EC-TPH (Epirubicin and Cyclophosphamide then Docetaxel, Pertuzumab and Trastuzumab)

Indication

Neo-adjuvant treatment for HER2 positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence.

(NICE TA424)

Adjuvant treatment for HER2 positive, early stage breast cancer with lymph node positive disease.

(NICE TA569)

ICD-10 codes

Codes with a prefix C50.

Regimen details

Cycles 1-3*

Day	Drug	Dose	Route
1	Epirubicin*	100mg/m^2	IV bolus
1	Cyclophosphamide	500mg/m^2	IV bolus

*lower doses of 60mg/m^2 or 75mg/m^2 may be used for patients with significant co-morbidity

Patients may receive treatment with either IV Pertuzumab and IV Trastuzumab or the combined SC Pertuzumab/Trastuzumab preparation, Phesgo.

IV Pertuzumab/Trastuzumab

Cycle 4

Day	Drug	Dose	Route
1	Pertuzumab	840mg	IV infusion
1	Trastuzumab	8mg/kg	IV infusion
1	Docetaxel	75mg/m^2	IV infusion

Due to the potential for hypersensitivity reactions, for this cycle pertuzumab may be administered on day 1 and trastuzumab and docetaxel on day 2.

Cycles 5-7:

Day	Drug	Dose	Route
1	Pertuzumab	420mg	IV infusion
1	Trastuzumab	6mg/kg	IV infusion
1	Docetaxel	*75mg/m^2	IV infusion

*Docetaxel may be escalated to 100mg/m^2 for subsequent cycles if the initial dose is tolerated, at the consultants' discretion.

Cycles 8-21

Day	Drug	Dose	Route
1	Pertuzumab	420mg	IV infusion
1	Trastuzumab	6mg/kg	IV infusion

If the dosing interval is > 4 weeks for trastuzumab or ≥ 6 weeks for pertuzumab, a loading dose will be required.

SC Pertuzumab/Trastuzumab

Cycle 4

Day	Drug	Dose	Route
1	Phesgo (Pertuzumab 1200mg/Trastuzumab 600mg)	1200mg/600mg	SC injection
1	Docetaxel	75mg/m^2	IV infusion

Cycles 5-7:

Day	Drug	Dose	Route
1	Phesgo (Pertuzumab 600mg/Trastuzumab 600mg)	600mg/600mg	SC injection
1	Docetaxel	*75mg/m^2	IV infusion

*Docetaxel may be escalated to 100mg/m^2 for subsequent cycles if the initial dose is tolerated, at the consultants' discretion.

Cycles 8-21

Day	Drug	Dose	Route
1	Phesgo (Pertuzumab 600mg/Trastuzumab 600mg)	600mg/600mg	SC injection

If the dosing interval is ≥ 6 weeks for Phesgo, a loading dose will be required.

Cycle frequency

21 days

Number of cycles

Maximum of 7 cycles (3 x EC followed by 3-4 x TPH).
Pertuzumab and trastuzumab should be continued to complete 1 year of treatment (maximum 18 cycles in total).

Administration

Cycles 1-3:

Epirubicin and cyclophosphamide are administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%. Cyclophosphamide may also be given as an IV infusion in 250-500mL sodium chloride 0.9% over 30 minutes.

Cycles 4-7:

IV Pertuzumab/Trastuzumab

IV Pertuzumab and trastuzumab may be administered in either order but the docetaxel should be administered last.

IV Pertuzumab is administered in 250mL sodium chloride 0.9% over 60 minutes (cycle 4) followed by a 60 minute observation period (before next drug administration). For cycle 5 onwards (providing pertuzumab is well tolerated) IV pertuzumab may be administered over 30 minutes followed by a 60 minute observation period.

IV Trastuzumab is administered in 250mL sodium chloride 0.9% over 90 minutes (cycle 4). The patient should be observed for 6 hours after the start of the infusion for symptoms of infusion related reactions (e.g. fever, chills). For cycle 5 onwards, (providing trastuzumab well tolerated) IV trastuzumab may be given over 30 minutes. Patients should be observed for 2 hours after the start of the infusion for symptoms of infusion related reactions.

It may not be necessary to stop treatment for minor hypersensitivity reactions e.g. flushing, localised rash but infusions must be stopped for major reactions, e.g. hypotension, dyspnoea, angioedema or generalised urticaria.

Subcutaneous Pertuzumab/Trastuzumab (Phesgo)

Phesgo should always be administered prior to Docetaxel administration.

