Supplementary Material

Table S1. Category of drug inhibitors and inducers of cytochrome p-450.

	Strong inhibitor	Moderate inhibitor	Weak inhibitor	Strong inducer	Moderate inducer	Weak inducer
Effect on the sensitive index substrate (SS)	Increases the AUC of SS ≥5-fold	Increases the AUC of SS ≥2 to <5-fold	Increases the AUC of SS ≥1.25 to <2-fold	Decreases the AUC of SS ≥80%	Decreases the AUC of SS ≥50% to <80%,	Decreases the AUC of SS ≥20% to <50%,
Clinical significance	Monitoring toxicity	Monitoring toxicity	Low risk of DDI	Monitoring efficacy	Monitoring efficacy	Low risk of DDI
Recommendations	Consider decreasing the dose of substrate	Monitoring	None	Consider increasing the dose of substrate	Monitoring	None

AUC: Area under the concentration-time curve; DDI: Drug-drug interaction.
Information about categorization of a particular drug can be obtained in several webpages [1–3]

Table S2. Membrane transporters involved in a possible DDI with palbociclib or ribociclib based on *in vitro* data [1,3,4].

Superfamilies	Transporter	Organs	Drug substrates
SLC (uptake the drug into the cells) (*except MATE 1/2 that is efflux pump)	**OATPB1/3:** Organic anion transporter polypeptide.	Hepatocyte	Pitavastatin, pravastatin, rosuvastatin, asunaprevir, atorvastatin, bosentan, cerivastatin, danoprevir, docetaxel, paclitaxel, repaglinide, simvastatin
	OCT1: Organic cation transporter	Hepatocyte and intestinal enterocyte	Metformin
	OCT2: Organic cation transporter	Kidney proximal tubule and neurons	Metformin
	OAT1-3: Organic anion transporter	Kidney	Ciprofloxacin, adefovir, cefaclor, ceftizoxime, famotidine furosemide, ganciclovir, methotrexate, oseltamivir, penicillin G
	MATE 1/2*: multidrug and toxin extrusion protein	Kidney and liver	Metformin
ABC efflux pump **(Take drugs out of the cells).**	**Pgp**: MDR1(Multi Drug Resistance 1), P-glycoprotein, ABCB1	Intestinal enterocytes, blood-brain barrier, hepatocyte, kidney proximal tubule	Digoxin, dabigatran, colchicine
	BCRP: Breast Cancer Resistance Protein	Gastrointestinal tract, liver, kidney, brain, mammary tissue, testis and placenta	Rosuvastatin, pravastatin
	BESP: Bile salt export pump	Hepatocytes	Pravastatin

SLC: Solute Carrier, ABC: ATP-binding cassette

Table S3. Equations used to correct QT duration according to heart rate

Equation 1. Bazett formula	$QT_c(JT_c) = QT\ (JT)/RR^{1/2}$
Equation 2 Fridericia formula	$QT_c = QT/\sqrt[3]{RR}$
Equation 3 Framingham formula	$QT_c = QT + 0.154\ x\ (1 - RR)$

QT: Duration of QT in milliseconds. RR: Duration of RR interval in seconds.

Table S4. Antidepressant drugs according to their mechanism of action [5].

