (1.2)	0	1 (0.8)
Acute leukemia	1 (1.2)	0	1 (0.8)
Anxiety	1 (1.2)	0	1 (0.8)
Constipation	0	1 (2.6)	1 (0.8)
Insomnia	0	1 (2.6)	1 (0.8)

[a] In case of more than one event/outcome, the worst outcome was considered.

[b] In case of more than one seriousness criteria described, the most serious was considered.

[c] 20 most reported PTs were considered.

[d] Disease progression includes PTs of disease progression, malignant neoplasm progression and neoplasm progression.

[e] Fatigue includes PTs of fatigue and asthenia.

3.1.2. EudraVigilance Database Results

3.1.2.1. Main Characteristics of ICSRs

A total of 3037 ICSRs were extracted and analyzed from the EV database, considering olaparib, niraparib and talazoparib as the suspected drug in 2022. In this context, it is possible to observe the difference in the number of ICSRs analyzed, namely: 1175 ICSRs related to olaparib, 1811 to niraparib and only 51 to talazoparib. Female patients were the most reported (N = 2838, 93.4%), particularly in the age groups 18-64 (N = 965, 31.8%) and 65-85 (N = 868, 28.6%) years. However, a high number of ICSRs were classified as "not specified" in terms of age group (N = 1164, 38.3%). HCP reported a large number of cases (N = 2385, 78.5%) from the Non-European Economic Area (N = 2593, 85.4%).

"Investigations" and "Blood and lymphatic disorders" were the most reported SOCs in the individual cases analyzed with 1141 and 1114 ICSRs, respectively. Also, it is notable the high number of cases mentioning symptoms included in other SOCs such as "General disorders and administration site conditions", "Neoplasms benign, malignant and unspecified (incl cysts and polyps)", "Gastrointestinal disorders", "Injury, poisoning and procedural complications" and "Nervous disorders", particularly related to niraparib.

Serious cases were the most highlighted (N = 2736, 90.1%) compared to non-serious cases (N = 301, 9.9%). In this sense, a statistically significant difference ($p < 0.00001$) was found between seriousness and the drugs in study. **Table 3.3**. describes these results in detail.

Table 3.3. Demographic characteristics of ICSRs involving olaparib, niraparib and talazoparib as the suspected drug in 2022, according to the EV database.

	Individual Case Safety reports (%)			
	Olaparib N=1175	Niraparib N=1811	Talazoparib N=51	Total N=3037
Sex				
Male	133 (11.3)	2 (0.1)	2 (3.9)	137 (4.5)
Female	1004 (85.5)	1786 (98.6)	48 (94.1)	2838 (93.4)
Not specified	38 (3.2)	23 (1.3)	1 (2.0)	62 (2.1)
Age group				
Pediatrics (<18 years)	1 (0.1)	0	0	1
Adult (18-64 years)	355 (30.2)	575 (31.8)	35 (68.6)	965 (31.8)
Elderly (65-85 years)	293 (24.9)	567 (31.3)	8 (15.7)	868 (28.6)
Very Elderly (>85 years)	13 (1.1)	26 (1.4)	0	39 (1.3)
Not Specified	513 (43.7)	643 (35.5)	8 (15.7)	1164 (38.3)
Reporter group				
HCP	1026 (87.3)	1330 (73.4)	29 (56.9)	2385 (78.5)
Non-HCP	149 (12.7)	481 (26.6)	22 (43.1)	652 (21.5)
Geographic origin				
European Economic Area	282 (24.0)	142 (7.8)	20 (39.2)	444 (14.6)
Non-European Economic Area	893 (76.0)	1669 (92.2)	31 (60.8)	2593 (85.4)
Individual cases reported by SOC				
Total number of individual cases	**2090**	**5929**	**84**	**8103**
Investigations	274 (13.1)	854 (14.4)	13 (15.5)	1141 (14.1)
Blood and lymphatic disorders	533 (25.5)	556 (9.4)	25 (29.7)	1114 (13.8)
General disorders and administration site conditions	220 (10.5)	776 (13.1)	5 (6.0)	1001 (12.4)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	242 (11.6)	673 (11.4)	6 (7.1)	921 (11.4)
Gastrointestinal disorders	217 (10.4)	581 (9.8)	5 (6.0)	803 (9.9)
Injury, poisoning and procedural complications	80 (3.9)	361 (6.1)	5 (6.0)	446 (5.5)
Nervous system disorders	80 (3.9)	336 (5.7)	0	416 (5.1)
Respiratory, thoracic, and mediastinal disorders	94 (4.5)	187 (3.2)	3 (3.6)	284 (3.5)
Psychiatric disorders	13 (0.6)	241 (4.1)	0	254 (3.1)
Musculoskeletal and connective tissue disorders	34 (1.6)	188 (3.1)	1 (1.2)	223 (2.8)
Vascular disorders	32 (1.5)	188 (3.1)	1 (1.2)	221 (2.7)

Infections and infestations	40 (1.9)	175 (2.9)	2 (2.4)	217 (2.6)
Skin and subcutaneous tissue disorders	56 (2.7)	142 (2.4)	4 (4.7)	202 (2.5)
Metabolism and nutrition disorders	48 (2.3)	143 (2.4)	1 (1.2)	192 (2.4)
Renal and urinary disorders	33 (1.6)	136 (2.3)	0	169 (2.1)
Surgical and medical procedures	2 (0.1)	121 (2.1)	2 (2.4)	125 (1.5)
Cardiac disorders	14 (0.6)	94 (1.6)	4 (4.7)	112 (1.4)
Hepatobiliary disorders	26 (1.3)	35 (0.6)	3 (3.6)	64 (0.8)
Eye disorders	7 (0.3)	46 (0.8)	0	53 (0.7)
Immune system disorders	15 (0.7)	16 (0.3)	4 (4.7)	35 (0.4)
Reproductive system and breast disorders	5 (0.2)	26 (0.4)	0	31 (0.4)
Ear and labyrinth disorders	2 (0.1)	24 (0.4)	0	26 (0.3)
Product issues	13 (0.6)	6 (0.1)	0	19 (0.2)
Social circumstances	5 (0.2)	13 (0.2)	0	18 (0.2)
Endocrine disorders	1 (0.1)	9 (0.1)	0	10 (0.1)
Congenital, familial, and genetic disorders	4 (0.2)	2	0	6 (0.1)
Number of individual cases [a]				
Serious	949 (80.8)	1745 (96.4)	42 (82.4)	2736 (90.1)
Non-serious	226 (19.2)	66 (3.6)	9 (17.6)	301 (9.9)

[a] Pearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).

Abbreviations: HCP, Healthcare professionals; SOC, System Organ Class.

3.1.2.2. Characteristics of Adverse Events

A detailed analysis of the ICSRs described above was performed considering olaparib, niraparib and talazoparib as the suspected drug in a more restricted period (2 months – from 1 November 2022 to 31 December 2022). In this context, 623 ICSRs were considered, being the female group (N = 564, 90.5%) in the 18-64 (N = 192, 30.8%) and 65-85 (N = 184, 29.6%) age groups the most reported in terms of sex and age group. In terms of outcome resolution, most cases were classified as "unknown" (N = 400, 64.2%). A similar number of cases were reported with an outcome of "recovered/resolved" and "not recovered/not resolved", 81 and 77 ICSRs, respectively. It is important to note that 22 ICSRs were considered fatal, especially in patients taking olaparib and niraparib. "Other medically important information" was the most described seriousness criteria (N = 350, 68.8%). In addition, 107 cases required/prolonged hospitalization.

Anemia was the most reported ADR within the PARPi studied, mainly in patients taking olaparib. Platelet count decreased, nausea and fatigue were more reported in patients taking niraparib. In patients with ovarian cancer (N=455, 73.0%), drug withdrawal was the most common action taken (N = 370, 59.4%). For concomitant medicines, many of

the ICSRs did not describe any information in this area (N = 501, 80.4%). These findings are described in **Table 3.4**.

Table 3.4. Characteristics of reported ADR involving olaparib, niraparib and talazoparib as the suspected drug along 2 months (from 1 November to 31 December 2022), according to the EV database.

	Individual Case Safety reports (%)			
	Olaparib N=297	Niraparib N=318	Talazoparib N=8	Total N=623
Sex				
Male	47 (15.8)	0	0	47 (7.6)
Female	242 (81.5)	314 (98.7)	8 (100.0)	564 (90.5)
Not specified	8 (2.7)	4 (1.3)	0	12 (1.9)
Age group				
Pediatrics (<18 years)	0	0	0	0
Adult (18-64 years)	97 (32.6)	90 (28.3)	5 (62.5)	192 (30.8)
Elderly (65-85 years)	67 (22.6)	116 (36.5)	1 (12.5)	184 (29.6)
Very Elderly (>85 years)	5 (1.7)	7 (2.2)	0	12 (1.9)
Not Specified	128 (43.1)	105 (33.0)	2 (25.0)	235 (37.7)
Outcome [a]				
Recovered/Resolved	46 (15.5)	33 (10.4)	2 (25.0)	81 (13.0)
Recovered/Resolved with Sequelae	0	0	0	0
Recovering/Resolving	19 (6.4)	24 (7.6)	0	43 (6.9)
Not recovered/Not resolved	38 (12.8)	38 (11.9)	1 (12.5)	77 (12.4)
Fatal	12 (4.0)	10 (3.1)	0	22 (3.5)
Unknown	182 (61.3)	213 (67.0)	5 (62.5)	400 (64.2)
Number of individual cases				
Serious	194 (65.3)	307 (96.5)	8 (100.0)	509 (81.7)
Non-serious	103 (34.7)	11 (3.5)	0	114 (18.3)
Seriousness criteria [b]				
Total number of serious cases	**194**	**307**	**8**	**509**
Other (other medically important information)	128 (66.0)	214 (69.7)	8 (100.0)	350 (68.8)
Congenital	0	0	0	0
Disability	0	1 (0.3)	0	1 (0.2)
Hospitalization	32 (16.5)	75 (24.4)	0	107 (21.0)
Life threatening	22 (11.3)	7 (2.3)	0	29 (5.7)
Death	12 (6.2)	10 (3.3)	0	22 (4.3)
Most reported symptoms [c]				
Total number of symptoms reported	**603**	**1580**	**21**	**2204**
Anemia	112 (18.6)	40 (2.5)	3 (14.3)	155 (7.0)
Platelet count decreased	15 (2.5)	77 (4.9)	1 (4.8)	93 (4.2)
Disease progression [d]	16 (2.7)	60 (3.8)	0	76 (3.4)
Nausea	30 (5.0)	44 (2.8)	0	74 (3.4)
Fatigue [e]	18 (3.0)	56 (3.5)	0	74 (3.4)
Off label use	11 (1.8)	31 (2.0)	1 (4.8)	43 (2.0)
Constipation	3 (0.5)	37 (2.3)	0	40 (1.8)
Neutrophil count decreased	25 (4.1)	11 (0.7)	0	36 (1.6)

