

TRASTUZUMAB EMTANSINE (Kadcyla)

INDICATION (ICD10) C50

Check the most recent Blumetq eligibility criteria before prescribing. Blumetq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (TRA2), (TRA1)

1. As adjuvant monotherapy for patients with HER2-positive (HER2 3+) early breast cancer who have residual invasive disease following the completion of neoadjuvant combination of taxane-based and HER2-targeted (at least 16 weeks of neoadjuvant cytotoxic including a minimum of 9 weeks of taxane-based chemotherapy and at least 9 weeks of HER2-targeted therapy) systemic therapy and adequately excised surgery. Trastuzumab emtansine is the only HER2-directed therapy to be given after surgery i.e. no adjuvant trastuzumab / pertuzumab has been administered since surgery, except may have received one cycle of adjuvant pertuzumab and trastuzumab whilst awaiting the pathology results to confirm the status of axillary lymph node involvement and any residual disease. PS 0 or 1. (TA632)
2. The treatment of HER2-positive locally advanced / unresectable or metastatic (stage IV) breast cancer, previously treated with a taxane and trastuzumab, which has progressed during or after the most recent treatment for advanced stage disease or within 6 months of completing treatment for early stage disease. PS 0, 1 or 2. (TA458)

REGIMEN

Day 1 TRASTUZUMAB EMTANSINE 3.6mg/kg in 250ml sodium chloride 0.9% IV infusion over 90 minutes

Observe for 90 minutes after completion of first infusion.

If the prior infusion was well tolerated subsequent infusions may be administered over 30 minutes and observed for at least 30 minutes after infusion.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Adjuvant – every 21 days up to 10-12 cycles (depending on neoadjuvant regimen previously ie 18 doses in total including all neoadjuvant doses anti-HER2 treatment).

Metastatic - every 21 days until disease progression or unacceptable toxicity.

ANTI-EMETICS

Low risk day 1

CONCURRENT MEDICATION REQUIRED

None required

EXTRAVASATION AND TYPE OF LINE / FILTERS

Trastuzumab emtansine – non-vesicant

Administer via polyethylene lined administration set with ≤ 0.22 micron filter

Peripheral or central line

INVESTIGATIONS

Blood results required before SACT administration

FBC, U&E and LFTs every cycle

Neutrophils x $10^9/L$ ≥ 1.5

Platelets x $10^9/L$ ≥ 75

Baseline weight and every 3 months

Monitor cardiac function as per network guidelines. The left ventricular ejection fraction prior to commencing treatment $\geq 50\%$.

MAIN TOXICITIES AND ADVERSE REACTIONS

Trastuzumab emtansine	Urinary tract infection Hypokalaemia Neuropathy, dizziness Stomatitis Rash Arthralgia, myalgia Increased transaminases Thrombocytopenia
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DOSE MODIFICATIONS

Dose reduction schedule

Starting dose is 3.6mg/kg

First dose reduction

Second dose reduction

Requirement for further dose reduction

Dose to be administered

3mg/kg

2.4mg/kg

Discontinue treatment

Early breast cancer

Haematological (early breast cancer)

Thrombocytopenia grade 2-3 on day of scheduled treatment (Platelets: $25 \times 10^9/L$ to $<50 \times 10^9/L$)	Do not administer trastuzumab emtansine until platelet count recovers to \leq grade 1 (ie platelets $\geq 75 \times 10^9/L$), and then treat at the same dose level. If a patient requires 2 delays due to thrombocytopenia, consider reducing dose by one level.
Thrombocytopenia grade 4 at any time (Platelets: $<25 \times 10^9/L$)	Do not administer trastuzumab emtansine until platelet count recovers to \leq grade 1 (ie platelets $\geq 75 \times 10^9/L$), and then dose reduce one dose level.

Non-haematological (early breast cancer)

Nodular regenerative hyperplasia all grades – permanently discontinue.

Peripheral neuropathy grade 3 or 4 peripheral neuropathy - withhold treatment until recovered to \leq grade 2.

Pulmonary toxicity, interstitial lung disease - permanently discontinue.

<https://thamesvalleycanceralliance.nhs.uk/wp-content/uploads/2023/03/Trastuzumab-emtansine-5.3.pdf> Heart failure, Symptomatic CHF, Grade 3-4 LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45% - permanently discontinue.

LVEF <45%	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF < 45% is confirmed, discontinue trastuzumab emtansine.
LVEF 45% to <50% and decrease is ≥10% points from baseline*	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to < 10% points from baseline, discontinue trastuzumab emtansine.
LVEF 45% to <50% and decrease is <10% points from baseline*	Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks.
LVEF ≥50%	Continue treatment with trastuzumab emtansine

Radiotherapy related pneumonitis

Grade 2	Discontinue trastuzumab emtansine if not resolving with standard treatment.
Grade 3	Discontinue trastuzumab emtansine.

