Indication	First line endocrine therapy for oestrogen receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. NB: Previous hormone therapy with anastrozole or letrozole whether as adjuvant therapy or as neoadjuvant treatment is allowed as long as the patient has had a disease-free interval of 12 months or more since completing treatment with anastrozole or letrozole. NB: No prior treatment with a CDK 4/6 inhibitor unless either ribociclib or abemaciclib has had to be stopped within 6 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression or a CDK 4/6 inhibitor has been received as adjuvant therapy and treatment was completed without disease progression at least 12 months prior to the first diagnosis of recurrent or metastatic disease.
Treatment Intent	Palliative
Frequency and number of cycles	Every 28 days Until disease progression or excessive toxicity or patient choice to discontinue.
Monitoring parameters	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor **FBC, U&E and LFT** at baseline then at the beginning of each cycle for 6 months and then every 3 months thereafter or as clinically indicated. • If neuts >/= 1 and PLT >/= 100 proceed with treatment. • If neuts >/= 1 and PLT 76 to 99 give one month's supply of palbociclib and inform consultant. • If neuts >/= 1 and PLT 50 to 75 withhold palbociclib and discuss with consultant. • NB SPC recommendation; patients can receive palbociclib if neuts >/=1 and PLT >/=50 • The most common Grade >/=3 adverse reactions of palbociclib were neutropenia, leukopenia, anaemia, fatigue, increased AST/ALT and infections. • If patient is pre or peri-menopausal they must have undergone ovarian ablation or suppression with LHRH agonist treatment • **Dose Modifications of palbociclib:** First dose reduction to 100mg/day, second dose reduction to 75mg/day. If further dose reduction required, discontinue treatment • **Haematological toxicities,** see table 1. • **Non-haematological toxicities,** see table 2. • **Hepatic impairment:** No dose adjustment required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of palbociclib is 75 mg once daily for 21 consecutive days followed by 7 days off treatment. Letrozole can be given in severe hepatic impairment, patients require close supervision. • **Renal impairment:** No dose adjustment is required for patients with mild, moderate or severe renal impairment (CrCl ≥15 mL/min). Insufficient data are available in patients requiring haemodialysis to provide any dose adjustment recommendation. • **Interstitial lung disease/pneumonitis:** Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspnoea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt treatment immediately and evaluate the patient. Permanently discontinue in patients with severe ILD or pneumonitis.

	• **Venous thromboembolic events:** Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. • **Drug interactions (for comprehensive list refer to BNF/SPC):** Avoid concomitant use of palbociclib with strong CYP3A inhibitors (e.g. ketoconazole, itraconazole, clarithromycin) and consider an alternative medication with no or minimal CYP3A inhibition. If patients must be co-administered a strong CYP3A inhibitor, reduce palbociclib dose to 75mg/day If the strong inhibitor is discontinued, increase the palbociclib dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Concomitant use of palbociclib with strong CYP3A4 inducers (carbamazepine, phenytoin, rifampicin) should be avoided as it may lead to reduced palbociclib exposure. Use with St Johns Wort is contraindicated. Caution with CYP3A substrates with a narrow therapeutic index (e.g. cyclosporine, fentanyl, tacrolimus); the dose may need to be reduced as palbociclib may increase their exposure. • **Driving and machinery:** Fatigue and dizziness has been reported in patients taking letrozole and palbociclib caution is advised when driving or using machines. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
Reference(s)	KMCC protocol BRE-062 V6 CDF list 1.344 accessed online 28.01.2025 SPC accessed online 13.02.2026

NB for funding information, refer to CDF and NICE Drugs Funding List

Table 1: SPC recommended dose modification and management of haematological Toxicities.
Table applies to all haematological adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
NB SPC recommendations are provided for information. Haematological parameters agreed by KMCC breast NOG differ. see monitoring parameters above for NOG guidance.

CTCAE grade	Dose modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3	**Day 1 of cycle**: Withhold palbociclib, until recovery to Grade ≤ 2, and repeat complete blood count monitoring within 1 week. When recovered to Grade ≤ 2, start the next cycle at the *same dose*. **Day 15 of first 2 cycles**: If Grade 3 on Day 15, continue palbociclib at the *current dose* to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (> 1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
Grade 3 ANC[b] (< 1,000 to 500/mm^3) + Fever ≥ 38.5 °C and/or infection	At any time: Withhold palbociclib until recovery to Grade ≤ 2 Resume at next lower dose.
Grade 4	At any time: Withhold palbociclib until recovery to Grade ≤ 2. Resume at next lower dose.
Grading according to CTCAE 4.0. ANC=absolute neutrophil counts; CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal. [b] ANC: Grade 1: ANC LLN - < 1.5; Grade 2: ANC 1 - <1.5; Grade 3: ANC 0.5 - < 1; Grade 4: ANC < 0.5	

Table 2 Non-haematological toxicities

CTCAE* Grade	Dose modifications of palbociclib
Grade 1 or 2	No dose adjustment is required
Grade ≥3 non-haematological toxicity (if persisting despite medical treatment)	Withhold until symptoms resolve to: • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient) Resume at the next lower dose.

* Grading according to CTCAE 4.0.

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**PALBOCICLIB**	**125mg**	PO	Once DAILY for 21 days followed by a 7-day break. Swallow whole, do not chew, crush or split tablets. Take the dose at approximately the same time each day. If a dose is missed or vomiting occurs, an additional dose should not be taken that day. Do not take with pomegranate, Seville orange, grapefruit or grapefruit juice. Available as 125mg, 100mg or 75mg tablets.
	LETROZOLE	**2.5mg**	PO	Once DAILY