Type of Antidepressant	Mechanism of action/Toxicity	Drugs
Tricyclic Antidepressants (TCAs)	Reuptake inhibition of serotonin and noradrenaline plus antihistaminic, antimuscarinic and anti-alpha 1 actions	Clomipramine, Imipramine, Amitriptyline
Monoamine Oxidase Inhibitors (MAOIs)	Inhibition of monoamine oxidase enzymatic activity and increase availability of serotonin, noradrenaline and dopamine	Fenelzine, Tranilcipromine Moclobemide, Selegiline
Selective Serotonine Reuptake Inhibitors (SSRIs)	Inhibition of serotonin reuptake	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
Serotonine and Noradrenaline Reuptake Inhibitors (SNRIs)	Inhibition of serotonin and noradrenaline reuptake	Venlafaxine, Desvenlafaxine, Duloxetine, Minalcipran
Noradrenaline Reuptake Inhibitors	Inhibition of noradrenaline reuptake and of G protein-coupled inwardly-rectifying potassium channels	Reboxetine
Noradrenergic and Specific Serotonergic	Blockade of presynaptic alpha-2 adrenergic inhibitory autoreceptor and blockade specific postsynaptic serotonergic 5-HT2 and 5-HT3 receptors	Mirtazapine
Selective Dopamine and Noradrenaline Reuptake Inhibitors	Release dopamine and noradrenaline and inhibit reuptake; non-competitive antagonism on nicotinic receptors	Bupropion
Serotonine Antagonist and Reuptake Inhibitors	Blockade postsynaptic serotonergic 5-HT2A receptor and reuptake of serotonin, noradrenaline and dopamine; antagonism alpha-1adrenergic receptor	Trazodone Nefazodone (not available in Spain)
Serotonine Modulators	Agonists, partial agonists or pure antagonists of serotonergic receptors Inhibition of serotonin reuptake	Vortioxetine Vilazodone
Melatonin Agonist M1 and M2 Receptors	M1 and M2 receptor agonist activity	Agomelatine
Psychostimulants	Inhibition of dopamine and noradrenaline reuptake	Methylphenidate

Agomelatine is not indicated due to liver toxicity; reboxetine has DDIs with palbociclib and ribociclib via CYP3A4 and increases blood pressure at higher doses; bupropion decreases the convulsive threshold, may decrease tamoxifen efficacy via inhibition of CYP2D6 and can provoke insomnia and headache.

Table S5. Incidence of neutropenia in palbociclib and ribociclib breast cancer trials.

Neutropenia as adverse event	***Palbociclib/Ribociclib Arm***				***Placebo Arm***			
	All Grades	***Grade1-2***	***Grade 3***	***Grade 4***	***All Grades***	***Grade1-2***	***Grade 3***	***Grade 4***
PALOMA-3[6]	*81%*	*16%*	*55%*	*10%*	*4%*	*3%*	*0*	*1%*
PALOMA-2[7]	*81.8%*	*12.7%*	*57.4%*	*11.7%*	*6%*	*4.6%*	*0.9%*	*0.5%*
MONALEESA-2[8]	*76.9%*	*14.9%%*	*52.4%*	*9.6%*	*5.8%*	*4.6%*	*1.2%*	*0%*
MONALEESA-7[9]	*76%*	*15%*	*51%*	*10%*	*8%*	*4%*	*3%*	*1%*
MONALEESA-3[10]	*69.6%*	*16.2%*	*46.6%*	*6.8%*	*2.1%*	*2.1%*	*0%*	*0%*
CompLEEment*	*47.3%*	*14.2%*	*29.4%*	*3.7%*	*NA*	*NA*	*NA*	*NA*

Treatment in PALOMA trials: Palbociclib 125 mg 3weeks on/1 week off. Two dose reductions permitted: to 100 and 75 mg, respectively. Treatment in MONALEESA trials: Ribociclib 600 mg 3weeks on/1 week off. Two dose reductions permitted: to 400 and 200 mg, respectively.
*Preliminary results[11]: Data from the first 1,008 first enrolled patients who completed 56 days of follow-up or discontinued study before the cut-off date (October, 3, 2017). So, lower reported incidence rates can be due to short follow-up; NR: Not reported; NA: Not applicable.

Table S6. Infections in ribociclib and palbociclib randomized breast cancer trials.