Hepatic impairment (early breast cancer)

No starting dose adjustment in mild or moderate hepatic impairment. Trastuzumab emtansine has not been studied in patients with severe hepatic impairment.

Increased ALT grade 2-3 (>3 to ≤20×ULN) on day of treatment	Do not administer trastuzumab emtansine until ALT recovers to grade ≤1 and then reduce dose one level.
Increased ALT grade 4 (>20×ULN)	Discontinue trastuzumab emtansine.
Increased AST grade 2 (>3 to ≤5×ULN) on day of treatment	Do not administer trastuzumab emtansine until AST recovers to grade ≤1 and then treat at the same dose level.
Increased AST grade 3 (>5 to ≤20×ULN) on day of treatment	Do not administer trastuzumab emtansine until AST recovers to grade ≤1 and then reduce dose one level.
Increased AST grade 4 (>20×ULN)	Discontinue trastuzumab emtansine.
Hyperbilirubinemia >1 to ≤2×ULN) on day of treatment	Do not administer trastuzumab emtansine until total bilirubin recovers to ≤1×ULN, and then reduce one dose level.
Hyperbilirubinemia >2×ULN	Discontinue trastuzumab emtansine.
Drug induced liver injury. Serum transaminases >3xULN and concomitant total bilirubin >2xULN	Permanently discontinue trastuzumab emtansine in the absence of another likely cause for the elevation of liver enzymes and bilirubin, eg liver metastasis or concomitant medication

Renal Impairment (early breast cancer)

CrCl \geq 30ml/min	No dose adjustment
CrCl <30ml/min	Limited data and so no dose recommendations can be made.

Metastatic breast cancer

Haematological (metastatic breast cancer)

Thrombocytopenia grade 3 (Platelets $25 \times 10^9/L$ to $<50 \times 10^9/L$)	Do not administer trastuzumab emtansine until platelet count recovers to \leq grade 1 (ie platelets $\geq 75 \times 10^9/L$), and then treat at the same dose level.
Thrombocytopenia grade 4 (Platelets $<25 \times 10^9/L$)	Do not administer trastuzumab emtansine until platelet count recovers to \leq grade 1 (ie platelets $\geq 75 \times 10^9/L$), and then dose reduce one dose level.

Non-haematological (metastatic breast cancer)

Nodular regenerative hyperplasia all grades – permanently discontinue.

Peripheral neuropathy grade 3 or 4 peripheral neuropathy - withhold treatment until recovered to \leq grade 2.

Pulmonary toxicity, interstitial lung disease - permanently discontinue.

LVEF <40%	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF <40% is confirmed, discontinue trastuzumab emtansine.
LVEF 40% to <45% and decrease is $\geq 10\%$ points from baseline*	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue trastuzumab emtansine.
LVEF 40% to <45% and decrease is <10% points from baseline*	Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks.
LVEF $\geq 45\%$	Continue treatment with trastuzumab emtansine

Hepatic impairment (metastatic breast cancer)

No starting dose adjustment in mild or moderate hepatic impairment. Trastuzumab emtansine has not been studied in patients with severe hepatic impairment.

Increased transaminases (AST/ALT) grade 2 (>2.5 to ≤5×ULN)	No dose modification is required.
Increased transaminases (AST/ALT) grade 3 (>5 to ≤20×ULN)	Do not administer trastuzumab emtansine until AST/ALT recovers to grade ≤2 (>2.5 to <5×ULN), and then dose reduce.
Increased transaminases (AST/ALT) grade 4 (>20×ULN)	Discontinue trastuzumab emtansine.
Hyperbilirubinemia grade 2 (>1.5 to ≤3×ULN)	Do not administer trastuzumab emtansine until total bilirubin recovers to grade ≤1 (>ULN to 1.5×ULN). No dose modification is required.
Hyperbilirubinemia grade 3 (>3 to ≤10×ULN)	Do not administer trastuzumab emtansine until total bilirubin recovers to grade ≤1 (>ULN to 1.5×ULN), and then dose reduce.
Hyperbilirubinemia grade 4 (>10×ULN)	Discontinue trastuzumab emtansine.
Drug induced liver injury. Serum transaminases >3xULN and concomitant total bilirubin >2xULN	Permanently discontinue trastuzumab emtansine in the absence of another likely cause for the elevation of liver enzymes and bilirubin, eg liver metastasis or concomitant medication

Renal Impairment (metastatic breast cancer)

CrCl ≥30ml/min	No dose adjustment
CrCl <30ml/min	Limited data and so no dose recommendations can be made.

REFERENCES

1. Kadcylya 100 mg & 160 mg Powder for Concentrate for Solution. Summary of Product Characteristics. Roche Products www.medicines.org.uk/emc/medicine last updated 11/02/2014.
2. NICE TA458 July 2017
3. NICE TA632 June 2020