Pertuzumab,Trastuzumab and Vinorelbine[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Pertuzumab in combination with trastuzumab and vinorelbine for the treatment of 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 deemed clinically unsuitable for taxane based therapy	C50	00526a	Pertuzumab -ODMS Trastuzumab -Hospital Vinorelbine- 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 administered every 21 days 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 and 8	Vinorelbine[b]	[c]25mg/m^2	IV infusion	50ml 0.9% NaCl over 15min. Then flush the line with 250ml 0.9% NaCl prior to removing/capping IV access
[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]Vinorelbine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer here.					
[c]Vinorelbine dose may be initiated or increased to 35 mg/m^2 at the treating physician's discretion.					

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 30-60 mins post infusion[a]	250ml NaCl 0.9% over 30min if no adverse reactions.[b]	Every 21 days
2 or 1	1	Trastuzumab	6mg/kg	IV infusion Observe post infusion[c]	250ml NaCl 0.9% over 30 min [d]	Every 21 days
3	1 and 8	Vinorelbine[e]	[f]30mg/m^2	IV infusion	50ml 0.9% NaCl over 15min. Then flush the line with 250ml 0.9% NaCl prior to removing/capping IV access	Day 1 and 8 of a 21 day cycle

[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]Trastuzumab is incompatible with glucose solution.

[e] Vinorelbine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer here.

[f] Vinorelbine dose may be initiated or increased to 35 mg/m^2 at the treating physician's discretion.

ELIGIBILITY:

- Indications as above
- HER2 positive as demonstrated by a validated test method
- ECOG status 0-1
- LVEF ≥ 50%
- Patients deemed clinically unsuitable for taxane based therapy

EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab, vinorelbine, 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
- Lactation

USE with CAUTION:

- Neutrophil count < 1.5 x 10^9/L or severe infection; current or recent (within 2 weeks)
- Platelet count < 100 x 10^9/L

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)
- Assessment of peripheral neuropathy

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.
  - If vinorelbine is discontinued due to toxicity, antibody therapy can be continued until disease progression; if antibody therapy is discontinued due to toxicity, vinorelbine can be continued until 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 modification for vinorelbine for haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥1	and	≥100	100% Dose
0.5-0.99	or	75-99	Delay until recovery and reduce subsequent does to 80%

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.		
Vinorelbine	No dose reduction required.	**AST/ALT**	**Bilirubin**	**Dose**
		>3 x ULN	> 2 x ULN	Reduce dose by 50%
		ULN = Upper Limit of Normal		

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
Vinorelbine	
Grade ≥3	Withhold treatment until recovery to grade 1 then reduce the dose to 80% of the original dose. Discontinue treatment

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- **Pertuzumab** Minimal (**Refer to local policy).**
- **Trasuzumab** Minimal (**Refer to local policy).**
- **Vinorelbine** Minimal **(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.

OTHER SUPPORTIVE CARE:

- Patients should be counseled on the risk of constipation associated with the use of vinca alkaloids. Dietary interventions or prophylactic laxatives may be required.
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

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**.** 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 pertizumab. 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. : Special care should be taken when prescribing vinorelbine for patients with history of ischemic heart disease.
- **Extravasation:** Vinorelbine causes pain and tissue necrosis if extravasated **(Refer to local guidelines).**
- **Constipation:** Constipation with vinorelbine should at a grade 1-2 be managed with dietary interventions or laxatives.

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 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 vinorelbine with CYP3A inhibitors.
- Risk of drug interactions causing decreased concentrations of vinorelbine with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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3. Andersson M, Lopez-vega J et al. Efficacy and safety of pertuzumab and trastuzumab administered in a single infusion bag, followed by vinorelbine: velvet cohort 2 final results. Oncologist *2017;* 22**:** 1160-1168.

4. Bergen, E, Berghoff, S et al 2014. Taxanes plus trastuzumab compared to oral vinorelbine plus trastuzumab in her2-overexpressing metastatic breast cancer. Breast care 2014; (9**):** 344-8.
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Version	Date	Amendment	Approved By
1	07/11/2018		Prof Maccon Keane
2	2/5/2019	Updated trastuzumab and pertuzumab infusion time from cycle 2 onwards. Update emetogenic potential.	Prof Maccon Keane
3	10/11/2020	Reviewed	Prof Maccon Keane
4	10/08/2023	Updated emetogenic potential of pertuzumab	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.