Infection as adverse events	***Palbociclib/Ribociclib Arm***				***Placebo Arm***			
	All Grades	***Grade1-2***	***Grade 3***	***Grade 4***	***All Grades***	***Grade1-2***	***Grade 3***	***Grade 4***
PALOMA-3[12]	*51%*	*48%*	*2%*	*1%*	*39%*	*36%*	*3%*	*0%*
PALOMA-2[12]	*59%*	*53%*	*6%*	*0%*	*42%*	*37.5%*	*4.5%*	*0%*
MONALEESA-2[13]	*50%*	*35.8%%*	*3.6%*	*0.6%*	*42%*	*39.8%*	*2.1%*	*0.3%*
MONALEESA-7[9]	*47%*	*43%*	*4%*	*0%*	*37%*	*36%*	*1%*	*0%*

Infections were not included in the table of frequent adverse events of the MONALEESA-3 and CompLEEment trials; in those studies, cut-off for including adverse events was 15% and 5%, respectively [14,15].

Table S7: Frequency of liver abnormalities in the MONALEESA-2, MONALEESA-7 and MONALEESA-3 trials.

MONALEESA-2 Adverse Event (%)	**Ribociclib plus Letrozole N=334**			**Placebo plus Letrozole N=334**			**Reference (M follow-up)**
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**	
ASTincreased	**15.6**	**7.5**	**1.8**	**3.9**	**1.2**	**0**	**Ref.**[13] **1^{ary} analysis (15.3 m)**
ALT increased	**15.0**	**4.8**	**0.9**	**3.6**	**1.2**	**0**	
Abnormal LFTs	**20.1**	**8.4**	**1.8**	**6.4**	**2.4**	**0**	**Update analysis Ref.**[8] **(26m)**
MONALEESA-7 Adverse Event (%)	**Ribociclib plus Goserelin plus Tamoxifen or Letrozole**			**Placebo plus Goserelin plus Tamoxifen or Letrozole N=334**			**Reference (M follow-up)**
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**	
AST increased	**12.8**	**5.4**	**0**	**7.4**	**1.5**	**0**	**Ref.** [9] **1^{ary} analysis (19.2m)**
ALT increased	**11.9**	**3.6**	**0**	**8.9**	**1.2**	**0**	
MONALEESA-3 Adverse Event (%)	**Ribociclib plus Fulvestrant N=483**			**Placebo plus Fulvestrant N=241**			**Reference (M follow-up)**
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**	
AST increased	**15**	**7**	**2**	**5**	**<1**	**0**	**Ref.** [10] **1^{ary} analysis (20.4 m)**
ALT increased	**15**	**5**	**1**	**5**	**<1**	**0**	

M: Median; m= months, AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LFTs: Liver function tests; 1^{ary}: Primary

Table S8. G3/4 liver toxicity in ribociclib arm of MONALEESA-2: Summary of the 37 reported cases according to FDA review [16].

Adverse event	Frequency N (%)	Duration of G3 toxicity (range in days)	Management of ribociclib and outcome
G3 increase of both AST and ALT	**16 (43.2%)***	ALT:10-72+ AST: 9-79+ Overall, longer duration of G3 ALT toxicity than G3 AST toxicity	• **Interruption**:5 patients; 3 in recovery, 2 recovered • **Withdrawal**: 6 patients; 2 not recovered**, **1 of them considered SAE**; 4 in recovery • **Dose reduction:** 3 patients; 2 in recovery, 1 recovered • **Not changed:** 2 patients not recovered
Only G3 increase of ALT	**11 (29.7%)**	12-56	• **Interruption:** 3 patients; 2 recovered, 1 non- applicable • **Withdrawal**:4 patients; 1 recovered, 2 in recovery, 1 not recovered • **Dose Reduction:** 2 cases; both in recovery • **Not changed:** 2 not recovered (+28 days)
G3 increase of AST, ALT and TB; One with additional G3 elevation of AP One with additional G3 elevation of GGT	**4 (10.8%)**	>30	• **3 cases considered SAEs** o 1 patient (with G3 elevation of Falc): Toxicity recovered, **no changes in dosage**, 2nd episode of G3 toxicity, not recovered o 1 patient (with G3 elevation of GGT): **Interruption,** not recovered o 1 (liver failure): **Withdrawal:** liver failure recovered, ALT not recovered at day +38 • 1 case not considered SAE**: Withdrawal,** at day 64 only bilirubin recovered
Hepatotoxicity (no specific toxicities mentioned)	**1 (0.3%)**	22	• **Considered SAE** • **Withdrawal:** In recovery
Only G3 increase of AST	**1 (0.3%)**	15	• Not changed, no dose reduction, recovered
G3 elevation of ALT and AP	**1 (0.3%)**	8	• **Dose reduction:** In recovery
Only G3 elevation of AP	**1 (0.3%)**	15	• **No changes**: Recovered