Thrombocytopenia	4 (0.7)	29 (1.8)	1 (4.8)	34 (1.5)
Hemoglobin decreased	14 (2.3)	17 (1.1)	1 (4.8)	32 (1.5)
Ovarian cancer metastatic	0	32 (2.0)	0	32 (1.5)
Decreased appetite	7 (1.2)	22 (1.4)	0	29 (1.3)
Malaise	16 (2.7)	13 (0.8)	0	29 (1.3)
Product dose omission issue	6 (1.0)	23 (1.5)	0	29 (1.3)
Dizziness	6 (1.0)	22 (1.4)	0	28 (1.3)
Hypertension	5 (0.8)	21 (1.3)	0	26 (1.2)
Vomiting	4 (0.7)	22 (1.4)	0	26 (1.2)
Blood pressure increased	0	25 (1.6)	0	25 (1.1)
Insomnia	0	25 (1.6)	0	25 (1.1)
Headache	1 (0.1)	23 (1.5)	0	24 (1.1)
Action Taken				
Dose reduced	45 (15.2)	32 (10.1)	2 (25.0)	79 (12.7)
Dose increased	1 (0.3)	3 (0.9)	0	4 (0.6)
Drug withdrawn	165 (55.5)	203 (63.8)	2 (25.0)	370 (59.4)
Dose not changed	37 (12.5)	14 (4.4)	1 (12.5)	52 (8.4)
Not possible to identify	5 (1.7)	0	0	5 (0.8)
Unknown	44 (14.8)	66 (20.8)	3 (37.5)	113 (18.1)
Concomitant therapy				
1	45 (15.2)	16 (5.0)	0	61 (9.8)
2	7 (2.3)	13 (4.1)	0	20 (3.2)
3	4 (1.3)	4 (1.3)	0	8 (1.3)
4	5 (1.7)	3 (0.9)	0	8 (1.3)
5 or more	7 (2.4)	18 (5.7)	0	25 (4.0)
Not reported	229 (77.1)	264 (83.0)	8 (100.0)	501 (80.4)
Clinical indications				
Ovarian, fallopian, and peritoneal cancer	175 (58.9)	280 (88.1)	0	455 (73.0)
Pancreatic cancer	5 (1.7)	0	0	5 (0.8)
Ovarian and pancreatic cancer	1 (0.3)	0	0	1 (0.2)
Breast cancer	37 (12.5)	0	5 (62.5)	42 (6.7)
Ovarian and breast cancer	0	3 (0.9)	0	3 (0.5)
Prostate cancer	38 (12.8)	0	0	38 (6.1)
Plasma cell myeloma refractory	1 (0.3)	0	0	1 (0.2)
Unknown	40 (13.5)	35 (11.0)	3 (37.5)	78 (12.5)

[a] In case of more than one event/outcome, the worst outcome was considered.

[b] In case of more than one seriousness criteria described, the most serious was considered.

[c] 20 most reported PTs were considered.

[d] Disease progression includes PTs of disease progression, malignant neoplasm progression and neoplasm progression.

[e] Fatigue includes PTs of fatigue and asthenia.

3.2. CDK4/6 inhibitors

3.2.1. National Database Results

3.2.1.1. Main Characteristics of ICSRs

A total of 176 ICSRs involving palbociclib, ribociclib and abemaciclib as the suspected drug were reported to the PPS database in 2020, 2021 and 2022. More specifically, 41 ICSRs were related to palbociclib, 82 to ribociclib and 53 to abemaciclib. Most cases were reported in female patients (N = 164, 93.2%) compared to male patients (N = 3, 1.7%). A high number of ICSRs involved patients aged 18-64 years (N = 87, 49.4%) and 65-85 years (N = 58, 33.0%). Only 30 ICSRs were classified as "not specified" in terms of age group. In addition, many of the cases were reported by HCP (N = 174, 98.9%).

Considering the individual cases reported by SOC, "Blood and lymphatic disorders" followed by "General disorders and administration site conditions" were the most described with 82 and 46 ICSRs, respectively. Similar to "General disorders and administration site conditions", "Gastrointestinal disorders" was also observed, with 43 ICSRs reporting at least one gastrointestinal symptom. In terms of seriousness, a high percentage of cases was classified as a serious (N = 132, 75.0%) compared to non-serious cases (N = 44, 25.0%). In this context, a statistically significance difference (p = 0.0040) was found between seriousness and the drugs studied. Regarding concomitant medicines, the majority of ICSRs reported at least one concomitant drug (N = 129, 73.3%). Breast cancer was identified as the main clinical indication of the ICSRs analyzed. These results are shown in **Table 3.5.**

Table 3.5. Demographic characteristics of ICSRs involving palbociclib, ribociclib and abemaciclib as the suspected drug in 2020, 2021 and 2022, according to the PPS database.

	Individual Case Safety reports (%)			
	Palbociclib N=41	Ribociclib N=82	Abemaciclib N=53	Total N=176
Sex				
Male	1 (2.4)	0	2 (3.8)	3 (1.7)
Female	39 (95.2)	78 (95.2)	47 (88.7)	164 (93.2)
Not specified	1 (2.4)	4 (4.8)	4 (7.5)	9 (5.1)
Age group				
Pediatrics (<18 years)	0	0	0	0
Adult (18-64 years)	19 (46.3)	45 (54.9)	23 (43.4)	87 (49.4)
Elderly (65-85 years)	19 (46.3)	17 (20.8)	22 (41.5)	58 (33.0)
Very Elderly (>85 years)	1 (2.4)	0	0	1 (0.6)
Not Specified	2 (5.0)	20 (24.3)	8 (15.1)	30 (17.0)

Reporter group				
HCP	40 (97.6)	82 (100)	52 (98.1)	174 (98.9)
Non-HCP	1 (2.4)	0	1 (1.9)	2 (1.1)
Individual cases reported by SOC				
Total number of individual cases	**77**	**205**	**85**	**367**
Blood and lymphatic disorders	31 (40.2)	38 (18.5)	13 (15.3)	82 (22.3)
General disorders and administration site conditions	8 (10.4)	33 (16.1)	5 (5.9)	46 (12.5)
Gastrointestinal disorders	11 (14.3)	12 (5.9)	20 (23.5)	43 (11.7)
Skin and subcutaneous tissue disorders	6 (7.8)	16 (7.8)	6 (7.1)	28 (7.6)
Investigations	2 (2.6)	16 (7.8)	9 (10.6)	27 (7.4)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	3 (3.9)	12 (5.9)	5 (5.9)	20 (5.4)
Hepatobiliary disorders	0	14 (6.8)	5 (5.9)	19 (5.1)
Respiratory, thoracic, and mediastinal disorders	0	8 (3.9)	6 (7.0)	14 (3.8)
Infections and infestations	4 (5.2)	6 (2.9)	4 (4.7)	14 (3.8)
Musculoskeletal and connective tissue disorders	2 (2.6)	9 (4.3)	1 (1.2)	12 (3.3)
Nervous system disorders	2 (2.6)	8 (3.9)	1 (1.2)	11 (3.0)
Injury, poisoning and procedural complications	2 (2.6)	6 (2.9)	2 (2.3)	10 (2.7)
Renal and urinary disorders	0	6 (2.9)	3 (3.5)	9 (2.5)
Metabolism and nutrition disorders	2 (2.6)	6 (2.9)	1 (1.2)	9 (2.5)
Vascular disorders	1 (1.3)	3 (1.5)	2 (2.3)	6 (1.6)
Eye disorders	2 (2.6)	2 (1.0)	1 (1.2)	5 (1.4)
Cardiac disorders	0	3 (1.5)	1 (1.2)	4 (1.1)
Reproductive system and breast disorders	1 (1.3)	3 (1.5)	0	4 (1.1)
Psychiatric disorders	0	2 (1.0)	0	2 (0.6)
Endocrine disorders	0	2 (1.0)	0	2 (0.6)
Number of individual cases [a]				
Serious	34 (82.9)	67 (81.7)	31 (58.5)	132 (75.0)
Non-serious	7 (17.1)	15 (18.3)	22 (41.5)	44 (25.0)
Concomitant medicines per ICSR				
1	9 (22.0)	13 (15.9)	26 (49.1)	48 (27.3)
2	8 (19.5)	13 (15.9)	4 (7.5)	25 (14.2)
3	2 (4.8)	8 (9.8)	2 (3.8)	12 (6.8)
4	5 (12.2)	4 (4.8)	5 (9.4)	14 (8.0)
5 or more	9 (22.0)	15 (18.3)	6 (11.3)	30 (17.0)
Not reported	8 (19.5)	29 (35.3)	10 (18.9)	47 (26.7)
Clinical indications				
Breast cancer	41 (100.0)	57 (69.5)	32 (60.4)	130 (73.9)
Unknown	0	25 (30.5)	21 (39.6)	46 (26.1)

[a] Pearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).
Abbreviations: HCP, Healthcare professionals; SOC, System Organ Class.

3.2.1.2. Characteristics of Adverse Events

A detailed analysis of the ADR of the ICSRs described above was performed considering the years 2020, 2021 and 2022 with a CDK4/6 inhibitor as the suspected drug. In this context, regarding the outcome of the ADR, the majority of cases were classified with an "unknown" outcome (N = 111, 63.1%), followed by "recovered/resolved" resolution (N = 29, 16.5%). "Other medically important information" was the most reported seriousness criteria (N = 108, 81.8%). A total of 7 fatal cases were reported.

Neutropenia was the most reported ADR among CDK4/6 inhibitors, particularly observed in patients taking palbociclib and ribociclib. In contrast, diarrhea was reported mainly in patients receiving abemaciclib. Fatigue was more common in patients taking ribociclib. These findings are detailed in **Table 3.6.**

Table 3.6. Characteristics of reported ADR involving palbociclib, ribociclib and abemaciclib as the suspected drug in 2020, 2021 and 2022, according to the PPS database.

