Cancer Chemotherapy and Pharmacology
https://doi.org/10.1007/s00280-021-04331-0

ORIGINAL ARTICLE

Impact of pharmacist consultation at clinical trial inclusion: an effective way to reduce drug–drug interactions with oral targeted therapy

Fanny Leenhardt[1,2,3,8] · Marie Alexandre[4] · Severine Guiu[3,4] · Stephane Pouderoux[4] · Melanie Beaujouin[5] · Gerald Lossaint[6] · Laurent Philibert[2] · Alexandre Evrard[1,3,7] · William Jacot[3,4]

Received: 11 May 2021 / Accepted: 10 July 2021

Abstract

Purpose Pharmacist consultation is unfrequently performed in oncology clinical trials that include patients who often have many co-treatments increasing the risk of drug–drug interactions (DDI). The aim of this study was to determine whether best possible medication history (BPMH) by hospital pharmacist at inclusion and therapeutic drug monitoring could be used for DDI risk evaluation and for current oral targeted therapy management.

Methods A prospective clinical trial (ALCINA 2, NCT04025541) was carried out in metastatic breast cancer cohort treated by palbociclib to conduct pharmacokinetics-toxicity correlation study. BPMH was prospectively performed by the hospital pharmacist at each trial inclusion, followed by a contact to the patient's community pharmacy to complete the collected data. Pharmacokinetic analysis was performed on blood samples collected at day 15 of cycle 1 of palbociclib treatment.

Results Pharmacist interventions indicated that at inclusion, current medications were incomplete for 63% of the enrolled patients (32/51). It allowed the real-time management of high-risk DDI detected in third of patients. The palbociclib C_{trough} geometric median (min–max) was significantly higher in cohort with potential DDI [106 ng/mL (66.7–113)], than cohort without potential DDI [70.1 ng/mL (54.1–89.7)], $p = 0.0284$.

Conclusion This is the first prospective study evaluating the relevance of proactive BPMH by pharmacist with contact to the community pharmacy during the inclusion step of a clinical trial to ensure the efficacy and safety of the investigated drug. This investigation was thus able to highlight the statistically significant impact of these DDI on palbociclib plasma concentration variation during the clinical trial.

Trial registration Clinicaltrials.gov identifier NCT04025541.

Keywords Clinical trial · Oncology breast cancer · Clinical pharmacy · Drug–drug interaction

✉ Fanny Leenhardt
fanny.leenhardt@icm.unicancer.fr

1 Laboratoire de Pharmacocinétique, Faculté de Pharmacie, Université de Montpellier, Montpellier, France

2 Service Pharmacie, Institut du Cancer de Montpellier, Université de Montpellier, 208 rue des Apothicaires, 34298 Montpellier, France

3 Institut de Recherche en Cancérologie de Montpellier (IRCM), INSERM U1194, Université de Montpellier, Montpellier, France

4 Département d'oncologie Médicale, Institut du Cancer de Montpellier, Université de Montpellier, 208 rue des Apothicaires, 34298 Montpellier, France

5 Centre de Recherche Clinique, Institut du Cancer de Montpellier, 208 rue des Apothicaires, 34298 Montpellier, France

6 Département de Recherche Clinique, Institut du Cancer de Montpellier, Université de Montpellier, 208 rue des Apothicaires, 34298 Montpellier, France