SAE: Serious Adverse Event; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; AP: Alkaline Phosphatase; GGT: Gamma-Glutamyl Transferase; TB: Total Bilirubin; 1ary: Primary; ET: Endocrine Therapy

TB: Total Bilirubin; *Include one case of "elevation of liver enzymes" without specifications. **Not recovered at the time of last assessment (period of assessment not always specified)

Table S9. Frequency of liver abnormalities in thePALOMA-1, PALOMA-2 and PALOMA-3 trials according to results presented at clinical.trials.gov and pivotal studies.

PALOMA-1 Adverse Event (%)	Palbociclib plus Letrozole N=83	Placebo plus Letrozole N=77	Reference

	AEs	SAEs	AEs	SAEs	(median follow-up)
AST increased	**7.23**	**1.2**	**1.3**	**0**	**Ref.[17] (≈28m)**
ALT increased	**7.23**	**1.2**	**1.3**	**0**	
AP increased	**8.43**	**1.2**	**2.60**	**0**	
GGT increased	**3.61**	**1.2**	**1.30**	**0**	

PALOMA-2 Adverse Event (%)	**Palbociclib plus Letrozole N=444**		**Placebo plus Letrozole N=222**		**Reference (median follow-up)**
	AEs	**SAEs**	**AEs**	**SAEs**	
AST increased	**9.46**	**2**	**4.95**	**0**	**Ref. [18] 1[ary] analysis (23 m)**
ALT increased	**9.68**	**3**	**4.05**	**1**	

PALOMA-3 Adverse Event (%)	**Palbociclib plus Fulvestrant N=345**			**Placebo plus Fulvestrant N=172**			**Reference (M follow-up)**
	All grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**	
AST elevation	**6**	**2**	**0**	**5**	**<1**	**0**	**Ref. [19] 1[ary] analysis (8.9 m)**
ALT elevation	**7**	**3**	**0**	**5**	**<1**	**0**	

LFTs* abnormalities (%)	**Palbociclib plus ET N=875**		**Placebo plus ET N=477**		**Reference (follow-up)**
	All grades	**G3/4**	**All grades**	**G3/4**	
ALT increased	**40.8**	**2.3**	**31.1**	**0.2**	**Ref.[20] Up to 50 m**
AST increased	**48.4**	**3.3**	**40.8**	**1.9**	
AP increased	**36.1**	**NR**	**43.7**	**NR**	
TB increased	**7.9**	**NR**	**6.0**	**NR**	

M: Median; m: months; AEs: Adverse Events; SAEs: Serious Adverse Events; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; AP: Alkaline Phosphatase; GGT: Gamma-Glutamyl Transferase; TB: Total Bilirubin; 1[ary]: Primary; ET: Endocrine Therapy; NR: not reported

*All grades: LFT elevations, including LFTs not considered AEs.

