Kadcyla®- Trastuzumab Emtansine (Breast)

Indication

Treatment of HER2 positive unresectable locally advanced or metastatic breast cancer for patients who have previously received a taxane and trastuzumab, separately or in combination.

Patients should have received prior therapy for locally advanced or metastatic disease OR have relapsed within 6 months of completing adjuvant therapy.

(NICE TA458)

Adjuvant treatment of HER2-positive early breast cancer in adults who have residual invasive disease in the breast or lymph nodes after neoadjuvant taxane-based and HER2-targeted therapy.

(NICE TA632)

ICD-10 codes

Codes pre-fixed with C50.

Regimen details

Day	Drug	Dose	Route
1	Kadcyla ®	3.6mg/kg	IV infusion

In order to reduce the risk of medication errors it is recommended that all trastuzumab products are referred to by brand name, i.e. **Kadcyla** (trastuzumab emtansine).

Cycle frequency

21 days

Number of cycles

Metastatic disease: Until disease progression or unacceptable toxicity.

Adjuvant treatment: Total of 14 cycles unless disease progression or unacceptable toxicity.

Administration

Kadcyla is administered in 250mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter. The first dose is administered over 90 minutes and patients should be observed for infusion related reactions (fever, chills or other infusion related reactions) for 90 minutes following completion of the infusion. The infusion site should be closely monitored for possible subcutaneous infiltration during administration.

If the previous infusion was well tolerated, subsequent doses may be administered over 30 minutes. Patients should be observed for at least 30 minutes following completion of the infusion.

In the event of infusion related reactions, the infusion rate should be slowed or discontinued in severe or life-threatening cases.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential.

Additional supportive medication
Antiemetics as per local policy.
PPI if required, as per local policy.
Mouthwashes as per local policy.
Loperamide if required

Extravasation
Kadcyla is irritant (Group 3)

Investigations – pre first cycle

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

Low potassium should be corrected prior to commencing treatment.

If BP ≥ 140/90 mmHg, this should be controlled and managed by the GP prior to commencing treatment.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Blood pressure	Baseline then 3 monthly or as clinically indicated
Echocardiogram	3 - 4 monthly or in metastatic patients every 6 months if stable (more frequently if patient develops asymptomatic cardiac dysfunction)

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 (at baseline, see haematology toxicity section for management during treatment)
Creatinine clearance (CrCl)	≥ 30mL/min
Bilirubin	< 1.5 x ULN
AST/ALT	< 2.5 x ULN
LVEF	≥ LLN for institution (usually 50%) and <10 point change from baseline (see below)

Note: Kadcyla has not been studied in patients with platelets < 100 x 10^9/L prior to initiation of treatment.

Dose modifications

Dose reduction level	Dose
Full dose	3.6mg/kg
1st dose reduction	3mg/kg
2nd dose reduction	2.4mg/kg

If more than 2 dose reductions are required treatment should be discontinued.

Doses should **not** be re-escalated following a dose reduction.

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L, delay until recovery.

Platelets:
Metastatic breast cancer:

Platelets (x 10^9/L)	**Action**
25-50	Withhold until ≥ 75 x 10^9/L Continue at same dose
< 25	Withhold until ≥ 75 x 10^9/L Reduce dose by 1 dose level

Early breast cancer:

Platelets (x 10^9/L)	**Action**
25-75	Withhold until ≥ 75 x 10^9/L Continue at same dose If patient requires 2 delays consider dose reduction.
< 25	Withhold until ≥ 75 x 10^9/L Reduce dose by 1 dose level

- **Renal impairment**

If CrCl < 30mL/min no need for dose adjustment is expected however consultant decision to proceed and close monitoring required.

- **Hepatic impairment**

No adjustment to the starting dose is required for patients with mild or moderate hepatic impairment (Child Pugh A or B). Kadcyla has not been studied in patients with severe hepatic impairment (Child Pugh C). Treatment of patients with hepatic impairment should be undertaken with caution due to known hepatotoxicity.

- **Other toxicities**

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.