	Individual Case Safety reports (%)			
	Palbociclib N=41	Ribociclib N=82	Abemaciclib N=53	Total N=176
Outcome [a]				
Recovered/Resolved	6 (14.6)	10 (12.2)	13 (24.5)	29 (16.5)
Recovered/Resolved with Sequelae	2 (4.9)	2 (2.4)	0	4 (2.2)
Recovering/Resolving	7 (17.1)	1 (1.2)	5 (9.4)	13 (7.4)
Not recovered/Not resolved	7 (17.1)	5 (6.1)	0	12 (6.8)
Fatal	1 (2.4)	3 (3.7)	3 (5.7)	7 (4.0)
Unknown	18 (43.9)	61 (74.4)	32 (60.4)	111 (63.1)
Seriousness criteria [b]				
Total number of serious cases	**34**	**67**	**31**	**132**
Other (other medically important information)	31 (91.3)	59 (88.1)	18 (58.1)	108 (81.8)
Congenital	0	0	0	0
Disability	1 (2.9)	1 (1.4)	0	2 (1.5)
Hospitalization	0	4 (6.0)	6 (19.4)	10 (7.6)
Life threatening	1 (2.9)	0	4 (12.9)	5 (3.8)
Death	1 (2.9)	3 (4.5)	3 (9.6)	7 (5.3)
Most reported symptoms [c]				
Total number of symptoms reported	**97**	**276**	**97**	**470**
Neutropenia	30 (30.9)	35 (12.7)	9 (9.3)	74 (15.7)
Fatigue [d]	7 (7.2)	18 (6.5)	1 (1.0)	26 (5.5)

Diarrhea	1 (1.0)	3 (1.1)	17 (17.5)	21 (4.5)
Disease progression [e]	3 (3.1)	9 (3.3)	5 (5.2)	17 (3.6)
Nausea	5 (5.2)	5 (1.8)	3 (3.1)	13 (2.8)
Anemia	6 (6.2)	4 (1.4)	1 (1.0)	11 (2.3)
Hepatotoxicity	0	9 (3.3)	2 (2.1)	11 (2.3)
Rash [f]	2 (2.1)	5 (1.8)	4 (4.1)	11 (2.3)
Vomiting	2 (2.1)	6 (2.2)	2 (2.1)	10 (2.1)
Thrombocytopenia	2 (2.1)	4 (1.4)	3 (3.1)	9 (1.9)
Alopecia	4 (4.1)	3 (1.1)	1 (1.0)	8 (1.7)
Decreased appetite	2 (2.1)	4 (1.4)	0	6 (1.3)
Transaminases increased	0	5 (1.8)	1 (1.0)	6 (1.3)
COVID-19 [g]	2 (2.1)	2 (0.7)	1 (1.0)	5 (1.1)
Metastases to bone	0	5 (1.8)	0	5 (1.1)
Arthralgia	1 (1.0)	3 (1.1)	0	4 (0.9)
Leukopenia	2 (2.1)	1 (0.3)	1 (1.0)	4 (0.9)
Weight decreased	1 (1.0)	1 (0.3)	2 (2.1)	4 (0.9)
Hepatic function abnormal [h]	0	2 (0.7)	2 (2.1)	4 (0.9)
Electrocardiogram QT prolonged	0	3 (1.1)	0	3 (0.6)

[a] In case of more than one event/outcome, the worst outcome was considered.

[b] In case of more than one seriousness criteria described, the most serious was considered.

[c] 20 most reported PTs were considered.

[d] Fatigue includes PTs of fatigue and asthenia.

[e] Disease progression includes PTs of disease progression, malignant neoplasm progression and neoplasm progression.

[f] Rash includes PTs of rash, rash macular, rash maculo-papular, rash pruritic and exfoliative rash.

[g] COVID-19 includes PTs of COVID-19 and Coronavirus infection.

[h] Hepatic function abnormal includes PTs of hepatic function abnormal and liver disorder.

3.2.2. EudraVigilance Database Results

3.2.2.1. Main Characteristics of ICSRs

A total of 4640 ICSRs were reported to the EV database, considering palbociclib, ribociclib and abemaciclib as the suspected drug in 2022. In this context, it is notable the difference in the number of ICSRs analyzed, namely: 3424 ICSRs related to palbociclib, 561 to ribociclib and 655 to abemaciclib. Female patients were the most reported (N = 4439, 95.6%), particularly in the 18-64 years (N = 1729, 37.3%) and 65-85 years (N = 1990, 42.9%) age groups. HCP reported a high number of cases (N = 3208, 69.1%) from the Non-European Economic Area (N = 3327, 71.7%).

Regarding the individual cases reported by SOC, “General disorders and administration site conditions” (N = 1374, 11.7%) and “Investigations” (N = 1327, 11.3%) were the most reported, followed by “Blood and lymphatic disorders” and “Gastrointestinal disorders”

with 1291 and 1204 ICSRs, respectively. Most cases were classified as serious (N = 3910, 84.3%) compared to non-serious cases (N = 730, 15.7%). A statistically significant difference ($p < 0.00001$) was found between seriousness and the drugs studied. **Table 3.7**. shows these results.

Table 3.7. Demographic characteristics of ICSRs involving palbociclib, ribociclib and abemaciclib as the suspected drug in 2022, according to the EV database.

	Individual Case Safety reports (%)			
	Palbociclib N=3424	Ribociclib N=561	Abemaciclib N=655	Total N=4640
Sex				
Male	63 (1.9)	6 (1.1)	9 (1.4)	78 (1.7)
Female	3278 (95.7)	542 (96.6)	619 (94.5)	4439 (95.6)
Not specified	83 (2.4)	13 (2.3)	27 (4.1)	123 (2.7)
Age group				
Pediatrics (<18 years)	0	0	0	0
Adult (18-64 years)	1302 (38.0)	171 (30.5)	256 (39.1)	1729 (37.3)
Elderly (65-85 years)	1661 (48.5)	112 (20.0)	217 (33.1)	1990 (42.9)
Very Elderly (>85 years)	156 (4.6)	8 (1.4)	5 (0.8)	169 (3.6)
Not Specified	305 (8.9)	270 (48.1)	177 (27.0)	752 (16.2)
Reporter group				
HCP	2097 (61.2)	519 (92.5)	592 (90.4)	3208 (69.1)
Non-HCP	1327 (38.8)	42 (7.5)	63 (9.6)	1432 (30.9)
Geographic origin				
European Economic Area	352 (10.3)	425 (75.8)	536 (81.8)	1313 (28.3)
Non-European Economic Area	3072 (89.7)	136 (24.2)	119 (18.2)	3327 (71.7)
Individual cases reported by SOC				
Total number of individual cases	**9657**	**833**	**1222**	**11712**
General disorders and administration site conditions	1176 (12.2)	68 (8.2)	130 (10.6)	1374 (11.7)
Investigations	1102 (11.4)	116 (14.0)	109 (8.9)	1327 (11.3)
Blood and lymphatic disorders	954 (9.9)	194 (23.3)	143 (11.7)	1291 (11.0)
Gastrointestinal disorders	798 (8.3)	65 (7.8)	341 (27.9)	1204 (10.3)
Injury, poisoning and procedural complications	708 (7.3)	16 (1.9)	21 (1.7)	745 (6.4)
Nervous system disorders	618 (6.4)	24 (2.9)	50 (4.1)	692 (5.9)
Infections and infestations	611 (6.3)	20 (2.4)	45 (3.7)	676 (5.8)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	541 (5.6)	47 (5.6)	38 (3.1)	626 (5.3)
Respiratory, thoracic, and mediastinal disorders	517 (5.4)	28 (3.4)	62 (5.1)	607 (5.2)
Skin and subcutaneous tissue disorders	453 (4.7)	85 (10.2)	62 (5.1)	600 (5.1)

Musculoskeletal and connective tissue disorders	438 (4.5)	13 (1.6)	17 (1.4)	468 (4.0)
Metabolism and nutrition disorders	234 (2.4)	17 (2.0)	60 (4.9)	311 (2.7)
Vascular disorders	235 (2.4)	14 (1.7)	19 (1.6)	268 (2.3)
Psychiatric disorders	246 (2.5)	4 (0.5)	11 (0.9)	261 (2.2)
Surgical and medical procedures	212 (2.2)	0	0	212 (1.8)
Eye disorders	169 (1.8)	15 (1.8)	18 (1.5)	202 (1.7)
Hepatobiliary disorders	79 (0.8)	67 (8.0)	39 (3.2)	185 (1.6)
Renal and urinary disorders	130 (1.4)	15 (1.8)	27 (2.2)	172 (1.5)
Immune system disorders	163 (1.7)	2 (0.2)	3 (0.2)	168 (1.4)
Cardiac disorders	98 (1.0)	19 (2.3)	24 (1.9)	141 (1.2)
Ear and labyrinth disorders	59 (0.6)	1 (0.1)	0	60 (0.5)
Reproductive system and breast disorders	40 (0.4)	2 (0.2)	1 (0.1)	43 (0.4)
Social circumstances	37 (0.4)	0	0	37 (0.3)
Endocrine disorders	17 (0.2)	0	2 (0.2)	19 (0.2)
Product issues	18 (0.2)	1 (0.1)	0	19 (0.2)
Congenital, familial, and genetic disorders	3	0	0	3
Pregnancy, puerperium, and perinatal conditions	1	0	0	1
Number of individual cases [a]				
Serious	3196 (93.3)	433 (77.2)	281 (42.9)	3910 (84.3)
Non-serious	228 (6.7)	128 (22.8)	374 (57.1)	730 (15.7)

[a] Pearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).

Abbreviations: HCP, Healthcare professionals; SOC, System Organ Class.

3.2.2.2. Characteristics of Adverse Events

A detailed analysis of the ICSRs described above was performed considering palbociclib, ribociclib and abemaciclib as the suspected drug in a more restricted period (2 months – from 1 November 2022 to 31 December 2022). A total of 755 ICSRs were collected, being female group (N = 729, 96.6%) in the age group of 18-64 years (N = 291, 38.5%) and 65-85 years (N = 324, 42.9%) the most reported in terms of sex and age group. Most cases were classified with an "unknown" outcome (N = 494, 65.4%), with "other medically important information" being the most reported seriousness criteria (N = 416, 67.6%). The outcomes "recovered/resolved" (N = 75, 10.0%), "recovering/resolving" (N = 70, 9.3%) and "not recovered/not resolved" (N = 77, 10.2%) had a similar number of ICSRs. A total of 38 fatal cases and 150 cases that required/prolonged hospitalization were reported, particularly associated with palbociclib.

Neutropenia was the most reported ADR within the CDK4/6 inhibitors group, followed by fatigue and diarrhea. Abnormal full blood count and peripheral neuropathy were

identified in palbociclib ICSRs. Drug withdrawal was the most common action taken (N = 295, 39.1%) in patients with breast cancer (N=456, 60.4%). For concomitant medicines, the majority of ICSRs did not provide information in this area (N = 406, 53.8%). These findings are described in **Table 3.8**.