Phesgo loading dose (1200mg Pertuzumab/600mg Trastuzumab) is administered in a volume of 15mL by subcutaneous injection over approximately 8 minutes. Phesgo maintenance dose (600mg Pertuzumab/600mg Trastuzumab) is administered in a volume of 10mL by subcutaneous injection over approximately 5 minutes. The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. The dose should not be split between two syringes or between two sites of administration.

Patients should be observed for 30 minutes after completion of the Phesgo loading dose and 15 minutes after completion of a Phesgo maintenance dose for injection-related reactions.

Docetaxel

Docetaxel is administered as an IV infusion in 250mL or 500mL (concentration dependent) PVC free sodium chloride 0.9% over 60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel and therefore facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy.

Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel, unless following a risk assessed desensitisation protocol.

Cycles 8-21:
Pertuzumab and trastuzumab are administered as above.

Pre-medication

EC cycles: none usually required

TPH cycles: Dexamethasone 8 mg BD (morning and lunchtime) for 3 days starting 24 hours prior to chemotherapy. (Note: Patients must receive 3 doses of dexamethasone prior to treatment).
In the case where 3 doses have not been taken, dexamethasone 16-20mg IV should be administered 30-60 minutes prior to chemotherapy and the remaining 3 oral doses should be taken as normal.

Emetogenicity

EC cycles: moderate – moderate - high emetic potential
TPH cycles: moderate-low emetic potential

Additional supportive medication

Primary G-CSF prophylaxis as per local policy
Mouthwashes as per local policy
H_2 antagonist or proton-pump inhibitor if required
Loperamide if required (particularly for TPH cycles)
Scalp cooling may be offered.

Extravasation

Epirubicin is a vesicant (Group 5)
Cyclophosphamide, pertuzumab and trastuzumab are neutral (Group 1)
Docetaxel is an exfoliant (Group 4)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Echocardiogram	Baseline

Investigations – pre cycles 2-7

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Echocardiogram	Pre cycle 4 and cycle 6 or according to local practice.

Investigations – pre HER-2 directed maintenance cycles 8-21

Investigation	**Validity period** (or as per local policy)
FBC	3 monthly
U+E (including creatinine)	3 monthly
LFTs	3 monthly
Echocardiogram	Every 3-4 months or according to local practice

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	> 20 mL/min
Bilirubin	≤ 1.0 ULN*
AST/ALT	≤ 1.5 x ULN*
Alkaline Phosphatase	≤ 2.5 x ULN
Echocardiogram (cycle 4 onwards) – LVEF	≥ LLN for institution (usually 50%) and <10 point change from baseline (see below)

*See table below for standard limits to go ahead for EC cycles

Dose modifications

- **Haematological toxicity**

If neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery.

If febrile neutropenia or neutrophils < 0.5 x 10^9/L for more than 1 week consider reducing doses of all cytotoxic drugs to 80% (except trastuzumab and pertuzumab) for future cycles.

Trastuzumab and pertuzumab may continue during periods of chemotherapy induced myelosuppression.

- **Renal impairment**

CrCl (mL/min)	**Cyclophosphamide dose**
> 20	100%
10-20	75%
<10	50%

Epirubicin: There is no data available in severe renal impairment. Consider dose reduction if CrCl <10mL/min (consultant decision).

Docetaxel: consider dose reduction if CrCl <10mL/min (consultant decision).

Trastuzumab: No dose modification for renal function is required.

Pertuzumab: No dose modification is required for mild or moderate impairment. No dose reductions can be made in severe renal impairment as there is limited data available.

- **Hepatic impairment**

EC cycles:

Bilirubin (x ULN)		**AST/ALT** (x ULN)		**Alkaline phosphatase** (xULN)	**Epirubicin dose**
< 1.5	and	≤ 2.0	and	≤ 2.5	100%
1.5 - < 3	or	> 2.0 -3.5	or	> 2.5 - <5	50%
≥3 - 5	or	> 3.5	and	5-10	25%
> 5			or	> 10	Omit

Cyclophosphamide is not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (consultant decision).

TPH cycles:

AST/ALT (x ULN)		**Alkaline phosphatase** (x ULN)	**Docetaxel dose**
≤ 1.5	and	< 2.5	100%
> 1.5 – 3.5	or	≥ 2.5- 6	75%
> 3.5	or	≥ 6	60% or discontinue - discuss with consultant

If AST/ALT is 1.5-2.5 x ULN and alkaline phosphatase is <2.5 x ULN the maximum recommended dose of docetaxel is 75 mg/m^2

If bilirubin > 1.0 x ULN withhold dose (or consultant decision to treat)

No dose modification is required for trastuzumab.

Pertuzumab has not been studied in hepatic impairment; no dose recommendations can be made

- **Other toxicities**

EC cycles:
For grade 3 or 4 mucositis/stomatitis – delay until resolved to ≤ grade 1 and reduce dose of fluorouracil and epirubicin to 80% dose.