Hepatotoxicity

Metastatic breast cancer:

Toxicity	Grade	Action
Increased Transaminase (AST/ALT)	Grade 2 (> 2.5 to ≤ 5× ULN)	Continue at the same dose level
	Grade 3 (> 5 to ≤ 20× ULN)	Withhold Kadcyla until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level
	Grade 4 (> 20× ULN)	Discontinue Kadcyla
Hyperbilirubinemia	Grade 2 (> 1.5 to ≤ 3× ULN)	Withhold Kadcyla until total bilirubin recovers to Grade ≤ 1, and then treat at the same dose level.
	Grade 3 (> 3 to ≤ 10× ULN)	Withhold Kadcyla until total bilirubin recovers to Grade ≤ 1 and then reduce one dose level.
	Grade 4 (> 10× ULN)	Discontinue Kadcyla
Drug Induced Liver Injury (DILI)	Serum transaminases > 3 x ULN and concomitant total bilirubin > 2× ULN	Permanently discontinue Kadcyla in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication

Early breast cancer

Toxicity	Grade	Action
Increased Alanine Transaminase (ALT)	Grade 2-3 (> 3.0 to ≤ 20 × ULN on day of scheduled treatment)	Do not administer Kadcyla until ALT recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20 × ULN at any time)	Discontinue Kadcyla
Increased Aspartate Transaminase (AST)	Grade 2 (> 3.0 to ≤ 5 × ULN on day of scheduled treatment)	Do not administer Kadcyla until AST recovers to Grade ≤ 1, and then treat at the same dose level
	Grade 3 (> 5 to ≤ 20 × ULN on day of scheduled treatment)	Do not administer Kadcyla until AST recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20 × ULN at any time)	Discontinue Kadcyla
Hyperbilirubinemia	TBILI > 1.0 to ≤ 2.0 × ULN on day of scheduled treatment	Do not administer Kadcyla until total bilirubin recovers to ≤ 1.0 × ULN, and then reduce one dose level
	TBILI > 2 × ULN at any time	Discontinue Kadcyla
Drug Induced Liver Injury (DILI)	Serum transaminases > 3 x ULN and concomitant total bilirubin > 2 × ULN	Permanently discontinue Kadcyla in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication

Peripheral neuropathy
If grade 3-4 withhold until ≤ grade 2. Consider dose reduction and monitor.

Pulmonary toxicity
Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported. Signs and symptoms include dyspnoea, cough, fatigue, and pulmonary infiltrates. If interstitial lung disease or pneumonitis or grade 3-4 radiotherapy related pneumonitis discontinue Kadcyla. If grade 2 radiotherapy induced pneumonitis does not resolve with standard treatment then discontinue Kadcyla.

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

- **Rare or serious side effects**

Myelosuppression
Cardiotoxicity
Haemorrhage
Hepatobiliary disorders
Neurotoxicity
ILD, Pneumonitis

- **Frequently occurring side effects**

Myelosuppression
Raised transaminases
Infusion related reactions
Hypokalaemia
Stomatitis
Diarrhoea
Musculoskeletal pain
Dyspnoea
Fatigue
Peripheral neuropathy

- **Other side effects**

Insomnia
Headaches, dizziness
Rash
Arthralgia, Myalgia

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.

CYP3A4 inhibitors: (ketoconazole, itraconazole, clarithromycin, atazanivir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole): avoid concomitant administration – increased risk of toxicity.

Additional comments

Women of childbearing potential should use effective contraception while receiving Kadcyla and for 7 months following the last dose. Male patients or their female partners should also use effective contraception.

Anthracyclines must not be given in combination with, or within 6 months of last dose of, Kadcyla.

References

- Summary of Product Characteristics Kadcyla (Roche) accessed 16 February 2023 via www.medicines.org.uk
- National Institute for Clinical Excellence (TA458) accessed 16 February 2023 via www.nice.org.uk
- National Institute for Clinical Excellence (TA632) accessed 16 February 2023 via www.nice.org.uk
- Von Minckwitz et al. Trastuzumab Emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019; 380:617-628.
- Verma S. et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. N Engl J Med 2012; 367(19): 1783-91
- Lyon, AR. et al. 2022 ESC Guidelines on cardio-oncology. European Heart Journal 43(41):4229-4361

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