7 Laboratoire de Biochimie et Biologie Moléculaire, Centre Hospitalier Universitaire Nîmes, Nîmes, France

8 Institut du Cancer de Montpellier, 208 Avenue des Apothicaires, Montpellier, France

Published online: 20 July 2021

Introduction

Clinical pharmacy activities are currently performed after hospital admission by hospital pharmacists with the aim of optimizing the current treatment efficacy and safety in patients who are already taking different drugs. Complete medication history is a base of medication reconciliation and allow clinicians to ensure optimized treatment decision-making and to limit prescription errors [1–5]. Patients with cancer often receive different treatments to manage the cancer and also other comorbid conditions, and sometimes also use over-the-counter drugs and complementary therapies (e.g. vitamins, nutraceuticals, health supplements). Therefore, the comprehensive collection of all current treatments and their comparison with the medications needed for cancer management could reduce the risk of drug–drug interactions (DDI) and misuse [6, 7]. The exhaustive collection of all the drugs taken by a patient is always difficult because this requires to cross-referencing the information sources (at least the patient's medication history and medical records). In this context, the medication list reported by the patient's usual dispensing pharmacist is a valuable tool for refining the information on treatments initiated by different prescribers. However, access to community pharmacies is essentially limited to telephone contacts that require a significant amount of time. In the framework of clinical trials on anticancer drugs, pharmacist consultation at the time of the inclusion visit is also relevant, although it is not routinely implemented [8]. Indeed, the sponsors of clinical trials normally establish a list of drugs that are prohibited or not recommended during the trial to limit DDI risk, and these compounds are typically part of the clinical study inclusion/exclusion criteria. For example, in clinical trials on palbociclib (a CDK4/6 inhibitor), prohibited and non-recommended drugs include strong CYP3A inhibitors/inducers, drugs known to cause QT interval prolongation, and also gastric acid-suppressive agents (GAS) [9]. There are relatively few studies on pharmacist interview in oncology clinical trials, with only one prospective study in an early phase trial in 469 patients (currently only released as an abstract) and retrospective studies [10–12]. These studies suggest that best possible medication history (BPMH) by the hospital pharmacist might have a significant impact in clinical research settings. A publication in 2017 provides recommendations on reviewing concomitant medications for participants in oncology clinical trials [8]. The characterization of DDI risk and their clinical relevance is very difficult to assess as few prospective studies have been published on the impact of DDI with oral targeted therapy. Therapeutic drug monitoring (f) is already used for tyrosine kinase inhibitors (TKIs) to characterize factors, like DDI, food effect or lack of observance that may influence pharmacokinetic parameters and thus the TKIs plasma concentration. During our clinical trial, we performed TDM of palbociclib for each patient in routine care to evaluate pharmacokinetic variabilities, including DDI, on palbociclib plasma concentration. The objective of this prospective study was to evaluate the relevance and impact of proactive pharmacist consultation and DDI management during the inclusion step of a clinical trial and the influence of these DDI on palbociclib pharmacokinetic profile.

Method

This study used the clinical data collected in the framework of a prospective and monocentric pharmacokinetics-toxicity correlation study (Clinicaltrials.gov identifier NCT04025541) carried out at the Institut du Cancer de Montpellier (ICM), France, in accordance with Good Clinical Practice (GCP). Patients with metastatic, hormone-sensitive, HER2-negative breast cancer were enrolled between June 2018 and July 2020 and received first-line treatment with palbociclib (125 mg per day for 3 of 4 weeks) associated with an aromatase inhibitor. This trial aims to evaluate, among others thing, the pharmacokinetic profile of palbociclib in real-life cohort and the occurrence and influence of DDI by pharmacist assessment. Patients were included after signature of the informed consent. After the medical consultation and inclusion in the clinical trial, patients underwent hospital pharmacist interview to identified co-treatments and DDI risk. BPMH was obtained and compared to all medicines dispensed by community pharmacy. The hospital pharmacist contacted each patient's community pharmacy to obtain additional information on the drugs dispensed to the patient. Pharmacist intervention was performed in front of DDI risk. The choice of therapeutic management (withdrawal, switch, or dose modification) was made in clinical staff (oncologist, pharmacist and more or less the general practitioner) depending on the patient and drug involved in the DDI, according to the clinical and pharmacological context. Patients were then classified in two groups according to their DDI risk toward palbociclib: a) clinically relevant DDI, and b) clinically relevant unknown DDI. If necessary, the hospital pharmacist and oncologist made treatment changes to limit the risk of DDI occurrence. We then quantified concentration of palbociclib (plasma trough concentration; C_{trough}) in the cohort of patients. For pharmacokinetic analysis, blood samples were collected at day 15 (steady-state reached) of the first cycle at the predose to estimate plasma exposure (C_{trough}) using our previously validated HPLC–MS/MS method [13]. Patients were classified, during pharmacist consultation, according to their risk of DDI that might lead to inhibition of CYP3A4 and/or P-glycoprotein, involved in

