Pertuzumab,Trastuzumab and Weekly PACLitaxel Therapy - 21 day cycle

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Pertuzumab is indicated in combination with trastuzumab and PACLitaxel in adult patients with HER2- positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti- HER2 therapy or chemotherapy for their metastatic disease where patients are intolerant of, have had significant toxicity to or are deemed clinically unsuitable for DOCEtaxel	C50	00507a	Pertuzumab-ODMS Feb 2014 Trastuzumab-Hospital PACLitaxel-Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Treatment is with pertuzumab and trastuzumab is administered on day 1, and PACLitaxel is administered on day 1, 8, 15 of a 21 day cycle. PACLitaxel should be continued for up to 8 cycles, pertuzumab and trastuzumab should be continued in responding patients until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Cycle 1: Pertuzumab and trastuzumab loading doses

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1 or 2	1	Pertuzumab	840mg	IV Observe for 1hr post infusion	250ml 0.9% NaCl over 60min
2 or 1	1	Trastuzumab	8mg/kg	IV infusion Observe post infusion[a]	250ml 0.9% NaCl over 90min
3	1, 8 15	PACLitaxel	80mg/m^2	IV infusion	[b]250ml 0.9% NaCl over 1hr
[a]Recommended observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.					
[b]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane. PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.					

Cycles 2 and subsequent cycles

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 or 2	1	Pertuzumab	420mg	IV infusion Observe for 30-60mins post infusion[a]	250ml 0.9% NaCl over 30min if no adverse reactions[b]	Every 21 days
2 or 1	1	Trastuzumab	6mg/kg	IV infusion Observe post infusion[c]	250ml 0.9% NaCl over 30 min	Every 21 days
3	1, 8 and 15	PACLitaxel	80mg/m^2	IV infusion	250ml 0.9% NaCl over 1hr[d]	Day 1, 8, 15 of a 21 day cycle up to maximum of 8 cycles
[a]Observation period not required after 3 consecutive treatments with pertuzumab with no reaction.						
[b]The infusion time of 30-60 minutes may be used at the discretion of the prescribing consultant						
[c]Recommended observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.						
[d]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane. PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.						
Trastuzumab is incompatible with glucose solution.						

ELIGIBILITY:

- Indications as above
- HER2 positive as demonstrated by a validated test method
- ECOG status 0-1
- LVEF ≥ 50%

EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab, PACLitaxel, or any of the excipients
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)
- Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction with trastuzumab
- Significant hepatic dysfunction, contraindicating PACLitaxel
- Baseline neutrophil count < 1.5 x 10^9/L
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Cardiac function (LVEF using ECHO or MUGA scan)

Regular tests:

- FBC, renal and liver profile before each cycle
- MUGA scan or echocardiogram every 12 weeks during treatment with trastuzumab and at completion of therapy. Where there are signs of cardiac impairment four to eight weekly checks may be more appropriate.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- **Pertuzumab and trastuzumab**
  - None usually recommended. Doses are held or discontinued if unacceptable toxicity occurs.
  - Discontinue pertuzumab if trastuzumab is discontinued.
  - Patient may continue to receive both pertuzumab and trastuzumab if PACLitaxel is discontinued due to toxicity or after 6-8 cycles and without evidence of disease progression.
- **Delayed or missed doses**
  - If the time between two sequential infusions is < 6 weeks, the 420 mg dose of pertuzumab should be administered as soon as possible without regard to the next planned dose.
  - Re-load pertuzumab if the time between two sequential infusions is ≥ 6 weeks or more.
  - Re-load trastuzumab if the time between two sequential infusions is ≥ 6 weeks.
  - If re-loading is required for either drug, the 3 drugs should be given in the same schedule as Cycle 1.
  - The next cycle should follow 21 days from the re-loading dose.

Haematological:

Table 1: Dose modifications for PACLitaxel for haematological toxicity

ANC (x10^9/L)		Platelets	Dose	Dose after neutropenic sepsis
≥ 1.5	and	> 90	80mg/m^2	65mg/m^2
*1-1.49	or	70-90	65mg/m^2	50mg/m^2
< 1	or	< 70	Delay and reduce next dose to 65mg/m^2 or add G-CSF	Delay
Patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks, should discontinue treatment.				