Table 3.8. Characteristics of reported ADR involving palbociclib, ribociclib and abemaciclib as the suspected drug along 2 months (from 1 November to 31 December 2022), according to the EV database.

	Individual Case Safety reports (%)			
	Palbociclib N=510	Ribociclib N=99	Abemaciclib N=146	Total N=755
Sex				
Male	9 (1.8)	2 (2.0)	2 (1.4)	13 (1.7)
Female	494 (96.8)	97 (98.0)	138 (94.5)	729 (96.6)
Not specified	7 (1.4)	0	6 (4.1)	13 (1.7)
Age group				
Pediatrics (<18 years)	0	0	0	0
Adult (18-64 years)	185 (36.3)	34 (34.3)	72 (49.3)	291 (38.5)
Elderly (65-85 years)	265 (52.0)	18 (18.2)	41 (28.1)	324 (42.9)
Very Elderly (>85 years)	24 (4.7)	2 (2.0)	0	26 (3.5)
Not Specified	36 (7.0)	45 (45.5)	33 (22.6)	114 (15.1)
Outcome [a]				
Recovered/Resolved	35 (6.9)	20 (20.2)	20 (13.7)	75 (10.0)
Recovered/Resolved with Sequelae	0	1 (1.0)	0	1 (0.1)
Recovering/Resolving	24 (4.7)	20 (20.2)	26 (17.8)	70 (9.3)
Not recovered/Not resolved	56 (11.0)	9 (9.1)	12 (8.2)	77 (10.2)
Fatal	30 (5.8)	2 (2.0)	6 (4.1)	38 (5.0)
Unknown	365 (71.6)	47 (47.5)	82 (56.2)	494 (65.4)
Number of individual cases				
Serious	477 (93.5)	75 (75.8)	63 (43.2)	615 (81.5)
Non-serious	33 (6.5)	24 (24.2)	83 (56.8)	140 (18.5)
Seriousness criteria [b]				
Total number of serious cases	**477**	**75**	**63**	**615**
Other (other medically important information)	326 (68.3)	59 (78.6)	31 (49.2)	416 (67.6)
Congenital	0	0	0	0
Disability	2 (0.4)	0	0	2 (0.3)
Hospitalization	114 (23.9)	11 (14.7)	25 (39.7)	150 (24.4)
Life threatening	5 (1.1)	3 (4.0)	1 (1.6)	9 (1.5)
Death	30 (6.3)	2 (2.7)	6 (9.5)	38 (6.2)
Most reported symptoms [c]				
Total number of symptoms reported	**2185**	**204**	**333**	**2722**
Neutropenia	89 (4.1)	38 (18.6)	15 (4.5)	142 (5.2)
Fatigue [d]	118 (5.4)	5 (2.5)	17 (5.1)	140 (5.1)
Diarrhea	39 (1.8)	0	66 (19.8)	105 (3.9)

Disease progression [e]	74 (3.4)	4 (2.0)	7 (2.1)	85 (3.1)
Nausea	51 (2.3)	6 (2.9)	13 (3.9)	70 (2.6)
White blood cell count decreased	69 (3.2)	0	2 (0.6)	71 (2.6)
Anemia	32 (1.5)	2 (1.0)	8 (2.4)	42 (1.5)
Off-label use	40 (1.8)	0	2 (0.6)	42 (1.5)
Alopecia	37 (1.7)	2 (1.0)	1 (0.3)	40 (1.5)
Product dose omission issue	37 (1.7)	0	0	37 (1.4)
Pain	31 (1.4)	1 (0.5)	0	32 (1.2)
Decreased appetite	22 (1.0)	2 (1.0)	8 (2.4)	32 (1.2)
Leukopenia	15 (0.7)	10	4 (1.2)	29 (1.1)
COVID-19	24 (1.1)	0	2 (0.6)	26 (1.0)
Dizziness	20 (0.9)	0	5 (1.5)	25 (0.9)
Cough	22 (1.0)	1 (0.5)	2 (0.6)	25 (0.9)
Constipation	21 (1.0)	1 (0.5)	1 (0.3)	23 (0.8)
Malaise	21 (1.0)	1 (0.5)	1 (0.3)	23 (0.8)
Abnormal full blood count	20 (0.9)	0	0	20 (0.7)
Peripheral neuropathy	20 (0.9)	0	0	20 (0.7)
Action Taken				
Dose Reduced	77 (15.1)	18 (18.2)	29 (19.9)	124 (16.4)
Dose Increased	0	0	0	0
Drug withdrawn	199 (39.0)	39 (39.4)	57 (39.0)	295 (39.1)
Dose not changed	62 (12.2)	15 (15.1)	26 (17.8)	103 (13.6)
Not possible to identify	0	0	1 (0.7)	1 (0.1)
Unknown	172 (33.7)	27 (27.3)	33 (22.6)	232 (30.8)
Concomitant therapy				
1	140 (27.5)	5 (5.1)	41 (28.1)	186 (24.7)
2	16 (3.1)	18 (18.2)	16 (11.0)	50 (6.6)
3	20 (3.9)	4 (4.0)	7 (4.8)	31 (4.1)
4	4 (0.8)	2 (2.0)	4 (2.7)	10 (1.3)
5 or more	67 (13.1)	2 (2.0)	3 (2.0)	72 (9.5)
Not reported	263 (51.6)	68 (68.7)	75 (51.4)	406 (53.8)
Clinical indications				
Breast cancer	267 (52.3)	77 (77.8)	112 (76.7)	456 (60.4)
Lung neoplasm malignant	1 (0.2)	0	0	1 (0.1)
Hepatic cancer and lung neoplasm malignant	1 (0.2)	0	0	1 (0.1)
Bone cancer	2 (0.4)	0	0	2 (0.3)
Bone and hepatic cancer	1 (0.2)	0	1 (0.7)	2 (0.3)
Soft tissue sarcoma	1 (0.2)	0	0	1 (0.1)
Unknown	237 (46.5)	22 (22.2)	33 (22.6)	292 (38.7)

[a] In case of more than one event/outcome, the worst outcome was considered.

[b] In case of more than one seriousness criteria described, the most serious was considered.

[c] 20 most reported PTs were considered.

[d] Fatigue includes PTs of fatigue and asthenia.

[e] Disease progression includes PTs of disease progression, malignant neoplasm progression and neoplasm progression.

3.3. Tyrosine kinase inhibitors

3.3.1. National Database Results

3.3.1.1. Main Characteristics of ICSRs

A total of 46 ICSRs involving cabozantinib and lorlatinib as the suspected drug were reported to the PPS database in 2020, 2021 and 2022. More precisely, 15 ICSRs related to cabozantinib and 31 to lorlatinib. Cases were reported in both female patients (N = 25, 54.3%) and male patients (N = 21, 45.7%). No cases were identified as "not specified". The majority of ICSRs involved patients aged 18-64 years (N = 21, 45.7%) and 65-85 years (N = 19, 41.3%). In addition, 3 lorlatinib-related cases were reported in the pediatric group. Almost all cases were reported by HCP, except 1 case.

Considering the individual cases reported by SOC, "General disorders and administration site conditions" and "Metabolism and nutrition disorders" were the most described with 23 ICSRs, followed by "Investigations", "Gastrointestinal disorders" and "Psychiatric disorders" with 17, 10 and 10 ICSRs, respectively. Regarding the seriousness, the number of serious cases was equal to the number of non-serious cases. No statistically significance difference (p = 0.7531) was found between seriousness and the drugs studied. For concomitant medicines, the majority of ICSRs did not describe any information about other medicines that patients were taking (N = 30, 65.2%). The most common clinical indications reported were NSCLC (associated with lorlatinib) and RCC and HCC (associated with patients taking cabozantinib). **Table 3.9.** describes the results presented.

Table 3.9. Demographic characteristics of ICSRs involving cabozantinib and lorlatinib as the suspected drug in 2020, 2021 and 2022, according to the PPS database.

	Individual Case Safety reports (%)		
	Cabozantinib N=15	Lorlatinib N=31	Total N=46
Sex			
Male	11 (73.3)	10 (32.3)	21 (45.7)
Female	4 (26.7)	21 (67.7)	25 (54.3)
Not specified	0	0	0
Age group			
Pediatrics (<18 years)	0	3 (9.7)	3 (6.5)
Adult (18-64 years)	7 (46.7)	14 (45.2)	21 (45.7)
Elderly (65-85 years)	7 (46.7)	12 (38.7)	19 (41.3)

Very Elderly (>85 years)	0	0	0
Not Specified	1 (6.6)	2 (6.4)	3 (6.5)
Reporter group			
HCP	14 (93.3)	31 (100.0)	45 (97.8)
Non-HCP	1 (6.7)	0	1 (2.2)
Individual cases reported by SOC			
Total number of individual cases	**45**	**79**	**124**
General disorders and administration site conditions	9 (20.0)	14 (17.7)	23 (18.6)
Metabolism and nutrition disorders	4 (8.9)	19 (24.0)	23 (18.6)
Investigations	2 (4.5)	15 (19.0)	17 (13.7)
Gastrointestinal disorders	8 (17.8)	2 (2.5)	10 (8.1)
Psychiatric disorders	0	10 (12.6)	10 (8.1)
Nervous system disorders	3 (6.7)	6 (7.6)	9 (7.3)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (2.2)	4 (5.1)	5 (4.0)
Vascular disorders	4 (8.9)	1 (1.3)	5 (4.0)
Skin and subcutaneous tissue disorders	5 (11.1)	0	5 (4.0)
Injury, poisoning and procedural complications	1 (2.2)	3 (3.8)	4 (3.2)
Respiratory, thoracic, and mediastinal disorders	1 (2.2)	1 (1.3)	2 (1.6)
Hepatobiliary disorders	0	2 (2.5)	2 (1.6)
Endocrine disorders	2 (4.5)	0	2 (1.6)
Blood and lymphatic disorders	1 (2.2)	0	1 (0.8)
Renal and urinary disorders	0	1 (1.3)	1 (0.8)
Cardiac disorders	0	1 (1.3)	1 (0.8)
Eye disorders	1 (2.2)	0	1 (0.8)
Infections and infestations	1 (2.2)	0	1 (0.8)
Musculoskeletal and connective tissue disorders	1 (2.2)	0	1 (0.8)
Reproductive system and breast disorders	1 (2.2)	0	1 (0.8)
Number of individual cases [a]			
Serious	8 (53.3)	15 (48.4)	23 (50.0)
Non-serious	7 (46.7)	16 (51.6)	23 (50.0)
Concomitant medicines per ICSR			
1	0	4 (12.9)	4 (8.7)
2	2 (13.3)	0	2 (4.3)
3	2 (13.3)	2 (6.5)	4 (8.7)
4	1 (6.7)	0	1 (2.2)
5 or more	4 (26.7)	1 (3.2)	5 (10.9)
Not reported	6 (40.0)	24 (77.4)	30 (65.2)
Clinical indications			
NSCLC	1 (6.7)	22 (71.0)	23 (50.0)
RCC	10 (66.7)	0	10 (21.7)
HCC	2 (13.3)	0	2 (4.4)
Neuroblastoma	0	1 (3.2)	1 (2.2)

Unknown	2 (13.3)	8 (25.8)	10 (21.7)

[a] Pearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).

