

## Trastuzumab deruxtecan (Enhertu®)

### Indication

1. HER2 positive unresectable locally advanced or metastatic breast cancer after 1 or more anti-HER2 therapies
2. HER-2 low metastatic or unresectable breast cancer after chemotherapy

### Regimen details

| DRUG                              | DOSE     | DILUENT             | ROUTE                                                  | FREQUENCY/DURATION                                                              |
|-----------------------------------|----------|---------------------|--------------------------------------------------------|---------------------------------------------------------------------------------|
| Trastuzumab deruxtecan (Enhertu®) | 5.4mg/kg | 100mL<br>Glucose 5% | Intravenous Infusion via<br>0.22 micron in-line filter | 1 <sup>st</sup> Dose over 90mins. If tolerated<br>subsequent doses over 30mins. |

### Cycle frequency

Every 3 weeks

### Number of cycles

Until disease progression or unacceptable toxicity

### Administration

Trastuzumab deruxtecan (Enhertu®) should be administered via a 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter

The initial dose should be administered as a 90-minute intravenous infusion. If the prior infusion was well tolerated, subsequent doses of Trastuzumab deruxtecan (Enhertu®) may be administered as 30-minute infusions

The infusion rate of Trastuzumab deruxtecan (Enhertu®) should be slowed or interrupted if the patient develops infusion-related symptoms. Trastuzumab deruxtecan (Enhertu®) should be permanently discontinued in case of severe infusion reactions

### Pre-medication

Antiemetics as per policy

### Emetogenicity

Moderate Risk (Category B)

### Additional supportive medication

Ondansetron 8mg twice daily for 2 days (in addition to standard dexamethasone and metoclopramide)

### Extravasation

No information currently available, consider non-vesicant.

### Investigations – pre first cycle

| Investigation              | Validity period |
|----------------------------|-----------------|
| FBC                        | 14 days         |
| U+E (including creatinine) | 14 days         |
| LFT (including AST)        | 14 days         |
| Magnesium                  | 14 days         |
| ECHO                       | Baseline        |

### Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), magnesium

LVEF of at least 50% on commencing treatment

Repeat echocardiogram/Muga scan for LVEF at 4-6 months

Trastuzumab deruxtecan (Enhertu) should be discontinued if LVEF falls below 40% or there is a 20% drop from baseline.

**Patients presenting with cough and/or increasing shortness of breath: defer treatment and ensure urgent medical review, for CT scan and/or ECHO depending on clinical picture a refer to dose modification section below.**

### Standard limits for administration to go ahead

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

| Investigation        | Limit                           |
|----------------------|---------------------------------|
| Neutrophil count     | $\geq 1.0 \times 10^9/\text{L}$ |
| Platelet count       | $\geq 100 \times 10^9/\text{L}$ |
| Creatinine clearance | $\geq 30 \text{ mL/min}$        |
| Bilirubin            | $\leq 1.5 \times \text{ULN}$    |
| AST                  | $< 5 \times \text{ULN}$         |

### Dose modifications

| Dose reduction schedule<br>(Starting dose is 5.4 mg/kg) | Dose to be administered |
|---------------------------------------------------------|-------------------------|
| First dose reduction                                    | 4.4 mg/kg               |
| Second dose reduction                                   | 3.2 mg/kg               |
| Requirement for further dose reduction                  | Discontinue treatment   |

| Adverse reaction                            | Severity                                         | Treatment modification                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Interstitial lung disease (ILD)/pneumonitis | Asymptomatic ILD/pneumonitis (Grade 1)           | Interrupt Trastuzumab deruxtecan (Enhertu®) until resolved to Grade 0, then: <ul style="list-style-type: none"><li>• if resolved in 28 days or less from date of onset, maintain dose.</li><li>• if resolved in greater than 28 days from date of onset, reduce dose one level</li><li>• consider corticosteroid treatment as soon as ILD/pneumonitis is suspected</li></ul> |
|                                             | Symptomatic ILD/pneumonitis (Grade 2 or greater) | <ul style="list-style-type: none"><li>• Permanently discontinue Trastuzumab deruxtecan (Enhertu®).</li><li>• Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected</li></ul>                                                                                                                                                                    |

### CTC grading for Interstitial Lung Disease:

|                |                                                                                  |
|----------------|----------------------------------------------------------------------------------|
| <b>Grade 1</b> | Asymptomatic, clinical or diagnostic observations only                           |
| <b>Grade 2</b> | Symptomatic, limiting instrumental activities of daily living                    |
| <b>Grade 3</b> | Severe symptoms, limiting self-care activities of daily living; oxygen indicated |
| <b>Grade 4</b> | Life-threatening respiratory compromise                                          |

| Adverse reaction           | Severity                                                                                                                                                                             | Treatment modification                                                                                                                                             |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Neutropenia</b>         | Grade 3 (less than $1.0-0.5 \times 10^9/L$ )                                                                                                                                         | <ul style="list-style-type: none"> <li>Interrupt Trastuzumab deruxtecan (Enhertu®) until resolved to Grade 2 or less, then maintain dose.</li> </ul>               |
|                            | Grade 4 (less than $0.5 \times 10^9/L$ )                                                                                                                                             | <ul style="list-style-type: none"> <li>Interrupt Trastuzumab deruxtecan (Enhertu®) until resolved to Grade 2 or less.</li> <li>Reduce dose by one level</li> </ul> |
| <b>Febrile neutropenia</b> | Absolute neutrophil count of less than $1.0 \times 10^9/L$ and temperature greater than $38.3^\circ C$ or a sustained temperature of $38^\circ C$ or greater for more than one hour. | <ul style="list-style-type: none"> <li>Interrupt Trastuzumab deruxtecan (Enhertu®) until resolved.</li> <li>Reduce dose by one level</li> </ul>                    |