*** If ANC 1 to less than 1.5 and patient fit and well can consider full dose of 80 mg/m^2 at discretion of prescribing Consultant**

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment			
Pertuzumab	No dose reduction required for mild or moderate renal impairment. No dose recommendations for severe impairment due to limited data.	No specific dose recommendations. Has not been studied in patients with hepatic impairment.			
Trastuzumab	No dose reduction required.	No dedicated studies of trastuzumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary.			
PACLitaxel	No dose modifications necessary.	**ALT**		**Total bilirubin**	**Dose of PACLitaxel**
		< 10xULN	and	≤ 1.25xULN	80mg/m^2
		< 10xULN	and	1.26-2xULN	60mg/m^2
		< 10xULN	and	2.01-5xULN	40mg/m^2
		≥10xULN	and/or	>5xULN	Not recommended

Management of adverse events:

Table 3: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Pertuzumab and Trastuzumab	
LVEF < 40% or 40-45% associated with ≥10% points below the pre-treatment value.	Withhold treatment with pertuzumab and trastuzumab. Repeat LVEF within 3 weeks. No improvement or further decline, consider discontinuation. Discuss with consultant and refer to cardiologist.
Symptomatic heart failure	Discontinue
NCI-CTCAE Grade 4 hypersensitivity reactions	Discontinue
PACLitaxel	
Grade >2 peripheral neuropathy	Decrease dose by 10mg/m^2.
All other grade 2 non-haematological toxicity	Hold treatment until toxicity resolves to ≤ grade 1. Decrease subsequent doses by 10mg/m^2.
≥ Grade 3 reaction	Discontinue
Patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks, should discontinue treatment.	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- **Pertuzumab** Minimal (**Refer to local policy)**
- **Trastuzumab** Minimal (**Refer to local policy)**
- **PACLitaxel** Low (**Refer to local policy)**

PREMEDICATIONS:

- **Trastuzumab and pertuzumab:** Not usually required unless the patient has had a previous hypersensitivity. Paracetamol and antihistamine cover should be considered.
  Patient should be educated about the possibility of delayed infusion-related symptoms.
- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment.
- The H_2 antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
  - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy.
  - Where a patient experiences hypersensitivity, consider the use of alternative H_2 antagonists **(Refer to local policy).**
- Table 4 outlines suggested premedications prior to treatment with PACLitaxel.

Table 4: Suggested premedications prior to treatment with PACLitaxel

Day of treatment	Drug	Dose	Administration prior to PACLitaxel
Day 1	dexAMETHasone[a]	8mg IV	30 minutes
Day 1	Chlorphenamine	10mg IV	30 minutes
Day 1	Famotidine	20mg IV	30 minutes
Day 8[b] and thereafter	dexAMETHasone[a]	None	
Day 8 and thereafter	Chlorphenamine	10mg IV	30 minutes
Day 8 and thereafter	Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexAMETHasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexAMETHasone orally 12 hr and 6 hr prior to re-challenge with PACLitaxel according to consultant guidance.			
[b]Dose of dexAMETHasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance.			
[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.			

OTHER SUPPORTIVE CARE:

Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Febrile neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Hypersensitivity/Infusion reactions**: There is a risk of hypersensitivity/infusion reactions with pertuzumab and PACLitaxel**.** Although hypersensitivity with trastuzumab is common, severe

hypersensitivity reactions are uncommon. Use with caution in patients with dyspnoea at rest from pulmonary/cardiac conditions as increased risk of infusion related symptoms**.**

- **Cardiac toxicity***:* Decreases in LVEF have been reported with medicinal products that block HER2 activity, including pertuzumab. Trastuzumab can produce declines in ventricular dysfunction and congestive heart failure (CHF). Baseline and 3 monthly cardiac function tests are required during treatment especially for those with prior anthracycline exposure.
- **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated **(Refer to local policy).**
- **Peripheral neuropathy:** Occurs frequently with PACLitaxel but the development of severe symptoms is rare.
- **Arthralgia/myalgia:** May be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of PACLitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after PACLitaxel administration, and resolving within days.
- **Hepatic Dysfunction:** Patients with hepatic impairment may be at increased risk of toxicity with PACLitaxel, particularly grade 3-4 myelosuppression.

DRUG INTERACTIONS:

- A possible interaction with warfarin has been reported. An increased INR and bleeding may occur in patients previously stabilised on warfarin. The interaction was noted in two patients after 8-10 doses of trastuzumab. An INR prior to starting the trastuzumab is recommended, then every 2 weeks for the first 3 months and then monthly if stable. Inform patient to watch for any bleeding. Modification of the warfarin dose may be needed.
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	13/08/2018		Prof Maccon Keane
2	17/10/2018	Updated order of administration on treatment table	Prof Maccon Keane
3	02/05/19	Updated trastuzumaband pertuzumab infusion time from cycle 2 onwards. Emetogenic potential updated	Prof Maccon Keane
4	09/09/2020	Updated pre-medications table in line with agreed standardisation	Prof Maccon Keane
5	10/08/2023	Updated PACLItaxel pre medications table. Updated emetogenic potential of pertuzumab	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.