pharmacokinetic of palbociclib. Database search (e.g. DDI predictor®, Drugs.com®, Pubmed®) allowed the identification of the candidate drugs that could cause DDI.

Statistical analysis

The Wilcoxon rank-sum test with continuity correction was used to compare the distribution of quantitative variables (palbociclib plasma exposure and risk of DDI).

Results

The analysis concerned a population of 51 patients included in the clinical trial and whose community pharmacy could be contacted. After consultation with the oncologist and clinical research associate, data on the current treatments were collected from the medical file and from the information given by the patient at enrolment in the clinical trial (patient interview or prescriptions, if available). The mean number of drugs taken by each patient was 2.5 (min–max: 0–7). Then, the hospital pharmacist carried out a medication consultation with each patient.

Pharmacist consultation

For 25.5% of patients (13/51), at least one additional co-treatment was identified during the consultation with the hospital pharmacist that was not mentioned during the inclusion visit: at least one allopathic treatment (15.7%, 8/51), but also nutritional supplements or herbal medicines (13.7%, 7/51). The most frequent additional allopathic treatments identified during the medication consultation were gastric acid-suppressive agents (pump proton inhibitors and histamine antagonists) and hypertension drugs (lercanidipine, amlodipine, bisoprolol, irbesartan, etc.).

Community pharmacy

Following the pharmacist consultation, BPMH was completed by a telephone call to the patient's usual dispensing pharmacy. For 37.2% of patients (19/51), this telephone call gave additional information (e.g. addition, modification) about allopathic and complementary (e.g. nutritional supplements or herbal medicines) co-treatments: at least another allopathic co-treatment and at least one herbal co-treatment were added to the already collected drugs for 18 and 2 patients, respectively. The most frequent additional allopathic treatments identified by interaction with the community pharmacist were gastric acid-suppressive agents (PPIs and histamine antagonists), cardiovascular drugs (manidipine, spironolactone, lysine acetylsalicylate, pravastatin), anxiolytics and sedatives (e.g. diazepam, alprazolam), and anti-diabetic treatment (repaglinide).

Complete medication history and drug–drug interaction management

The DDI risk for each patient was determined by combining the information on current drug use obtained from the patient, the pharmacist consultation and the telephone call with the community pharmacy. At inclusion time, the list of current medications would not have been complete for 63% of patients (32/51) without the proactive coordination between hospital and city pharmacists. Specifically, allopathic drug collection was incomplete for 47% of patients (24/51) and use of herbals and nutritional supplements was not reported by 16% of patients (8/51) (Fig. 1). In conclusion, information on poly-drug use was complete only for 37% (19/51) of patients at enrolment, before pharmacist consultation. The risk of DDI was then characterized according to whether palbociclib was a victim or perpetrator.

The medication history and the DDI database search allowed identifying the patients at risk of DDIs towards palbociclib ($n = 30/51$; 59%) and optimizing the use of