| Adverse reaction                                           | Severity                                                                  | Treatment modification                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Left ventricular ejection fraction (LVEF) decreased</b> | LVEF greater than 45% and absolute decrease from baseline is 10% to 20%   | <ul style="list-style-type: none"> <li>Continue treatment with Trastuzumab deruxtecan (Enhertu®).</li> </ul>                                                                                                                                                                                                                                                                                               |
|                                                            | LVEF 40% to 45%<br>And absolute decrease from baseline is less than 10%   | <ul style="list-style-type: none"> <li>Continue treatment with Trastuzumab deruxtecan (Enhertu®).</li> <li>Repeat LVEF assessment within 3 weeks.</li> </ul>                                                                                                                                                                                                                                               |
|                                                            | And absolute decrease from baseline is 10% to 20%                         | <ul style="list-style-type: none"> <li>Interrupt Trastuzumab deruxtecan (Enhertu®).</li> <li>Repeat LVEF assessment within 3 weeks.</li> <li>If LVEF has not recovered to within 10% from baseline, permanently discontinue Trastuzumab deruxtecan (Enhertu®).</li> <li>If LVEF recovers to within 10% from baseline, resume treatment with Trastuzumab deruxtecan (Enhertu®) at the same dose.</li> </ul> |
|                                                            | LVEF less than 40% or absolute decrease from baseline is greater than 20% | <ul style="list-style-type: none"> <li>Interrupt Trastuzumab deruxtecan (Enhertu®)</li> <li>Repeat LVEF assessment within 3 weeks.</li> <li>If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue Trastuzumab deruxtecan (Enhertu®).</li> </ul>                                                                                            |
|                                                            | Symptomatic congestive heart failure (CHF)                                | <ul style="list-style-type: none"> <li>Permanently discontinue Trastuzumab deruxtecan (Enhertu®).</li> </ul>                                                                                                                                                                                                                                                                                               |

### Hepatic impairment

| AST or ALT                                       | Bilirubin                                                       | Action                                                                                                              |
|--------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Grade 2 ( $< 5 \times \text{ULN}$ )              | Grade 1 ( $1.5 \times \text{ULN}$ ) or no change from baseline  | Continue                                                                                                            |
| Grade 3 ( $5 \text{ to } 20 \times \text{ULN}$ ) | Grade 2 (increased to between $1.5$ and $3 \times \text{ULN}$ ) | Hold treatment and repeat in 7 days. If resolved to baseline within 7 days continue on current dose                 |
|                                                  | Grade 3 ( $3 \text{ to } 10 \times \text{ULN}$ )                | Hold treatment and repeat in 7 days. If resolved to less than $1.5 \times \text{ULN}$ then resume at dose reduction |
| Grade 4 ( $>20 \times \text{ULN}$ )              | Grade 4 ( $>10 \times \text{ULN}$ )                             | Discontinue                                                                                                         |

### Renal impairment

No dose adjustment is required in patients with mild (creatinine clearance  $[\text{CLcr}] \geq 60$  and  $< 90 \text{ mL/min}$ ) or moderate ( $\text{CLcr} \geq 30$  and  $< 60 \text{ mL/min}$ ) renal impairment. The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data. A higher incidence of Grade 1 and 2 ILD has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully.

### Adverse effects – for full details consult product literature/ reference texts

Neutropenia  
Thrombocytopenia  
Anaemia  
LVEF reduction  
Hypokalaemia  
Nausea  
Vomiting  
Diarrhoea  
Constipation  
Decreased appetite  
Abdominal pain  
Interstitial lung disease/pneumonitis  
Dyspnoea/cough  
Raised LFTs  
Infusion reactions  
Fatigue  
Headache  
Alopecia  
Dry eyes  
Epistaxis  
Rash

### Significant drug interactions

– for full details consult product literature/ reference texts

None expected

### Additional comments

None

### References

1. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer N Engl J Med 2020; 382:610-621 (DESTINY-Breast01 trial)
2. NICE TA704 Published 26/05/2021
3. Enhertu® SPC: <https://www.medicines.org.uk/emc/product/12135> - Revised 10/06/2021 (accessed 18/06/2021)
4. Systemic Anti Cancer Therapy Protocol Enhertu (Trastuzumab Deruxtecan) HER2 Positive Advanced Breast Cancer PROTOCOL REF: MPHAENTDBR (Version No: 1.0) - THE CLATTERBRIDGE CANCER CENTRE NHS FOUNDATION TRUST
5. NICE ID 3909 Published 20/12/2023

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**THIS PROTOCOL HAS BEEN DIRECTED BY DR BADEA, DESIGNATED LEAD CLINICIAN FOR BREAST CANCER**

**RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE**

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