**Systemic Anti Cancer Treatment Protocol**

# Kadcyla (Trastuzumab Emtansine) - Early Breast Cancer and Locally Advanced or Metastatic Breast Cancer

**PROTOCOL REF: MPHAKADBR**
**(Version No: 1.2)**

## 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 | Every 21 days |

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

**Palliative- until disease progression or unmanageable toxicity.**

## Supportive treatments:

Dexamethasone tablets, 4mg twice daily for 3 days. If no nausea/vomiting then consider reducing and stopping after the first two cycles.

Domperidone 10mg tablets, to be taken three times a day as required

## Extravasation risk:

Non-vesicant: no specific antidote

## Dosing in renal and hepatic impairment:

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

| **Hepatic impairment:** |
|---|
| Mild or moderate hepatic impairment (Child-Pugh A and B) - no adjustment to the starting dose<br>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 |

## Administration:

| Day | Medicine | Dose | Route | Diluent and rate |
|---|---|---|---|---|
| 1 | **Ondansetron** | **16mg** | **PO** | 30mins before chemotherapy |
| | **Dexamethasone** | **12mg** | **PO** | 30mins before chemotherapy |
| | **KADCYLA** | **3.6mg/kg** | **IV** | 250mL sodium chloride 0.9%.<br>1st dose to be given over 90mins, if tolerated subsequent doses to be given over 30mins<br>Give via 0.22 micron filter |

## Main Toxicities:

| | |
|---|---|
| **Haematological** | Neutropenia, anaemia, thrombocytopenia, |
| **Cardiac and Vascular disorders** | LVEF reduction<br>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<br>Fatigue, pneumonitis, dyspneoa<br>Infertility and early menopause |

## Investigations and Treatment Plan:

| | Pre | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | Comments |
|---|---|---|---|---|---|---|---|---|
| Clinical Assessment | X | | X | | X | | X | Then every 12 weeks |
| SACT Assessment (to include PS and toxicities) | | 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 | Every cycle |
| U&E & LFT | X | | X | X | X | X | X | Every cycle |
| Informed Consent | X | | | | | | | |
| CT scan | X | | | | | | | EBC: Not required. Locally advanced/MBC: Every 8 to 12 weeks as clinically indicated |
| Blood pressure measurement | X | | | | | | | Repeat if clinically indicated |
| Respiratory Rate | | | | | | | | If clinically indicated |
| Weight recorded | X | X | X | X | X | X | X | Every cycle |
| Height | X | | | | | | | |

## 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-

| | |
|---|---|
| Plt ≥ 75 x $10^9$/L | ANC ≥ 1.0 x $10^9$/L |

Delay 1 week on day 1 if-

| | |
|---|---|
| Plt ≤ 74 x $10^9$/L | ANC ≤ 0.9 x $10^9$/L |

### Haematological Toxicity

| Adverse reaction | Severity | Treatment modification |
|---|---|---|
| Neutropenia | Grade 3<br>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<br>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<br>< 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. |

### Hepatotoxicity

| Adverse reaction | Severity | Treatment modification |
|---|---|---|
| Increased Alanine Transaminase (ALT) | Grade 2-3<br>> 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<br>> 20 × ULN | Discontinue Kadcyla |
| Increased Aspartate Transaminase (AST) | Grade 2<br>> 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<br>> 5 to ≤ 20×ULN | Do not administer Kadcyla until AST recovers to Grade ≤ 1, and then reduce one dose level |
| | Grade 4<br>> 20 × ULN at any time | Discontinue Kadcyla |
| Hyperbilirubinemia | Total Bilirubin<br>> 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<br>> 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 | Discontinue Kadcyla |

| | | |
|---|---|---|
| | Systolic Dysfunction LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45% | |

**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:

Kadcyla 100 mg & 160 mg Powder for Concentrate for Solution. Summary of Product Characteristics. Roche Products.

NICE TA458 July 2017

NICE Technology Appraisal Final Appraisal Determination: Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer May 2020.

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.

Verma S, Miles D, Gianni L, et al (2012). Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 367:1783–1791,

Von Minckwitz G, Huang C-S, Mano MS, et al (2019).Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med.* 380: 617-628