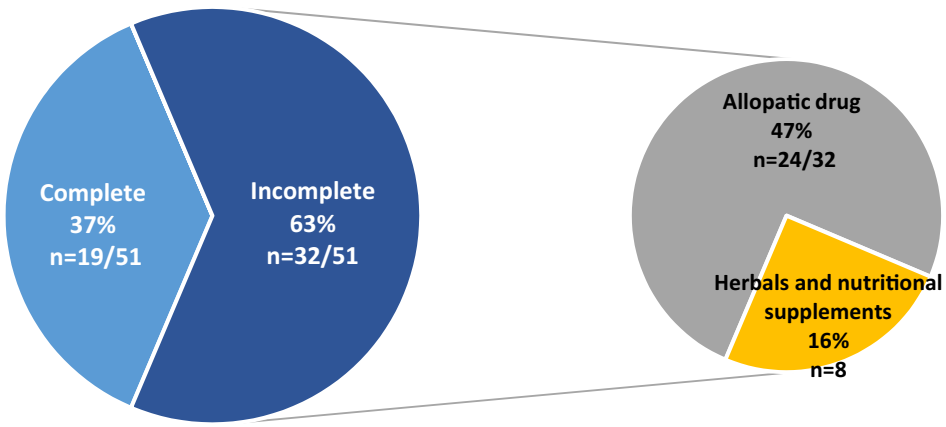

Fig. 1 Medication history at inclusion. Patient with complete/incomplete data on the currently used drugs before BPMH, and additional treatments identified by pharmacist consultation and community pharmacy (*n* patients)

allopathic co-treatments (withdrawal, switch, or dose modification) to limit this risk (Fig. 2). Patients were then classified in two groups according to their DDI risk on palbociclib pharmacokinetic: (a) clinically relevant DDI (GAS therapy) and (b) clinically relevant unknown DDI. Specifically, a clinically relevant DDI risk between palbociclib and GAS was identified in 25.5% of patients (13/51) because these compounds can reduce palbociclib absorption and thus, exposition [14–16] (Fig. 2). For nine patients, pharmaceutical intervention led to medication optimization (stop, switch or taking during palbociclib pause). However, a DDI risk remained for 6/10 patients (Fig. 2).

Moreover, a risk of overexposure to palbociclib was identified for 33.3% (17/51) of patients, due to co-treatment-mediated inhibition of CYP3A4 or P-glycoprotein (implicated in the pharmacokinetic pathway of palbociclib) (e.g. amlodipine, nifedipine, ivabradine, simvastatin) [17, 18]. However, the compound and dosage were not modified in these cases due to the unknown clinical impact of these DDIs and the indication of these treatments (Fig. 2). On the other hand, palbociclib weakly inhibits CYP3A4 and may increase the concentration of drugs metabolized by this enzyme (as indicated in the summary of the product characteristics) [16]. These interactions ($n=5$) were managed by the oncologist and pharmacist to limit the risk of increased toxicity related to co-treatment. This involved anticoagulants and statins treatments, leading to patient overexposition due to the combination with palbociclib: apixaban treatment was switch to warfarin or atorvastatin was stopped or switch to pravastatin. A patient could thus be part of different groups (DDI mediated by palbociclib and/or co-medciations) as long as he or she is taking several drugs that may interact.

Pharmacokinetic impact of DDI on palbociclib concentration

The occurrence of drug interactions is relatively frequent, but the most difficult thing is to characterize the clinical relevance of these DDI. In our clinical trial, we were able to quantify palbociclib plasma concentration at day 15 of cycle 1 (trough concentration, C_{trough}). C_{trough} was asses by HPLC–MS quantification. The method has been developed, validated and published [13]. Predose palbociclib plasma concentration at day 15 of the first treatment cycle (D15C1) was analyzed for 47 patients (four patients excluded of pharmacokinetic analysis because blood samples were not collected at C_{trough}). The D15C1 C_{trough} [geometric mean (min–max)] was 80.4 ng/mL (21.2 ng/mL–139.3 ng/mL). Therefore, they were divided in two groups based on the presence ($n=17$) or not ($n=30$) of potential DDI (mediated by CYP3A4 and P-glycoprotein inhibitors). D15C1 palbociclib C_{trough} was significantly different in patients with and without potential DDI ($p<0.05$) (Fig. 3). The C_{trough} geometric mean and median (min–max) was significantly lower in cohort without potential DDI [73.9 ng/mL and 70.1 ng/mL (54.1–89.7)] than cohort with potential DDI [91.7 ng/mL and 106 ng/mL (66.7–113)], $p=0.0284$. Pharmacokinetic impact of DDI GAS agent mediated, could not be assessed in the cohort due to the size of the population.