Abbreviations: HCP, Healthcare professionals; SOC, System Organ Class; NSCLC, Non-small cell lung cancer; RCC, Renal cell carcinoma; HCC, Hepatocellular carcinoma.

3.3.1.2. Characteristics of Adverse Events

A more detailed analysis of the ADR reported in the ICSRs described above was performed in 2020, 2021 and 2022, considering cabozantinib and lorlatinib as the suspected drug. Regarding the outcome of the ADR, most cases were classified as "unknown" (N = 25, 54.3%) and 3 cases were considered fatal (N = 3, 6.5%). "Other medically important information" was the most reported seriousness criteria (N = 15, 65.2%) and 4 cases required/prolonged hospitalization (N = 4, 17.4%).

Hypercholesterolemia was the most reported ADR, particularly in patients taking lorlatinib. Peripheral edema, hypertriglyceridemia and weigh increased were also more associated with lorlatinib. Other ADR such as hypertension, decreased appetite, diarrhea and PPES were more reported in patients taking cabozantinib. These findings are detailed in **Table 3.10**.

Table 3.10. Characteristics of reported ADR involving cabozantinib and lorlatinib as the suspected drug in 2020, 2021 and 2022, according to the PPS database.

	Individual Case Safety reports (%)		
	Cabozantinib N=15	Lorlatinib N=31	Total N=46
Outcome [a]			
Recovered/Resolved	0	5 (16.1)	5 (10.9)
Recovered/Resolved with Sequelae	0	0	0
Recovering/Resolving	2 (13.3)	5 (16.1)	7 (15.2)
Not recovered/Not resolved	1 (6.7)	5 (16.1)	6 (13.1)
Fatal	1 (6.7)	2 (6.5)	3 (6.5)
Unknown	11 (73.3)	14 (45.2)	25 (54.3)
Seriousness criteria [b]			
Total number of serious cases	**8**	**15**	**23**
Other (other medically important information)	6 (75.0)	9 (60.0)	15 (65.2)
Congenital	0	0	0
Disability	0	1 (6.7)	1 (4.3)
Hospitalization	1 (12.5)	3 (20.0)	4 (17.4)
Life threatening	0	0	0
Death	1 (12.5)	2 (13.3)	3 (13.1)
Most reported symptoms [c]			

Total number of symptoms reported	61	105	166
Hypercholesterolemia	0	17 (16.2)	17 (10.2)
Peripheral edema	0	7 (6.7)	7 (4.2)
Hypertriglyceridemia	0	6 (5.7)	6 (3.6)
Weight increased	0	6 (5.7)	6 (3.6)
Fatigue [d]	5 (8.2)	1 (1.0)	6 (3.6)
Disease progression [e]	1 (1.6)	4 (3.8)	5 (3.0)
Hypertension	4 (6.6)	1 (1.0)	5 (3.0)
Decreased appetite	4 (6.6)	0	4 (2.4)
Diarrhea	4 (6.6)	0	4 (2.4)
Transaminases increased	1 (1.6)	3 (2.9)	4 (2.4)
PPES	4 (6.6)	0	4 (2.4)
Arthralgia	0	3 (2.9)	3 (1.8)
Hyperlipidemia	0	3 (2.9)	3 (1.8)
Mood altered	0	3 (2.9)	3 (1.8)
Stomatitis	3 (4.9)	0	3 (1.8)
Dizziness	2 (3.3)	1 (1.0)	3 (1.8)
Headache	3 (4.9)	0	3 (1.8)
Hypothyroidism	2 (3.3)	0	2 (1.2)
Nausea	2 (3.3)	0	2 (1.2)
Dysphagia	2 (3.3)	0	2 (1.2)

[a] In case of more than one event/outcome, the worst outcome was considered.

[b] In case of more than one seriousness criteria described, the most serious was considered.

[c] 20 most reported PTs were considered.

[d] Fatigue includes PTs of fatigue and asthenia.

[e] Disease progression includes PTs of disease progression, neoplasm progression and malignant neoplasm progression.

Abbreviations: PPES, Palmar-plantar erythrodysaesthesia syndrome.

3.3.2. EudraVigilance Database Results

3.3.2.1. Main Characteristics of ICSRs

A total of 1209 ICSRs were extracted and analyzed from the EV database, considering cabozantinib and lorlatinib as the suspected drug in 2022. In more detail, 1075 ICSRs were associated with cabozantinib and only 134 ICSRs were associated with lorlatinib. Male patients (N = 845, 69.9%), particularly in the 18-64 (N = 300, 24.8%) and 65-85 (N = 364, 30.1%) age groups were the most reported. In addition, 7 ICSRs related to the pediatrics group were reported. A high percentage of ICSRs were classified as “not specified” (N = 520, 43.0%) in terms of age group. Most reports were made by HCP (N = 1157, 95.7%) in the Non-European Economic Area (N = 854, 70.6%).

Concerning the individual cases reported by SOC, "General disorders and administration site conditions" (N = 452, 15.1%) were the most reported, followed by "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" (N = 397, 13.3%), "Gastrointestinal disorders" (N = 349, 11.7%) and "Skin and subcutaneous tissue disorders" (N = 232, 7.8%). In general, most cases were classified as serious (N = 1004, 83.0%), especially in patients taking cabozantinib (N = 937, 87.2%). However, when looking at the ICSRs of lorlatinib, an equal number of cases were classified as serious and non-serious (N = 67, 50.0%). A statistically significant difference ($p < 0.00001$) was found between seriousness and the drugs studied. **Table 3.11**. shows the results described above.

Table 3.11. Demographic characteristics of ICSRs involving cabozantinib and lorlatinib as the suspected drug in 2022, according to the EV database.

	Individual Case Safety reports (%)		
	Cabozantinib N=1075	Lorlatinib N=134	Total N=1209
Sex			
Male	773 (71.9)	72 (53.7)	845 (69.9)
Female	250 (23.3)	54 (40.3)	304 (25.1)
Not specified	52 (4.8)	8 (6.0)	60 (5.0)
Age group			
Pediatrics (<18 years)	4 (0.3)	3 (2.2)	7 (0.6)
Adult (18-64 years)	251 (23.3)	49 (36.6)	300 (24.8)
Elderly (65-85 years)	334 (31.1)	30 (22.4)	364 (30.1)
Very Elderly (>85 years)	16 (1.5)	2 (1.5)	18 (1.5)
Not Specified	470 (43.8)	50 (37.3)	520 (43.0)
Reporter group			
HCP	1043 (97.0)	114 (85.1)	1157 (95.7)
Non-HCP	32 (3.0)	20 (14.9)	52 (4.3)
Geographic origin			
European Economic Area	240 (22.3)	115 (85.8)	355 (29.4)
Non-European Economic Area	835 (77.7)	19 (14.2)	854 (70.6)
Individual cases reported by SOC			
Total number of individual cases	**2712**	**274**	**2986**
General disorders and administration site conditions	426 (15.7)	26 (9.5)	452 (15.1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	376 (13.9)	21 (7.7)	397 (13.3)
Gastrointestinal disorders	334 (12.3)	15 (5.5)	349 (11.7)
Skin and subcutaneous tissue disorders	227 (8.4)	5 (1.8)	232 (7.8)
Investigations	165 (6.1)	27 (9.9)	192 (6.4)
Metabolism and nutrition disorders	128 (4.7)	27 (9.9)	155 (5.2)

Nervous system disorders	97 (3.6)	46 (16.8)	143 (4.8)
Endocrine disorders	138 (5.1)	1 (0.4)	139 (4.6)
Injury, poisoning, and procedural complications	126 (4.7)	12 (4.4)	138 (4.6)
Vascular disorders	136 (5.0)	2 (0.7)	138 (4.6)
Renal and urinary disorders	114 (4.2)	5 (1.8)	119 (4.0)
Hepatobiliary disorders	117 (4.3)	0	117 (3.9)
Respiratory, thoracic, and mediastinal disorders	97 (3.6)	13 (4.7)	110 (3.7)
Infections and infestations	76 (2.8)	10 (3.6)	86 (2.9)
Musculoskeletal and connective tissue disorders	52 (1.9)	11 (4.0)	63 (2.1)
Psychiatric disorders	9 (0.3)	34 (12.4)	43 (1.4)
Cardiac disorders	33 (1.2)	5 (1.8)	38 (1.3)
Blood and lymphatic disorders	31 (1.2)	2 (0.7)	33 (1.1)
Eye disorders	11 (0.4)	6 (2.2)	17 (0.6)
Reproductive system and breast disorders	6 (0.2)	2 (0.7)	8 (0.3)
Ear and labyrinth disorders	4 (0.1)	3 (1.1)	7 (0.2)
Surgical and medical procedures	5 (0.2)	0	5 (0.2)
Social circumstances	3 (0.1)	0	3 (0.1)
Congenital, familial, and genetic disorders	1	1 (0.4)	2 (0.1)
Number of individual cases [a]			
Serious	937 (87.2)	67 (50.0)	1004 (83.0)
Non-serious	138 (12.8)	67 (50.0)	205 (17.0)

[a] Pearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).

Abbreviations: HCP, Healthcare professionals; SOC, System Organ Class.

3.3.2.2. Characteristics of Adverse Events

Considering the ICSRs described in the previous section, a detailed analysis was performed involving cabozantinib and lorlatinib as the suspected drug. In this context, a more restricted period was considered (2 months – from 1 November 2022 to 31 December 2022). A total of 192 ICSRs were collected, 167 ICSRs related to cabozantinib and 25 ICSRs related to lorlatinib. During this period, male patients were the most reported (N = 128, 66.7%), mainly in the age groups of 18-64 years (N = 50, 26.1%) and 65-85 years. (N = 58, 30.2%). The "Not specified" group represented almost half of the cases analyzed (N = 81, 42.2%). In terms of outcome, most cases were classified as "unknown" (N = 121, 63.0%). However, 15 cases (N = 15, 7.8%) revealed to be fatal, particularly in patients taking cabozantinib. Regarding serious cases, most were

classified as “other medically important information” criteria (N = 116, 71.6%), followed by 28 patients who required/prolonged hospitalization (N = 28, 17.3%).

