Pertuzumab, Trastuzumab, PACLitaxel and CARBOplatin Therapy (TRAIN-2)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.	C50	00775a	Trastuzumab, CARBOplatin and PACLitaxel: Hospital Pertuzumab: ODMS 01/07/2020

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.

Trastuzumab, pertuzumab and CARBOplatin are administered on day 1 and PACLitaxel is administered on day 1 and 8 of a 21 day cycle for 6 cycles or until disease progression or unacceptable toxicity develops.

Following surgery, patients should be treated with adjuvant therapy (e.g. trastuzumab OR trastuzumab emtansine as appropriate) to complete 1 year of treatment.

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

Cycle 1: Pertuzumab and trastuzumab loading doses

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 or 2	1	Pertuzumab	840mg	IV infusion. Observe for 1hr post infusion	250ml 0.9% sodium chloride over 60 min	Cycle 1 only
2 or 1	1	Trastuzumab[a]	8mg/kg	IV infusion. Observe post infusion[b]	250ml 0.9% sodium chloride over 90 min	Cycle 1 only
3	1, 8	PACLitaxel	80mg/m^2	IV infusion	250ml 0.9% NaCl over 1hr[c]	Cycle 1 only
4	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 30 min	Cycle 1 only

[a]Trastuzumab is incompatible with glucose solution.

[b]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.

[c]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22µm filter with a microporous membrane. PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.

Cycle 2-6

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 or 2	1	Pertuzumab	420mg	IV infusion. Observe for 30-60 mins post infusion[a]	250ml 0.9% sodium chloride over 30 min if no adverse reactions[b]	Every 21 days
2 or 1	1	Trastuzumab[c]	6mg/kg	IV infusion. Observe post infusion[d]	250ml 0.9% sodium chloride over 30 min	Every 21 days
3	1, 8	PACLitaxel	80mg/m^2	IV infusion	250ml 0.9% NaCl over 1hr[e]	Every 21 days
4	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 30 min	Every 21 days
[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]Trastuzumab is incompatible with glucose solution.						
[d]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.						
[e]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22µm filter with a microporous membrane. PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.						

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.
- **Estimation of GFR** (eGFR) can be done by using the Wright formula or using the Cockcroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, the formulae may not give accurate results and measured GFR is recommended.
    - Where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available, the use of the adjusted ideal body weight for Cockcroft and Gault may be considered.
    - Where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered.
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above
- HER2 positive as demonstrated by a validated test method
- ≥ 18 years
- ECOG status 0-1
- LVEF ≥ 50%
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab, PACLitaxel, CARBOplatin 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
- Pregnancy / Breast feeding
- Baseline neutrophil count < 1.5×10^9 cells/L
- Severe hepatic impairment (PACLitaxel)

*If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- HER2 positive as demonstrated by a validated test method
- FBC, renal and liver profile
- Cardiac function (LVEF using ECHO or MUGA scan)
- Audiometry and creatinine clearance as clinically indicated
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation

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
- Assessment of peripheral neuropathy status as clinically indicated

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.

Trastuzumab and Pertuzumab:

- None usually recommended. Doses are held or discontinued if unacceptable toxicity occurs. Please see Table 1 below for recommendations on resuming dosing pertuzumab and trastuzumab after a dose delay or missed doses.
- Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time.
- If trastuzumab treatment is discontinued, treatment with pertuzumab should be discontinued.

Table 1: Dose modifications of pertuzumab and trastuzumab for delayed or missed doses

Time between two sequential infusions	Pertuzumab	Trastuzumab
<6 weeks	The 420mg dose of pertuzumab should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule.	The 6mg/kg dose of trastuzumab IV should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule.
≥6 weeks	The 840mg loading dose of pertuzumab should be re-administered as a 60min infusion, followed by a maintenance dose of 420mg IV administered every 3 weeks thereafter.	The loading dose of 8mg/kg of trastuzumab IV should be re-administered over approximately 90min, followed by a maintenance dose of 6mg/kg IV administered every 3 weeks thereafter.

PACLitaxel and CARBOplatin:

Table 2: Dose Reduction Levels for PACLitaxel and CARBOplatin

	Dose Level	Dose Level -1	Dose Level -2
PACLitaxel	80mg/m^2	70mg/m^2	60mg/m^2
CARBOplatin	AUC 6	AUC 5	AUC 4

Haematological:

Table 3: Dose modification of CARBOplatin and PACLitaxel in haematological toxicity (CYCLE 2-4)

Day	ANC (x10^9/L)		Platelets (x10^9/L)	CARBOplatin Dose	PACLitaxel Dose
Day 1	≥1	and	≥ 75	100% Dose	100% Dose
	<1	and/or	<75	Delay treatment until recovery[a]	Delay treatment until recovery[a]
Day 8, 15	<0.5	and/or	<50		Omit day 8 and day 15 PACLitaxel dose
Day 1	Febrile Neutropenia			Decrease CARBOplatin dose by one dose level	
	<0.5 for ≥ 7 days	or	<10		
			10 to 50 with bleeding tendencies		
	Treatment delay for haematological toxicity > 1 week 1st occurrence			Decrease CARBOplatin dose by one dose level to AUC 5	
	2nd occurrence			Decrease CARBOplatin dose further for subsequent cycles to AUC 4	

[a]Treatment may be delayed for a maximum of 3 weeks.