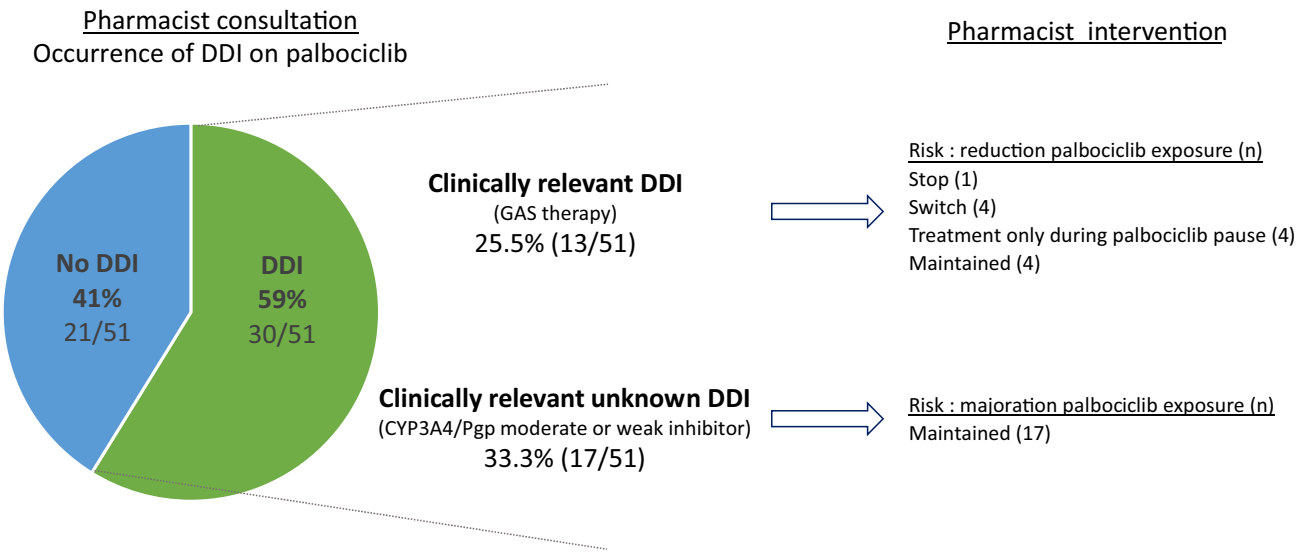

Fig. 2 Patients at risk of DDIs towards palbociclib (%, *n*) and pharmacist intervention