Any other grade 3 or 4 toxicity- discuss with consultant.

TPH cycles:

Toxicity	Definition	Docetaxel dose
Peripheral neuropathy	Grade 2	75%
	Grade 3 or 4	Discuss with consultant
Diarrhoea*	Grade 3 or 4	1st occurrence – 75%
		2nd occurrence – 60%
Stomatitis	Grade 3 or 4	1st occurrence – 75%
		2nd occurrence – 60%

*Pertuzumab may cause severe diarrhoea. If severe diarrhoea an anti-diarrhoeal treatment should be instituted and interruption of the treatment with pertuzumab should be considered if no improvement of the condition is achieved. When the diarrhoea is under control the treatment with pertuzumab may be reinstated.

Cardiac toxicity

LVEF must be above LLN for treatment to go ahead. If LVEF percentage drops ≥10 points from baseline AND to below 50% (cardiotoxicity), treatment should be withheld, patients should be started on a beta-blocker (e.g. bisoprolol 1.25mg od) and an angiotensin-converting enzyme (ACE) inhibitor (e.g. ramipril 1.25mg od), referred to a cardiologist and a repeat LVEF assessment performed within 3 weeks.

Anti- HER2 therapy may be resumed if the LVEF has recovered to > 45%, or to 40-45% associated with a difference of < 10 points below pre-treatment values. If LVEF has not improved, or declined further, or symptomatic cardiac failure has developed, anti-HER2 should be discontinued, unless the benefits for the individual patient are deemed to outweigh the risks.

Other indications to refer to cardiology and repeat LVEF assessment within 3 weeks include LVEF percentage drop of <10% to below 50% (Possible subclinical cardiotoxicity) and if LVEF percentage drops ≥10 points from baseline but remains above 50% AND an accompanying relative decline in global longitudinal strain (GLS) >15% (probable subclinical cardiotoxicity). However, providing patients are not symptomatic they should continue on treatment.

Any other grade 3 or 4 toxicity- discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Anaphylaxis
Teratogenicity
Infertility/Early menopause
Cardiotoxicity
Peripheral neuropathy
Interstitial lung disease
Other primary cancer

- **Frequently occurring side effects**

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Arthralgia and myalgia
Alopecia

- **Other side effects**

Fluid retention
Red urine (for 24 hours post epirubicin)
Deranged liver function
Phlebitis
Skin toxicity
Nail changes
Taste disturbances
Bladder irritation

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.
Phenytoin: requires close monitoring if using concurrently.
Co-trimoxazole/trimethoprim: enhances antifolate effect. Avoid if possible, if essential, monitor FBC regularly.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Docetaxel:
CYP3A4 Enzyme inducers/inhibitors: in vitro studies suggest that CYP3A inhibitors (such as ketoconazole, ritonavir, clarithromycin and erythromycin) may raise docetaxel levels, whereas CYP3A inducers (such as rifampicin and barbiturates) may reduce docetaxel levels.
There is no data regarding drug interactions with trastuzumab or pertuzumab.

Additional comments

Epirubicin has a lifetime maximum cumulative dose of 900mg/m^2

Women of childbearing potential should use effective contraception while receiving treatment and for 6 months at least 6 months after completion.

References

- National Institute for Health and Clinical Excellence. TA569 accessed 28th April 2022 via www.nice.org.uk
- Summary of Product Characteristics Epirubicin (Accord) accessed 28th April 2022 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide (Sandoz) accessed 28th April 2022 via www.medicines.org.uk
- Summary of Product Characteristics Docetaxel (Accord) accessed 28th April 2022 via www.medicines.org.uk
- Summary of Product Characteristics Trastuzumab ® (Roche) accessed 28th April 2022 via www.medicines.org.uk
- Summary of Product Characteristics Pertuzumab (Roche) accessed 28th April 2022 via www.medicines.org.uk
- Summary of Product Characteristics Phesgo ® (Roche) accessed 28th April 2022 via www.medicines.org.uk
- Gunter von Mickwitz et al, Adjuvant Pertuzumab and Trastuzumab in Early HER 2 positive breast cancer. N Engl J Med 2017; 377:122-131.
- Lyon, AR. et al. 2022 ESC Guidelines on cardio-oncology. European Heart Journal 43(41):4229-4361

Written/reviewed by: Based on FEC-TPH SWSCN protocol written by: Professor M Beresford (Consultant Oncologist, RUH Bath NHS Trust), Dr R Bowen (Consultant Oncologist, RUH Bath NHS Trust), Dr T Strawson-Smith (Consultant Oncologist, UHBW NHS Trust)

Checked by: Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)

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