SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti-Cancer Therapy Protocol

Kadcyla (Trastuzumab Emtansine) HER-2 Positive Breast Cancer

PROTOCOL REF: MPHAKADBR
(Version No.: 1.3)

Approved for use in:

Early Breast Cancer (EBC)

As a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

Locally Advanced/Metastatic Breast Cancer (MBC)

As a single agent, is indicated for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either progression:

- During or after the most recent treatment for advanced stage disease, or
- Within 6 months of completing treatment for early stage disease.

Due to risk of error with different dosing schedule to trastuzumab, this conjugate product will be referred to by its brand name **Kadcyla** throughout all documentation.

**************Blueteq Registration Required*************

Dosage:

Drug	Dose	Route	Frequency
Kadcyla	3.6mg/kg	IV Infusion	Every 21 days

Adjuvant- total of 14 cycles unless there is disease recurrence or unmanageable toxicity.

Palliative- until disease progression or unmanageable toxicity.

Counselling points:

- Trastuzumab, a component of Kadcyla, can cause foetal harm or death when administered to a pregnant woman. 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.

- Kadcyla has minor influence on the ability to drive and use machines. The significance of reported adverse reactions such as fatigue, headache, dizziness and blurred vision on the ability to drive or use machines is unknown. Patients experiencing infusion-related reactions (flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm, and tachycardia) should be advised not to drive and use machines until symptoms abate.

Emetogenic risk:

Mild/moderate

Supportive treatments:

Dexamethasone tablets, 4mg twice daily for 3 days. If no nausea/vomiting then consider reducing and stopping after the first two cycles.
Metoclopramide 10mg tablets, to be taken up to three times a day as required for nausea and vomiting. Maximum 5 consecutive days.

Extravasation risk:

Irritant- Reactions, observed more frequently within 24 hours of infusion, were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site however exceptional cases of severe tissue lesions and epidermal necrosis may occur. **If extravasation occurs, the infusion should be terminated immediately and the patient should be examined regularly as necrosis may occur within days to weeks after infusion.**

Extravasation of Kadcyla during intravenous injection may produce local pain.

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	CrCl ≥ 30mL/min- No dose adjustment is required. CrCl < 30ml/min- No need for dose adjustment expected but limited information therefore should be used with caution.

Hepatic

Mild or moderate hepatic impairment (Child-Pugh A and B) - no adjustment to the starting dose
Severe hepatic impairment (Child-Pugh C) - not been studied in patients with severe hepatic impairment therefore should be used with caution due to known hepatotoxicity with Kadcyla.

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening. **If patient**

	develops suspected treatment-related hepatotoxicity refer to 'Dose Modification and Toxicity Management' section.

Interactions:

No formal interaction studies have been performed. However in vitro studies suggest that DM1 – a component of Kadcyla is metabolised mainly by CYP3A4 and to a less extent CYP3A5. Concomitant use of STRONG CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atanazavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided.

For more detailed interactions please refer to the SmPC

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**12mg**	**PO**	30 minutes before chemotherapy
	Ondansetron	**24mg**	**PO**	30 minutes before chemotherapy
	KADCYLA	**3.6mg/kg**	**IV**	250mL sodium chloride 0.9% via 0.22 micron filter 1st dose to be given over 90 minutes, if tolerated subsequent doses to be given over 30 minutes.

Every 21 days until progression or unacceptable toxicity.

Patients should be observed closely for hypersensitivity/allergic reactions, which may have the same clinical presentation as an IRR; flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm and tachycardia. For management refer to 'Hypersensitivity: Management and Prevention' guideline.

Main toxicities:

Haematological	Neutropenia, anaemia, thrombocytopenia,
Cardiac and Vascular disorders	LVEF reduction Hypokalaemia
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis
Nervous system	Peripheral neuropathy
Hepatobiliary	Elevation of liver transaminases, alkaline phosphatase and bilirubin.
General disorders and administration site conditions	Infusion related reactions Fatigue, pneumonitis, dyspneoa Infertility and early menopause

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Comments
Informed Consent	X							
Clinical Assessment	X		X		X		X	Then every 12 weeks
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every cycle
On treatment review (OTR)/ Go-ahead		X	X	X	X	X	X	Every cycle
ECHO	X				X			**Adjuvant**-12 weekly **Palliative**-12 weekly for the first 12 months, then if stable only repeat if clinically appropriate.
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFTs	X	X	X	X	X	X	X	Every Cycle
CT scan	X							Every 8 to 12 weeks as clinically indicated
Full Observations *(HR, RR and O2 saturations)*	X							Repeat if clinically indicated*
Height recorded	X							
Weight recorded	X	X	X	X	X	X	X	Every cycle

* Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical studies with Kadcyla. Monitor for signs and symptoms including; dyspnoea, cough and fatigue.