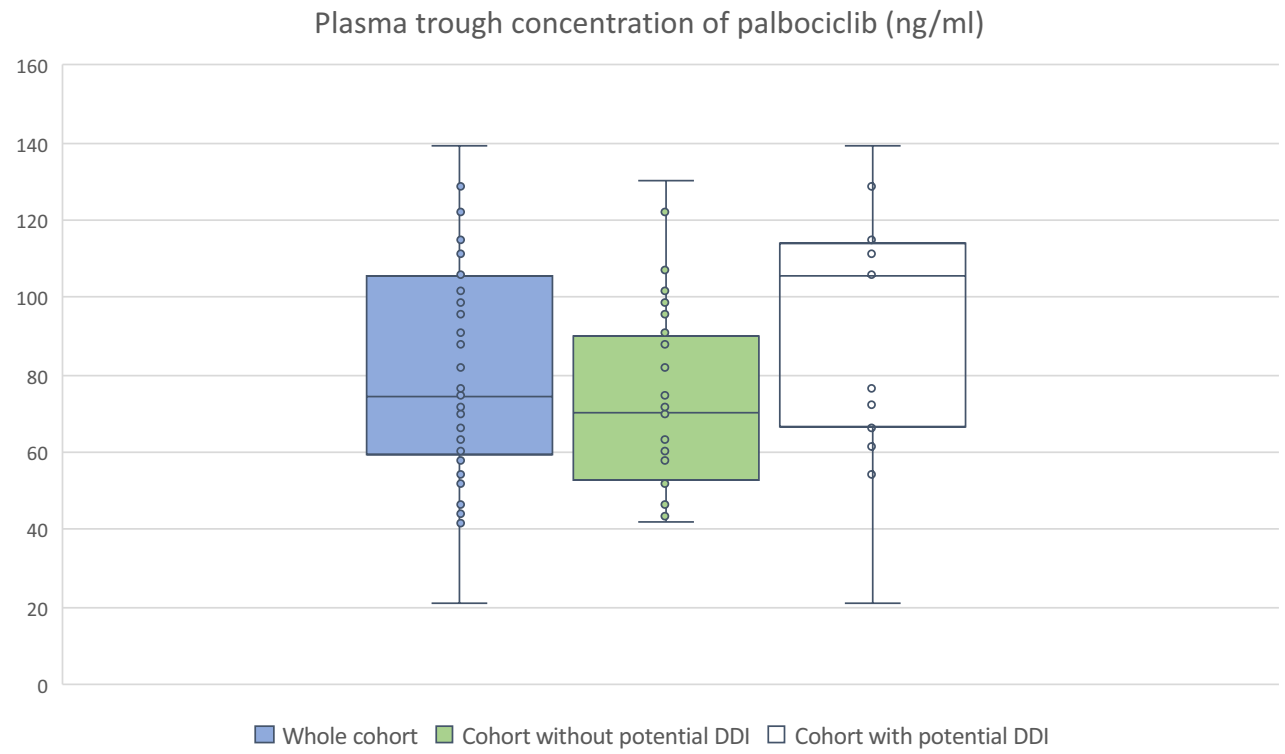

Fig. 3 Palbociclib plasma exposure at cycle 1 day 15 in the whole cohort ($n=47$) and in the two subgroups with ($n=17$) and without ($n=30$) potential DDI by CYP3A4 inhibitor

Discussions

Here, we report the results of complete medication history performed by hospital pharmacist at inclusion in a prospective clinical trial to determine poly-drug use and DDI risk. Based on the cooperation between oncologist, hospital pharmacist and patient's community pharmacy, BPHM indicated that the information on the current treatments was incomplete for 63% of the included patients. Moreover, the pharmaceutical intervention allowed reducing DDI risk in almost one third of patients. The impact of pharmacist consultation on DDI reduction and on medication safety is widely acknowledged, but limited resources are allocated to this activity. Therefore, in many centers, DDI screening at trial inclusion is often performed by the oncologist/nurse and/or clinical research associate. The hospital pharmacist or other hospital departments are rarely involved [19]. Usually, the trial sponsors give a list of prohibited treatments to limit DDI risk. For example, the PALOMA trials (palbociclib in patients with advanced breast cancer) listed prohibited and non-recommended treatments, such as strong CYP3A inhibitors/inducers and GAS, to limit DDI risk [9]. In our study, except for GAS, none of the prohibited and not recommended treatments listed in the PALOMA study protocols and investigator's brochures was identified in the included patients. However, DDI can be caused also by other compounds [9, 14]. Herbal medicines are classically not recommended or prohibited during the active treatment phase and also in many clinical trials. However, patients are increasingly using herbals, in addition to complementary therapies, particularly in oncology, while rarely informing their oncologist about it [20]. Thus, the collection of co-medications, in addition to being complex to carry out, is most often under-representative of the exhaustive list of compounds taken by patients. For instance, the French retrospective analysis of early phase clinical trials in oncology ($n=469$ patients) identified 12% of DDIs, half of which concerned prohibited treatments and which could have been avoided by real-time pharmaceutical analysis, as was the case for our clinical trial [10]. In our subgroup with potential DDI mediated by CYP3A4 inhibition ($n=17$), interactions between palbociclib and these inhibitors could explain the mean palbociclib concentration variability (73.9 ng/mL vs 91.7 ng/mL with DDI), $p=0.0284$. Thanks to the TDM of palbociclib, we were able to investigate the impact of DDI on the pharmacokinetics of palbociclib; however, the impact on the effectiveness and safety of the palbociclib is currently not known. Our study allowed highlighting the contribution of prospective pharmacist consultation and BPHM in oncology clinical trials, resulting in the real-time management of DDI. The addition of a clinical pharmacy activity for clinical trials is a strategy to ensure the correct evaluation of the