Disease progression was the most reported ADR among the TKIs studied, particularly in patients taking cabozantinib. Other ADR such as hypothyroidism, diarrhea, PPES and hypertension were also seen in cabozantinib patients. Peripheral swelling was more associated with patients taking lorlatinib. In addition to “unknown” reports in the variable “action taken” (N = 92, 47.9%), drug withdrawal was the most common action reported (N = 68, 35.4%) in patients with RCC, HCC and NSCLC. For concomitant medicines, the majority of ICSRs did not provide any information in this area (N = 165, 85.9%). These results are shown in **Table 3.12**.

Table 3.12. Characteristics of reported ADR involving cabozantinib and lorlatinib as the suspected drug along 2 months (from 1 November to 31 December 2022), according to the EV database.

	Individual Case Safety reports (%)		
	Cabozantinib N=167	Lorlatinib N=25	Total N=192
Sex			
Male	119 (71.3)	9 (36.0)	128 (66.7)
Female	41 (24.5)	15 (60.0)	56 (29.2)
Not specified	7 (4.2)	1 (4.0)	8 (4.1)
Age group			
Pediatrics (<18 years)	0	1 (4.0)	1 (0.5)
Adult (18-64 years)	38 (22.8)	12 (48.0)	50 (26.1)
Elderly (65-85 years)	54 (32.3)	4 (16.0)	58 (30.2)
Very Elderly (>85 years)	1 (0.6)	1 (4.0)	2 (1.0)
Not Specified	74 (44.3)	7 (28.0)	81 (42.2)
Outcome [a]			
Recovered/Resolved	13 (7.8)	3 (12.0)	16 (8.3)
Recovered/Resolved with Sequelae	0	0	0
Recovering/Resolving	22 (13.1)	1 (4.0)	23 (12.0)
Not recovered/Not resolved	15 (9.0)	2 (8.0)	17 (8.9)
Fatal	13 (7.8)	2 (8.0)	15 (7.8)
Unknown	104 (62.3)	17 (68.0)	121 (63.0)
Number of individual cases			
Serious	148 (88.6)	14 (56.0)	162 (84.4)
Non serious	19 (11.4)	11 (44.0)	30 (15.6)
Seriousness criteria [b]			
Total number of serious cases	**148**	**14**	**162**
Other (other medically important information)	107 (72.3)	9 (64.3)	116 (71.6)
Congenital	0	0	0

Disability	1 (0.7)	1 (7.1)	2 (1.2)
Hospitalization	26 (17.5)	2 (14.3)	28 (17.3)
Life threatening	1 (0.7)	0	1 (0.6)
Death	13 (8.8)	2 (14.3)	15 (9.3)
Most reported symptoms [c]			
Total number of symptoms reported	**428**	**85**	**513**
Disease progression [d]	39 (9.1)	6 (7.1)	45 (8.8)
Hypothyroidism	30 (7.0)	0	30 (5.8)
Diarrhea	23 (5.4)	1 (1.2)	24 (4.7)
PPES	18 (4.2)	0	18 (3.5)
Hypertension	16 (3.7)	1 (1.2)	17 (3.3)
Off-label use	12 (2.8)	2 (2.4)	14 (2.7)
Fatigue [e]	14 (3.3)	0	14 (2.7)
Hepatic function abnormal [f]	13 (3.0)	0	13 (2.5)
Malaise	13 (3.0)	0	13 (2.5)
Decreased appetite	11 (2.6)	0	11 (2.1)
Hepatocellular carcinoma	10 (2.3)	0	10 (1.9)
Proteinuria	8 (1.9)	1 (1.2)	9 (1.8)
Inappropriate schedule of product administration	8 (1.9)	0	8 (1.6)
Metastatic renal cell carcinoma	8 (1.9)	0	8 (1.6)
Renal cell carcinoma	8 (1.9)	0	8 (1.6)
Stomatitis	5 (1.2)	1 (1.2)	6 (1.2)
Peripheral swelling	1 (0.2)	4 (4.7)	5 (1.0)
Blood pressure increased	5 (1.2)	0	5 (1.0)
Platelet count decreased	5 (1.2)	0	5 (1.0)
Hypercholesterolemia	0	4 (4.7)	4 (0.8)
Action Taken			
Dose Reduced	17 (10.2)	4 (16.0)	21 (11.0)
Dose Increased	0	0	0
Drug withdrawn	62 (37.1)	6 (24.0)	68 (35.4)
Dose not changed	8 (4.8)	3 (12.0)	11 (5.7)
Unknown	80 (47.9)	12 (48.0)	92 (47.9)
Concomitant medicines per ICSR			
1	4 (2.4)	3 (12.0)	7 (3.6)
2	5 (3.0)	1 (4.0)	6 (3.1)
3	2 (1.2)	1 (4.0)	3 (1.6)
4	4 (2.4)	0	4 (2.1)
5 or more	6 (3.6)	1 (4.0)	7 (3.7)
Not reported	146 (87.4)	19 (76.0)	165 (85.9)
Clinical indications			
RCC	110 (65.9)	0	110 (57.3)
HCC	32 (19.1)	0	32 (16.6)
NSCLC	0	12 (48.0)	12 (6.2)

Gastrointestinal stromal tumor	3 (1.8)	0	3 (1.6)
Osteosarcoma	3 (1.8)	0	3 (1.6)
Thyroid carcinoma	3 (1.8)	0	3 (1.6)
Bronchial carcinoma	0	3 (12.0)	3 (1.6)
Alveolar rhabdomyosarcoma	1 (0.6)	0	1 (0.5)
Neuroblastoma	0	1 (4.0)	1 (0.5)
Unknown	15 (9.0)	9 (36.0)	24 (12.5)

[a] In case of more than one event/outcome, the worst outcome was considered.

[b] In case of more than one seriousness criteria described, the most serious was considered.

[c] 20 most reported PTs were considered.

[d] Disease progression includes PTs of disease progression, neoplasm progression and malignant neoplasm progression.

[e] Fatigue includes PTs of fatigue and asthenia.

[f] Hepatic function abnormal includes PTs of hepatic function abnormal and liver disorder.

Abbreviations: PPES, Palmar-plantar erythrodysesthesia syndrome; RCC, Renal cell carcinoma; HCC, Hepatocellular carcinoma; NSCLC, Non-small cell lung cancer.

Chapter 4
Discussion

Chapter 4

Discussion

4.1. PARP inhibitors

PARPi are one of the most successful examples of clinical translation of targeted therapies in the field of oncology, namely for their effective treatment in several types of cancer [1]. Due to their recent approval, real-world studies are crucial to improve knowledge of the safety of these drugs. Regarding the national database, in 2020, 2021 and 2022, only 53 ICSRs were reported considering olaparib and niraparib as a suspected drug. In fact, this result was expected due to the underreporting phenomenon described in the field of oncology [2] and the fact that the financing of these drugs in Portugal require individual approval for each patient. In addition, 3037 ICSRs were analyzed in the European database, including olaparib, niraparib and talazoparib as a suspected drug. The main findings from both databases are discussed below.

Female patients were the most reported cases, mainly in the age groups of 18-64 years and 65-85 years in both databases. The approved clinical indications for these drugs justify these results. Olaparib and niraparib are both indicated for the treatment of ovarian cancer [3,4]. Olaparib and talazoparib are also approved for the treatment of recurrent, metastatic breast cancer [5]. HCP were the main reporting group. “Blood and lymphatic disorders” was one of the most reported SOCs among the PARPi studied. In fact, anemia was the most reported symptom experienced by these patients. Neutropenia and thrombocytopenia were also among the most reported symptoms. According to the literature, treatment of cancer patients with PARPi has been widely associated with an increased risk of hematological toxicities. Zhou *et al.* conducted a review of phase II and III randomized control trials of olaparib and niraparib in patients with various types of cancer. PARPi treatment was found to significantly more than double the relative risk of severe neutropenia, thrombocytopenia, and anemia compared with control groups [6]. Also, based on real-world data extracted from the FAERS database, Shu *et al.* described anemia as the most common hematological ADR associated with olaparib, niraparib and talazoparib [7]. Although not well-defined, it is suggested that PARPi may cause hematological toxicities by inhibiting the expression of PARP1 and PARP2. Animal studies have shown that PARP1 regulates cell differentiation in the bone marrow or blood system and PARP2 plays a role in regulating erythropoiesis [8,9]. Looking at the EV

database results in more detail, anemia was more associated with patients taking olaparib. However, anemia may be more common in patients taking niraparib. According to Berek *et al.*, grade≥3 hematological effects occurred only during the first three months of a daily administration of niraparib. However, after dose reduction, the incidence of hematological effects decreased significantly, except for anemia, which remained the same after the third month of treatment [10]. Usually, discontinuations due to the most common hematological treatment-emergent are considered low [11]. Considering the EV database results, drug withdrawal was the main action taken, especially in niraparib patients. In addition, thrombocytopenia is described to be more common in patients taking niraparib [12]. These results are consistent with what has been described by the European database results, considering the PTs "Thrombocytopenia" and "Platelet count decreased" (which may evidence the occurrence of thrombocytopenia). Considering the most reported outcome, most patients generally recovered/resolved or were in the process of recovering/resolving their condition. Thrombocytopenia events usually occur soon after the start of treatment and many patients were able to continue the treatment after blood transfusions, erythropoietin use, dose reduction or drug withdrawal [13]. Regular hematological monitoring should be performed to better determine the best therapeutic option for each patient.

In terms of gastrointestinal disorders, symptoms such as nausea, constipation and vomiting were reported in both databases. According to the SmPC of each PARPi, vomiting, diarrhea, and nausea are classified as very common ADR [3,4,14]. However, diarrhea was not described as one of the most reported symptoms in the analyzed ICSRs. In addition, our results suggest that gastrointestinal ADR were more common with niraparib. Bao *et al.* performed a meta-analysis showing that talazoparib was safer for gastrointestinal function [15]. Tian *et al.* also highlighted in a real-world study using the FAERS database that the overall signals for niraparib were stronger than those for olaparib. These symptoms included diarrhea, nausea, vomiting and constipation [16]. Depending on the patient's condition, talazoparib may be a good therapeutic option in case of severe gastrointestinal disorders.

Fatigue was also reported in both databases. According to Smith *et al.*, severe fatigue was mostly observed in patients taking niraparib in clinical studies [17]. Long treatment duration is usually associated with a higher risk of any-grade fatigue, eventually leading to dose reduction or drug withdrawal [18]. Li *et al.* also described in their systematic review and meta-analysis that patients receiving PARPi monotherapy tended to have a higher risk of all-grade fatigue than patients receiving combination therapy. The authors

suggested that PARPi monotherapy with poor curative effect may result in a higher risk of fatigue than combination therapy [19]. The experience of fatigue in patients taking PARPi may also be related to disease progression, which was also reported in our study.