Renal and Hepatic Impairment:

Table 4: 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**
		< 10 x ULN	and	≤ 1.25 x ULN	80mg/m^2
		< 10 x ULN	and	1.26 - 2 x ULN	60mg/m^2
		< 10 x ULN	and	2.01 - 5 x ULN	40mg/m^2
		≥10 x ULN	and/or	>5 x ULN	Not recommended
CARBOplatin	See note below*	No dose modification required			

*Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of <60ml/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30ml/min, CARBOplatin should be administered with extreme caution
- If GFR ≤ 20ml/min, CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 5: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Pertuzumab and Trastuzumab	
Reduction in LVEF to <50% - associated with a fall of ≥ 10% points below pre-treatment values	Withhold treatment with pertuzumab and trastuzumab for at least 3 weeks. Pertuzumab and trastuzumab may be resumed if the LVEF has recovered to ≥50% or to a difference of <10% points below pre-treatment values. 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 motor or sensory neuropathy First Occurrence Persistent Grade ≥2 or 2nd occurrence	Decrease dose of PACLitaxel by 10mg/m^2. Decrease dose of PACLitaxel by a further 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)**
CARBOplatin: High **(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.

PACLitaxel:

- 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 6 outlines the suggested premedications prior to treatment with PACLitaxel.

Table 6: 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.
- G-CSF support may be required **(refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Hypersensitivity**: Severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in <1% of patients receiving PACLitaxel after adequate premedication. In the case of severe hypersensitivity reactions, PACLitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug. Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Febrile neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.

Pertuzumab:

- **Ventricular dysfunction (including congestive heart failure):** The incidence of symptomatic left ventricular systolic dysfunction (LVD) was higher in patients treated with pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy.
  Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines. The majority of cases of symptomatic heart failure reported in the adjuvant setting were in patients who received anthracycline-based chemotherapy .
  Pertuzumab has not been studied in patients with: a pre-treatment LVEF value of < 50%; a prior history of congestive heart failure (CHF); LVEF declines to < 50% during prior trastuzumab adjuvant therapy; or conditions that could impair left ventricular function such as uncontrolled hypertension,

recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to >360mg/m^2 of doxorubicin or its equivalent.
Assess LVEF prior to initiation of pertuzumab and at regular intervals during treatment with pertuzumab (e.g. every 12 weeks in the adjuvant setting) to ensure that LVEF is within normal limits. If the LVEF has declined and has not improved, or has declined further at the subsequent assessment, discontinuation of pertuzumab and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

- **Infusion reactions, hypersensitivity reactions/anaphylaxis:** Pertuzumab has been associated with infusion and hypersensitivity reactions. Close observation of the patient during and for 60 minutes after the first infusion and during and for 30-60 minutes after subsequent infusions of pertuzumab is recommended. If a significant infusion reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.
  Pertuzumab must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome.
- **Diarrhoea:** Pertuzumab may elicit severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. Elderly patients (≥ 65 years) may have a higher risk of diarrhoea compared with younger patients (< 65 years). Early intervention with loperamide, fluids and electrolyte replacement should be considered, particularly in elderly patients, and in case of severe or prolonged diarrhoea.
  Interruption of treatment with pertuzumab should be considered if no improvement in the patient's condition is achieved. When the diarrhoea is under control treatment with pertuzumab may be reinstated.

Trastuzumab

- **Cardiac toxicity**:
  - Trastuzumab has been associated with moderate to severe cardiac failure. Baseline and three monthly cardiac function tests are required during treatment especially for those with prior anthracycline exposure.
  - If LVEF drops ≥ 10 ejection fraction (EF) points from baseline AND to below 50 %, treatment should be withheld and a repeat LVEF assessment carried out within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.
  - Trastuzumab and anthracyclines should not be given concurrently in combination due to cardiotoxicity risk.
  - Trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.
- **Trastuzumab infusion-associated symptoms:** Usually chills and fever may occur. Stop infusion and consider antihistamine cover. When symptoms have resolved the infusion may be recommenced. For serious reactions, discontinue the trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.
- **Pulmonary events:** Severe pulmonary adverse reactions can occur in association with the use of trastuzumab and have been associated with a fatal outcome. These events may occur as part of an

infusion-related reaction or with a delayed onset. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

PACLitaxel

- **Hypersensitivity:** Severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in <1% of patients receiving PACLitaxel after adequate premedication. In the case of severe hypersensitivity reactions, PACLitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug.
- **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated **(Refer to local policy).**
- **Peripheral neuropathy:** Occurs frequently 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, particularly grade 3-4 myelosuppression.
- **Cardiac conduction abnormalities**: If patients develop significant conduction abnormalities during PACLitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with PACLitaxel. Hypotension, hypertension, and bradycardia have been observed during PACLitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of PACLitaxel infusion, is recommended.

CARBOplatin

- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.

DRUG INTERACTIONS:

- A possible interaction with warfarin has been reported. An increased INR and bleeding may occur in patients previously stabilized 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 two weeks for the first three 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.
- Avoid concurrent use with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.

- Avoid concurrent use with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). If necessary perform regular audiometric testing.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	12/12/2022		Prof Maccon Keane
2	10/08/2023	Updated exclusions section and emetogenic potential of pertuzumab	Prof Maccon keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.