tested drug safety and efficacy. Thus, we were able to highlight that palbociclib exposition is significantly influenced according to the combined medications (such as CYP3A4 or Pgp inhibitors). The next step is to characterize the relationship between plasma concentration and the occurrence of high-grade neutropenia, a frequent toxicity of palbociclib. Further studies are in progress to assess PK/toxicity correlation of palbociclib and this will be soon evaluated after the clinico-biological data will be available.

Author contributions FL: conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; roles/writing—original draft. MA: Investigation; validation; writing—review and editing. SG: Investigation; validation; writing—review and editing. SP: Investigation; validation; writing—review and editing. MB: Investigation; supervision; resources; data curation; project administration. GL: Methodology; supervision; data curation; project administration; visualization. LP: Conceptualization; roles/writing—original draft; writing—review and editing. AE: Conceptualization; methodology; supervision; validation; roles/writing—original draft; writing—review and editing. WJ: Conceptualization; formal analysis; investigation; methodology; project administration; supervision; validation; visualization; roles/writing—original draft; writing—review and editing.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

Data availability The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval This study used the clinical data collected in the framework of a prospective and monocentric pharmacokinetics-toxicity correlation study (Clinicaltrials.gov identifier NCT04025541) carried out at the Institut du Cancer de Montpellier (ICM), France, in accordance with Good Clinical Practice (GCP). Committee for the protection of persons: Positive opinion issued on September 4, 2018; IdRCPN°2018-A00064-51.

Informed consent All patient included in the clinical trial have signed the consent form.

Permission to reproduce material from other sources Not concerned.