Other ADR were highlighted in patients taking niraparib. Dizziness and headache, which belong to the SOC "Nervous system disorders", are very common symptoms in patients taking niraparib [4]. According to the SmPC, these symptoms are classified as very common in patients taking olaparib and talazoparib. A recent comparative study performed by Cai *et al.* showed that although headache is a very common symptom with PARPi, olaparib was considered safer than niraparib in terms of this ADR. However, with regard to dizziness, patients treated with olaparib were more likely to experience dizziness than patients treated with niraparib [20].

Psychiatric disorders, including insomnia, was also reported in our study. In the EV database results, insomnia was particularly reported in association with niraparib. Insomnia is very common in patients taking niraparib [4]. According to Sandhu *et al.*, psychiatric disorders such as sleep disorders, anxiety, delirium, and mania/bipolar disorder were more common in patients taking niraparib than in those taking olaparib. However, in our results, anxiety was only mentioned once, in the national database results, in association with olaparib ICSRs. Furthermore, anxiety is not mentioned in the olaparib SmPC. Due to the COVID-19 pandemic, women with ovarian cancer treated with olaparib reported higher levels of cancer-related worry, anxiety, and depression [21]. Given the period of our study, this case may be explained by the reasons mentioned above. Additionally, the difference in psychiatric ADR between niraparib and olaparib may also be related to the pan-neurotransmitter pharmacology of niraparib [22].

Other symptoms were less common. For example, pneumonitis was reported in two cases associated with olaparib. According to Tian *et al.* study, 45 cases of pneumonitis were found in the FAERS database, from December 2014 to October 2021. These authors suggested that the reported odds ratios indicate an increased risk of serious respiratory ADR for olaparib, particularly ILD and pneumonitis [16]. Another recent study involving clinical trials and a real-life setting reported by Ma *et al.*, described the increased risk of pneumonitis associated with PARPi. In this study, the authors noted the association of pneumonitis with olaparib, but also in patients taking niraparib. Most cases were considered serious and fatal outcomes were also described [23]. In our study, although the frequency of this ADR is considered rare, a causal relationship between PARPi therapy and pneumonitis should be established.

Regarding the seriousness of the analyzed ICSRs, the majority of them were classified with the seriousness criteria “other medically important information”, followed by hospitalization.

Further real-world research should be conducted with PARPi, given their widespread use in cancer treatment and other potential conditions such as cardiovascular diseases [5].

4.2. CDK4/6 inhibitors

CDK4/6 inhibitors are a recent pharmacological class of targeted drugs for the treatment of breast cancer that have shown promising and effective results when used in combination with an AI, fulvestrant, or as monotherapy (in the case of abemaciclib) [24,25]. In this context, we intended to investigate national and European spontaneous reports related to the approved CDK4/6 inhibitors in order to better characterize their safety profile in a real-world setting. A total of 176 ICSRs were reported to the PPS in 2020, 2021 and 2022 considering a CDK4/6 inhibitor as a suspected drug. In addition, 4640 ICSRs were extracted and analyzed from the EV database in 2022, considering the same suspected drugs. The main results of both databases are discussed below.

Female patients were the most reported cases by HCP in both databases, especially in the 18-64 and 65-85 age groups. This may be explained considering the approved clinical indications for this class of drugs. All CDK4/6 inhibitors are approved for the treatment of breast cancer patients [26]. According to the literature, male breast cancer is rare. In men, approximately 1% of cancers that occur are breast cancer and less than 0.2% of cancer deaths can be attributed to male breast cancer [27].

In a general way, “Blood and lymphatic disorders” is one of the most reported SOCs for CDK4/6 inhibitors with a total of 82 ICSRs from the national database and 1291 ICSRs from the EV database. “General disorders and administration site conditions”, “Investigations” and “Gastrointestinal disorders” were also highlighted in the reports analyzed. The frequency of these SOCs can be explained by considering the most reported symptoms experienced by these patients. Looking at the SOC “Blood and lymphatic disorders”, neutropenia was the most reported symptom in patients taking these drugs, both in the national and European databases. According to the information described in the SmPC, neutropenia, regardless of grade, is considered to be a very common symptom in these patients [28–30]. Nevertheless, CDK4/6 inhibitor-induced neutropenia is rapidly reversible with discontinuation of treatment [31]. Masuda *et al.*

reported a study involving Japanese patients that enrolled in PALOMA-2, PALOMA-3, and in a Japanese phase 2 clinical trial (NCT01740427, NCT01942135 and NCT01684215, respectively). This study provided evidence that neutropenia can be managed with dose modifications, without compromising the efficacy of palbociclib [32,33]. Looking at the results provided by the EV database, in particular the variable "Action Taken", most cases involved drug withdrawal, mainly in patients taking palbociclib, followed by dose reduction. Anemia, thrombocytopenia, and leukopenia were also reported as one of the most common hematological symptoms in patients taking CDK4/6 inhibitors, particularly highlighted in the national database results. According to the SmPC, anemia, thrombocytopenia and leukopenia are described as very common symptoms in patients taking palbociclib and abemaciclib [28,30]. In patients taking ribociclib, thrombocytopenia is characterized as a common reaction [29]. A recent real-world study developed by our research group described the suspected leukopenia and thrombocytopenia ICSRs induced by CDK4/6 inhibitors. Most reports of palbociclib and ribociclib were considered serious cases of both suspected leukopenia and thrombocytopenia. However, most patients recovered/resolved their leukopenia and thrombocytopenia. On the contrary, reports of abemaciclib were mostly characterized as non-serious cases for both suspected leukopenia and thrombocytopenia [34]. These findings suggested that hematological disorders are easy to manage and, consequently, most cases have a successful outcome. In our study, most cases were classified with an "unknown" outcome in both databases. In detail, cases with an "unknown" accounted for more than half of the reports analyzed (63.1% and 65.4% in the national and European databases, respectively). These discrepancies underline the need for reports of suspected ADR to be as complete as possible [35].

In terms of gastrointestinal toxicities, diarrhea was widely reported in this class of drugs. Although abemaciclib showed a lower frequency of neutropenia compared to palbociclib and ribociclib, patients taking abemaciclib were more likely to experience diarrhea in terms of gastrointestinal disorders. These data are consistent with what has been described in the literature [36]. Also, diarrhea was manageable using conventional antidiarrheal agents or by dose reduction [33]. Other gastrointestinal symptoms reported included nausea, vomiting and constipation. These results are in line with what was described in the clinical trials. Shohdy *et al.* described the incidence of gastrointestinal ADR in four eligible trials, namely PALOMA-1 phase II, PALOMA-2 phase III, PALOMA-3 phase III and MONALEESA-2 phase III. Nausea and vomiting were classified as very common symptoms in patients taking palbociclib and ribociclib. The results of MONARCH-2 also showed that abemaciclib was associated with a

significant increase in the risk of all grades of nausea and vomiting [37]. According to the EV database, constipation was identified as one of the most reported symptoms, especially in palbociclib patients. However, this ADR is not described in the palbociclib SmPC [28].

Fatigue was reported in both databases. This symptom is reported to be very common in the SmPC of CDK4/6 inhibitors [28-30]. Lasheen *et al.* performed a systematic review and meta-analysis highlighting the importance to assessing the additional burden of fatigue in patients, especially as this burden may be largely related to the hematological toxicity of CDK4/6 inhibitors [38]. In addition, a review of the preclinical and clinical results of abemaciclib by Corona *et al.* noted that the dose-limiting toxicity of abemaciclib was fatigue, whereas neutropenia was the dose-limiting toxicity of palbociclib and ribociclib [39]. Fatigue is a common and distressing symptom experienced by most cancer patients. HCP should provide comprehensive care for these patients and promote supportive interventions [40,41].

“Skin and subcutaneous tissue disorders” have also been reported with CDK4/6 inhibitors, in particular alopecia. Our findings are consistent with the information reported in the SmPC for each CDK4/6 inhibitor [28–30]. A real-world study conducted by Raschi *et al.* using the FAERS database, highlighted the diverse reporting patterns of cutaneous ADR associated with CDK4/6 inhibitors. A high percentage of cutaneous events were considered serious, leading to hospitalization, life threatening events and death [42]. In addition, a published data-based meta-analysis of 8 randomized phase II and III trials evaluating the addition of a CDK4/6 inhibitor to ET in HR+/HER2- metastatic breast cancer suggested that patients receiving abemaciclib with fulvestrant appear to be at a higher risk of developing alopecia [43]. Considering the ICSRs included in our study, it appears that suspected alopecia is more likely to be associated with palbociclib. Therefore, future real-world pharmacovigilance studies should be conducted to more accurately determine the profile of cutaneous and subcutaneous disorders associated with CDK4/6 inhibitors.

A few cases of suspected peripheral neuropathy associated with palbociclib were reported in the EV database. In 2021, a case report and literature review presented peripheral neuropathy as a commonly reported symptom associated with palbociclib [44]. It is well known that chemotherapeutic agents can induce peripheral neuropathy, manifested by symptoms such as paresthesia, allodynia, and hyperalgesia [45,46].

However, it should be noted that this symptom is not described in the palbociclib SmPC [28].

Suspected COVID-19 ADR were also reported in the national and European databases. A recent study reported by Xiao *et al.* mentioned that CDK4/6 inhibitors, namely palbociclib, may induce increased expression level of angiotensin-converting enzyme 2 (ACE2), which may contribute to increased pseudoviral infection of SARS-CoV-2. The authors also highlighted that palbociclib or other cell cycle inhibitors may facilitate COVID-19 infection [47]. In fact, at the beginning of the COVID-19 pandemic, significant changes were applied in the management of cancer patients. A guideline manuscript suggested caution in the use of potentially immunosuppressive cancer therapies [48]. In patients whose disease was controlled by the combination of this targeted therapy with ET, it was recommended to discontinue the CDK4/6 inhibitor. This recommendation was based on reducing the risk of myelosuppression, in particular neutropenia, a predictive factor for unfavorable COVID-19 evolution [49]. Martin *et al.* did not consider it reasonable to discontinue the CDK4/6 inhibitor and continue ET alone, even in women with stable disease. The authors described in their study that the withdrawal of the CDK4/6 inhibitor resulted in disease progression in a large number of patients [50]. Based on the information described, further investigation is needed to understand the relationship between CDK4/6 inhibitors and the development of SARS-CoV-2 infection.

In general, considering the seriousness of the ICSRs analyzed, many of them were classified as “other medically important information”, followed by hospitalization. As reported, CDK4/6 inhibitors are well tolerated, and ADR induced by these drugs are typically easily managed with dose modification and supportive care measures [51].