References

1. UpToDate Online [Internet]. Waltham, MA. 2018 [cited 2018 Jun 1]. Available from: https://www.uptodate.com

2. Micromedex® (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA.

3. Center for Drug Evaluation and Research. U.S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers [Internet]. Center for Drug Evaluation and Research; 2017 [cited 2018 Jun 1]. Available from: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm

4. Giacomini KM, Huang S, Tweedie DJ, Benet LZ. Membrane transporters in drug development. Nature. 2012;9(3):215–36.

5. Grassi L, Nanni MG, Rodin G, Li M, Caruso R. The use of antidepressants in oncology: a review and practical tips for oncologists. Ann Oncol Off J Eur Soc Med Oncol. 2018 Jan;29(1):101–11.

6. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im S-A, Masuda N, et al. Fulvestrant plus palbociclib

versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phas. Lancet Oncol. 2016 Apr;17(4):425–39.

7. Rugo HS, Finn RS, Dieras V. Palbociclib (PAL)+ Letrozole (LET) as firstline therapy in estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC): efficacy and safety updates with longer follow-up across patient subgroups. In: San Antonio Breast Cancer Symposium. 2017.

8. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol Off J Eur Soc Med Oncol. 2018 Jul;29(7):1541–7.

9. Tripathy D, Im S-A, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018 May;19(7):904–15.

10. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im S-A, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018;36(24):2465–72.

11. DeLaurentiis M, Neven P, Jerusalem GHM, Bachelot TD, Jacot W, Dent SF, et al. Ribociclib+letrozole in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC) with no prior endocrine therapy for ABC:Preliminary results from the phase 3b CompLEEment-1 trial. J Clin Oncol. 2018 May;36(15_suppl):1056.

12. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report: Palbociclib. EMA/652627/2016 [Internet]. 2016 [cited 2018 Jun 1]. Available from: https://www.ema.europa.eu/documents/assessment-report/ibrance-epar-public-assessment-report_en.pdf

13. Hortobagyi GN, Stemmer SM, Burris HA, Yap Y-S, Sonke GS, Paluch-Shimon S, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016 Nov;375(18):1738–48.

14. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Ribociclib (RIB) + fulvestrant (FUL) in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2 –) advanced breast cancer (ABC): Results from MONALEESA-3. J Clin Oncol. 2018 Jun;36((Suppl. Abst 1000)):Presented at 2018 ASCO Annual Meeting; June 1-5, 2.

15. DeLaurentiis M, Neven P, Jerusalem GHM, Bachelot TD, Jacot W, Dent SF, et al. Ribociclib (RIBO) + letrozole (LET) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC) with no prior endocrine therapy (ET) for ABC: Preliminary results from the p. J Clin Oncol. 2018 May;36(15_suppl):1056.

16. Center for Drug Evaluation and Research. NDA/BLA Multi-disciplinary Review and Evaluation NDA 209092 KISQALI (ribociclib) [Internet]. 2017 [cited 2018 Jun 1]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209092Orig1s000MultidisciplineR.pdf

17. Study Of Letrozole With Or Without Palbociclib (PD-0332991) For The First-Line Treatment Of Hormone-Receptor Positive Advanced Breast Cancer - Study Results - ClinicalTrials.gov [Internet]. Clinical Trials.gov. 2018 [cited 2018 Jun 1]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT00721409?term=NCT00721409&rank=1&view=results#outcome1

18. Finn RS, Martin M, Rugo HS, Jones S, Im S-A, Gelmon K, et al. Palbociclib and Letrozole in Advanced

Breast Cancer. N Engl J Med. 2016 Nov;375(20):1925–36.

19. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med. 2015 Jul;373(3):209–19.

20. Finn R, Hurvitz S, Allison M, Applebaum S, Glaspy J, DiCarlo B, et al. Phase I Study of PD 0332991, a Novel, Oral, Cyclin-D Kinase (CDK) 4/6 Inhibitor in Combination with Letrozole, for First-Line Treatment of Metastatic Post-Menopausal, Estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor Receptor 2 (HER2)-Negati. Cancer Res. 2009;69(24 Suppl):Abstract nr 5069.