References

1. Cousins DD, Heath WM (2008) The National Coordinating Council for medication error reporting and prevention: promoting patient safety and quality through innovation and leadership. Jt Comm J Qual Patient Saf 34:700–702. https://doi.org/10.1016/s1553-7250(08)34091-4
2. Ballerie A, Alix L, Bajeux E, Jégo P, Lescoat A, Hue B (2019) The collaboration of clinical pharmacists and physicians for medication safety. Lancet 394:2240. https://doi.org/10.1016/S0140-6736(19)32608-X
3. Dufay E, Morice S, Dony A, Baum T, Doerper S, Rauss A et al (2016) The clinical impact of medication reconciliation on admission to a French hospital: a prospective observational study. Eur J Hosp Pharm Sci Pract 23:207–212. https://doi.org/10.1136/ejhpharm-2015-000745
4. EMA (2015) Good practice guide on recording, coding, reporting and assessment of medication errors. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practice-guide-recording-coding-reporting-assessment-medication-errors_en.pdf
5. WHO World Health Organization (2014) The high5s project—standard operating protocol for medication reconciliation. https://www.who.int/patientsafety/implementation/solutions/high5s/h5s-sop.pdf
6. Patel E, Pevnick JM, Kennelty KA (2019) Pharmacists and medication reconciliation: a review of recent literature. Integr Pharm Res Pract 8:39–45. https://doi.org/10.2147/IPRP.S169727
7. Almanasreh E, Moles R, Chen TF (2016) The medication reconciliation process and classification of discrepancies: a systematic review. Br J Clin Pharmacol 82:645–658. https://doi.org/10.1111/bcp.13017
8. McGahey KE, Weiss GJ (2017) Reviewing concomitant medications for participants in oncology clinical trials. Am J Health-Syst Pharm 74:580–586. https://doi.org/10.2146/ajhp151052
9. FDA (2020) Center for drug evaluation and research, labeling (207103Orig1s002, Palbociclib) 2016. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207103Orig1s002.pdf. Accessed 17 Nov 2020
10. Malifarge L, Deppenweiler M, Italiano A, Lortal B (2020) 1842P Impact of medication reconciliation for patients enrolled in oncology early phases clinical trials: a drug-drug interactions retrospective study. Ann Oncol 31:S1057. https://doi.org/10.1016/j.annonc.2020.08.1489
11. Redic KA, Skyles A, Zaccardelli J (2017) Potential role of a pharmacist to enhance medication-related aspects of clinical trials conducted in a dedicated clinical research unit. Contemp Clin Trials Commun 6:55–57. https://doi.org/10.1016/j.conctc.2017.03.003
12. Marcath LA, Coe TD, Hoylman EK, Redman BG, Hertz DL (2018) Prevalence of drug-drug interactions in oncology patients enrolled on National Clinical Trials Network oncology clinical trials. BMC Cancer 18:1155. https://doi.org/10.1186/s12885-018-5076-0
13. Leenhardt F, Gracia M, Perrin C, Muracciole-Bich C, Marion B, Roques C et al (2020) Liquid chromatography–tandem mass spectrometric assay for the quantification of CDK4/6 inhibitors in human plasma in a clinical context of drug-drug interaction. J Pharm Biomed Anal 188:113438. https://doi.org/10.1016/j.jpba.2020.113438
14. Bellet M, Ahmad F, Villanueva R, Valdivia C, Palomino-Doza J, Ruiz A et al (2019) Palbociclib and ribociclib in breast cancer: consensus workshop on the management of concomitant medication. Ther Adv Med Oncol 11:175883591983386. https://doi.org/10.1177/1758835919833867
15. Sun W, Klamerus KJ, Yuhas LM, Pawlak S, Plotka A, O'Gorman M et al (2017) Impact of acid-reducing agents on the pharmacokinetics of palbociclib, a weak base with pH-dependent solubility, with different food intake conditions. Clin Pharmacol Drug Dev 6:614–626. https://doi.org/10.1002/cpdd.356
16. EMA (2020) RÉSUMÉ DES CARACTÉRISTIQUES DU PRODUIT, Ibrance n.d. https://www.ema.europa.eu/en/documents/product-information/ibrance-epar-product-information_fr.pdf. Accessed 23 March 2020
17. Tod M, Goutelle S, Bleyzac N, Bourguignon L (2019) A generic model for quantitative prediction of interactions mediated by

efflux transporters and cytochromes: application to P-glycoprotein and cytochrome 3A4. Clin Pharmacokinet 58:503–523. https://doi.org/10.1007/s40262-018-0711-0

18. Drugs.com (2020) Drug Interaction Report : Palbociclib information from Drugs.com. DrugsCom n.d. https://www.drugs.com/interactions-check.php?drug_list=1717-0,3602-0. Accessed 23 March 2020
19. Hertz DL, Siden R, Modlin J, Gabel LL, Wong SF (2018) Drug interaction screening in SWOG clinical trials. Am J Health-Syst Pharm 75:607–612. https://doi.org/10.2146/ajhp170449
20. Correard F, Blanc-léger F, Roux C, Lobrot F, Pinguet F, Pourrat X et al (2019) Complementary medicine and cancer: a French multicenter survey. J Clin Oncol 37:e23127–e23127. https://doi.org/10.1200/JCO.2019.37.15_suppl.e23127