4.3. Tyrosine kinase inhibitors

TKIs are widely used in the treatment of malignant tumors and play an important role in targeted cancer therapy [52]. Spontaneous reports from the national and European databases were analyzed to better understand the toxicity profile of TKIs in a real-world setting. In this context, the results from our study showed that reports involving RCC, HCC and NSCLC were analyzed, highlighting the different clinical indications of the two TKIs considered, cabozantinib and lorlatinib. A total of 46 ICSRs, involving cabozantinib and lorlatinib as a suspected drug, were reported to the PPS database in 2020, 2021 and 2022. In addition, 1209 ICSRs involving the same suspected drugs were extracted and analyzed from the EV database in 2022. The main results from the two databases are discussed below.

In general, male patients were the most reported by HCP, especially in the 18-64 and 65-85 age groups in both databases. This may be explained by the incidence of the approved clinical indications for cabozantinib and lorlatinib. Globally, HCC is the fifth most common cancer in men and the seventh most common cancer in women [53]. In addition, according to the 2018 GLOBOCAN data, the cumulative global risk of developing RCC is 0.69% in men and 0.35% in women [54]. Men are also twice as likely as women to be diagnosed with lung cancer [55].

According to the national and European databases, "General disorders and administration site conditions" is the most reported SOC, with 23 and 452 ICSRs analyzed, respectively. However, there are some differences in the individual cases reported by SOC. For example, "Psychiatric disorders" and "Nervous system disorders" were mentioned in the national database. On the other hand, "Skin and subcutaneous tissue disorders" were more pointed in the EV database than in the national database. Considering the serious cases versus non-serious cases, a high number of serious cases were reported in the EV database.

In the national database, hypercholesterolemia was the most reported symptom in patients taking lorlatinib. This symptom is classified as very common in the SmPC [56]. Hypercholesterolemia and hypertriglyceridemia normally occur in 81% and 60% of patients with NSCLC, respectively [57]. However, according to the literature, the incidence of permanent discontinuation due to these treatment-emergent ADR is low, with cognitive effects being the most common ADR associated with treatment discontinuation [58]. In our study, cognitive effects were not reported in both databases as one of the main symptoms reported by patients taking lorlatinib.

In addition, according to the EV database results, hypothyroidism is one of the most reported ADR associated with cabozantinib, after disease progression. Peverelli *et al.* retrospectively analyzed 12 patients with RCC treated with cabozantinib, based on real-world experience. In their study, the most common symptoms reported were hypertension, fatigue, aminotransferase elevation, hypothyroidism, and gastrointestinal toxicity such as diarrhea and nausea. The authors emphasized that there were no treatment interruptions due to toxicities, and only 3 patients out of a total of 12 had their dose reduced [59]. Additionally, based on real-world data from an Italian Managed Access Program, patients taking cabozantinib had dose reductions due to a grade 3 increases in aminotransferases and grade 3 diarrhea and fatigue [60]. In our study,

hypertension, fatigue, diarrhea, nausea, and increased transaminases were also reported. However, it was not possible to identify the main action taken. In the EV database, most reports were not clear on this variable ("unknown" reports accounted for almost half of all ICSRs analyzed). Though, drug withdrawal was reported in a significant percentage of ICSRs in patients taking cabozantinib. Another study conducted by our research group involved patients taking cabozantinib and lorlatinib. In this study, hypertension was associated with cabozantinib and dyslipidemia with lorlatinib [61]. These findings are consistent with what has been described previously. According to guidelines, patients taking cabozantinib should have their blood pressure monitored in a regular way, and appropriate antihypertensive therapy should be considered if needed [62].

Stomatitis, an inflammation of the oral tissues, was also reported to be associated with cabozantinib in our study. Stomatitis is considered to be a very common symptom in patients taking these drugs [62]. According to the literature, 25% of patients treated with multitargeted angiogenesis kinase inhibitors develop oral ADR within 2 months of therapy [63]. Arena *et al.* showed that although there was a clear prevalence of stomatitis in patients treated with cabozantinib, the onset of severe stomatitis (grade 3/4) was very low. Patients treated with targeted therapy develop grade 1/2 stomatitis, whereas the effects of conventional chemotherapy are mainly grade 3/4 [64].

In terms of skin disorders, PPES was reported in patients taking cabozantinib in both databases. PPES is a dermatological condition that manifests mainly on the palms of the hands or soles of the feet. Symptoms are described as redness, swelling, and tingling and usually occur within the first 2-5 weeks of treatment. The incidence of PPES during cabozantinib therapy ranges from 21.7% to 56.1% [65,66]. In our study, although most cases were classified as serious, the most reported seriousness criteria was "other medically important information". In fact, most symptoms of this syndrome required dose reduction or discontinuation of treatment for complete resolution. Urea cream 20% and clobetasol propionate are usually recommended [67]. In the lorlatinib ICSRs, peripheral edema was one of the most reported ADR, especially in the national database. In fact, this reaction is classified as very common in the lorlatinib SmPC. Edema is described as one of the most common ADR leading to dose reductions [56]. Peripheral edema is also considered to be a very common reaction in patients taking cabozantinib [62]. However, in our study, this reaction is only associated with lorlatinib.

As mentioned above, the main clinical indication for lorlatinib is NSCLC and for cabozantinib is the treatment of RCC, HCC and thyroid cancer. Looking at the clinical indications reported in the EV database, cabozantinib has also been reported in cases involving the treatment of gastrointestinal stromal tumor (GIST), osteosarcoma and alveolar rhabdomyosarcoma. In this context, a phase II trial, CaboGIST EORTC 1317 (NCT02216578), has shown antitumor activity in GIST. These encouraging results led to the inclusion of cabozantinib in the recent GIST NCCN (National Comprehensive Cancer Network) guidelines as an option in this cancer after failure of other approved regimens [68,69]. Some studies have described the use of cabozantinib in the treatment of patients with osteosarcoma and advanced Ewing sarcoma [70,71]. In addition, one case report was found in the literature describing a patient treated with cabozantinib who was diagnosed with alveolar rhabdomyosarcoma. However, the patient had no clinical benefit from this treatment [72]. In the future, cabozantinib may represent a new therapeutic option in other oncological settings. The importance of the PhV approach is highlighted to better understand the best therapeutic choice for patients.

4.4. References

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Chapter 5
General Conclusions, Limitations and Future Trends

Chapter 5

General Conclusions, Limitations, and Future Trends

5.1. General conclusions

Targeted therapies have changed the landscape of cancer treatment. Their effectiveness is demonstrated through the significant number of preclinical and clinical studies described in the literature for the treatment of various types of cancer. Compared with chemotherapy, targeted therapies have lower toxicity and need to be used for extended periods. High incidences of some ADR may also occur as rare and delayed ADR.

In our study, we explored and discussed, through a retrospective, descriptive and statistical analysis, the toxicity profile associated with three targeted therapeutic classes, namely: PARPi, including olaparib, niraparib and talazoparib; CDK4/6 inhibitors, including palbociclib, ribociclib and abemaciclib and TKIs, namely cabozantinib and lorlatinib. A national and a European database were used to carry out this research. Hematological disturbs were the most common among PARPi class, in particular anemia, neutropenia, and thrombocytopenia. However, the occurrence of anemia did not seem to be the same between the inhibitors studied. Other ADR were reported less frequently such as pneumonitis. In fact, several cases of pneumonitis have been reported in the literature. Nevertheless, the causal association between PARPi therapy and pneumonitis is not well defined. CDK4/6 inhibitors were also very associated with hematological disorders, especially neutropenia in patients taking palbociclib and ribociclib. Patients taking abemaciclib were more likely to experience diarrhea. Peripheral neuropathy was also reported in a few ICSRs associated with palbociclib. However, this symptom is not described in the SmPC of palbociclib. Among TKIs, hypercholesteremia and hypothyroidism were reported frequently, in line with what is described in the SmPC of lorlatinib and cabozantinib, respectively. Cognitive effects appear to be the most common ADR in patients taking lorlatinib that led to treatment discontinuation. In our study, cognitive effects were not among the most reported symptoms by these patients. In fact, the drugs involved in this study are considered to be relatively new to the market, highlighting the need for more high-quality PhV studies.

PhV studies are fundamental in building the safety profile of medicines in a real-world setting, particularly for medicines for which most of the available safety data has been obtained in clinical trials. Patients and HCP should be aware of the great importance of reporting ADR in order to establish new treatment guidelines with maximum therapeutic efficacy, fewer ADR and reduced development of resistance by neoplastic cells.

5.2. Limitations

Despite our efforts to minimize bias in our study, some limitations should be considered. Crucial information on the ICSRs was missing, such as ADR outcomes, action taken, concomitant therapy (no concomitant therapy reported does not mean that the patient did not take it; it may simply not have been reported) and clinical indication. A significant percentage of cases had an "unknown" outcome, action taken and clinical indication. The phenomenon of underreporting and underestimation of the frequency of ADR in oncology is very common. The quality of the individual data collected has a significant impact on PhV studies.

Additionally, in our study, when a report was made through the PPS, the same report was also introduced in the EV database. In this context, some ICSRs may have been analyzed twice. Also, it is important to mention that these data cannot provide evidence on the causal relationship between the ADR and the suspected drugs.

5.3. Future trends

Targeted therapies appear to be revolutionary in the treatment of various types of cancer. The potential of these drugs is noticeable through their approved clinical indications and through those that are ongoing. Several examples can be mentioned highlighting that the potential therapeutic indications of these drugs are expected to increase. Recently, the FDA has approved the combination of enzalutamide with talazoparib as an initial treatment for some patients with mCRPC. In addition, several clinical trials are investigating olaparib (NCT03459846, NCT02546661, NCT04579133, NCT03375307, NCT03448718) and niraparib (NCT03945084, NCT03425201) in bladder or urothelial cancer as monotherapy or in combination with immune checkpoint inhibitors. Other potentially approved PARPi, such as veliparib, have shown significant therapeutic activity in phase III trials for the treatment of BRCA breast cancer and ovarian cancer. Phase I and phase II trials have also investigated the potential of abemaciclib (NCT03837821) and palbociclib (NCT02334527) in the treatment of bladder cancer. In addition, palbociclib has been clinically tested in combination with immune checkpoint

inhibitors. Given this, it is expected that more pharmacological combinations involving these classes of drugs and other agents with different mechanisms of action will be explored in the future, considering the synergistic effects that can be achieved. PhV studies, especially in a real-world setting, are essential to ensure patient safety in these new clinical indications or therapeutic combinations involving the drugs studied in this thesis.