Dose Modifications and Toxicity Management:

Dose reduction schedule	Dose to be administered
1st dose reduction	3mg/kg
2nd dose reduction	2.4mg/kg
Requirement for further dose reduction	Discontinue Kadcyla

Proceed Rules:

Cardiac function testing prior to cycle 1 day 1

Baseline LVEF ≥ 50%

Refer to Cardiotoxicity section below for subsequent monitoring

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 75 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 74 x 10^9/L

Adverse reaction	Severity	Treatment modification
Neutropenia	Grade 3 0.5 to < 1.0 x 10^9/L	Consider dose reduction to next dose level if neutropenia persists for more than 7 days or 2 subsequent deferrals
Thrombocytopenia	Grade 2-3 25 to < 75 x 10^9/L	Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75 x 109/L), and then treat at the same dose level. If a patient requires 2 delays due to thrombocytopenia, consider reducing dose by one level.
	Grade 4 at any time < 25 x 10^9/L	Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75 x 109/L), and then reduce one dose level.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Hepatotoxicity- Patients with baseline elevation of ALT (e.g. due to liver metastases) may be predisposed to liver injury with a higher risk of a Grade 3-5 hepatic event or liver function test increase.

Adverse reaction	Severity	Treatment modification
Increased Alanine Transaminase (ALT)	Grade 2-3 > 3.0 to ≤ 20×ULN	Do not administer Kadcyla until ALT recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 at any time > 20 × ULN	Discontinue Kadcyla
Increased Aspartate Transaminase (AST)	Grade 2 > 3.0 to ≤ 5×ULN	Do not administer Kadcyla until AST recovers to Grade ≤ 1, and then treat at the same dose level
	Grade 3 > 5 to ≤ 20×ULN	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	Total Bilirubin > 1.0 to ≤ 2.0×ULN	Do not administer Kadcyla until total bilirubin recovers to ≤ 1.0× ULN, and then reduce one dose level
	Total Bilirubin > 2× ULN at any time	Discontinue Kadcyla
Drug Induced Liver Injury (DILI)	Serum transaminases > 3 x ULN **and concomitan**t 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
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue Kadcyla

Cardiotoxicity

Adverse reaction	Severity	Treatment modification

Left Ventricular Dysfunction	LVEF < 45%	Do not administer Kadcyla. Repeat LVEF assessment within 3 weeks. If LVEF < 45% is confirmed, discontinue Kadcyla.
	LVEF 45% to < 50% and decrease is ≥ 10% points from baseline*	Do not administer Kadcyla. Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to < 10% points from baseline, discontinue Kadcyla
	LVEF 45% to < 50% and decrease is < 10% points from baseline*	Continue treatment with Kadcyla. Repeat LVEF assessment within 3 weeks.
	LVEF ≥ 50%	Continue treatment with Kadcyla
Heart Failure	Symptomatic Congestive Heart Failure (CHF), Grade 3-4 Left Ventricular Systolic Dysfunction LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45%	Discontinue Kadcyla

Other Toxicities

Adverse reaction	Severity	Treatment modification
Peripheral Neuropathy	Grade 3-4	Do not administer Kadcyla until resolution ≤ Grade 2
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue Kadcyla
Radiotherapy-Related Pneumonitis	Grade 2	Discontinue Kadcyla if not resolving with standard treatment
	Grade 3-4	Discontinue Kadcyla

Kadcyla Given via Clatterbridge in the Community (CIC) Team

IV Kadcyla should only be given in a community setting following 2 cycles of treatment in a clinical setting where no adverse reactions have been reported. Please refer to the Kadcyla CIC risk assessment for full details.

Patients will be fully assessed for their suitability for SACT in the community as it is not suitable for all patients so it is important to ensure they meet the eligibility criteria as outlined in the Kadcyla CIC risk assessment.

References:

1. Kadcyla 100mg powder for concentrate for solution for infusion - https://www.medicines.org.uk/emc accessed 20/04/2022, last updated 27th April 2022.
2. NICE TA458 Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane. Published: 19 July 2017
3. NICE TA632: Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer. Published: 10 June 2020
4. Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; **20:** e201–08.

Circulation/Dissemination

Date added into Q-Pulse	8th June 2022
Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
		Helen Flint Consultant Pharmacist	New regimen protocol V1.0
		Hala Ghoz Breast SRG Pharmacist	Adjuvant indication added V1.2
		Hala Ghoz Lead Protocols Pharmacist	Protocol updated as per licensing changes (hypersensitivity, extravasation, child-pugh table added, drug interactions, and counselling points) V1.3