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Methods for Estimating Long-Term Outcomes for Trastuzumab Deruxtecan in HER2-Positive Unresectable or Metastatic Breast Cancer After Two or More Anti-HER2 Therapies

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Estimation of comparative efficacy

Matching-adjusted indirect comparison methods

Clinical outcomes of interest for comparison for inclusion in the model were progression-free survival (PFS), time to discontinuation (TTD) and objective response rate (ORR). A systematic literature review (SLR) was conducted to identify studies describing the efficacy and safety of trastuzumab deruxtecan (T-DXd) and comparators in a population of patients with unresectable or metastatic (u/m) breast cancer (BC) and human epidermal growth factor receptor-positive (HER2+), mixed, or unknown HER2 status. Four relevant studies were identified investigating eribulin [1-4], three investigating capecitabine [5-9], and one investigating vinorelbine [10]. A summary of the studies that were used to inform the matching-adjusted indirect comparisons (MAIC), model base case and scenario analyses are presented in Table S1.

The principal source of data for T-DXd was the DESTINY-Breast01 June 2020 data-cut, the latest available at the time of analysis [11]. As DESTINY-Breast01 is a single arm trial, unanchored MAICs were used to inform comparisons against eribulin, and capecitabine. A comparison with vinorelbine is not reported, as clinical experts did not consider overall survival (OS) data to be clinically plausible from the only identified vinorelbine study (Sim 2019) [10] as compared with the reported PFS or expected OS in UK patients; the reported OS may be driven by subsequent therapies. Consequently, MAIC results between T-DXd and vinorelbine for PFS and ORR are not presented. It was not possible to make comparisons of TTD, as Kaplan-Meier (KM) data for TTD were not available for any comparator studies.

MAIC is a reweighting method that allows a propensity score logistic regression model to be estimated with individual patient data (IPD) in one of the treatment arms and only aggregate data for the other [12]. Prognostic factors and treatment effect modifiers, used as covariates in the matching process, were identified based on published evidence and discussions with a UK clinical expert. Matching factors included in the analyses were number of lines of prior therapy, hormone receptor status, visceral disease, age, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), HER2 status, and prior hormone therapy. It was not possible to match on prior trastuzumab as 100% of patients in DESTINY-Breast01 had received prior trastuzumab treatment. As far as possible, HER2+ subgroup data were extracted from the comparator studies; this could not be adjusted for in the analyses as all
patients in DESTINY-Breast01 were HER2+. For factors where matching was possible, baseline characteristics are reported in Table S1.

Estimation of T-DXd efficacy versus the model comparators was conducted using IPD from DESTINY-Breast01 and published, aggregate-level data from comparator studies. For the comparators, PFS over time was extracted from published KM curves, reconstructing pseudo IPD using the algorithm proposed by Guyot 2012 [13]. The ORR was extracted as number of patients with an event and total number of patients in the relevant treatment arm (where reported). If the number of patients with a response event was not available, this was calculated from the percentage of patients with an event and total number in the treatment arm.

MAICs were performed separately for each comparison, by study. IPD for T-DXd was weighted using a logistic regression model to match the mean baseline characteristics of patients in the comparator trial; each individual patient’s weight was equal to their estimated odds of being in the comparator trial of interest versus DESTINY-Breast01. Hazard ratios (HRs) were calculated for PFS and odds ratios (ORs) for ORR. The standard error for HR and OR MAIC estimates were calculated using a bootstrap or sandwich estimator, respectively [14].
Table S1: Summary of comparator studies used in the MAICs and comparison of baseline characteristics

| Study summary | T-DXd | Eribulin | Capecitabine |
|---------------|-------|----------|--------------|
| Study design  | DESTINY-Breast01 (unadjusted) [11, 15] | Cortes 2011 (EMBRACE) [3] | Barni 2019 [1] | Study EGF100151 [7-9] | Fumoleau 2004 [6] |
| Comparator    | –     | TPC      | –            | Lapatinib + capecitabine | – |
| HER2 status   | HER2+  | Mixed    | Mixed, with HER2+ subgroup data for OS and PFS | HER2+ | Mixed |
| Previous therapy | T-DM1 | Previous chemotherapies | – | Anthracycline, taxane, and trastuzumab containing regimens; must have contained trastuzumab alone or in combination | Anthracycline and taxane |
| N             | 184   | 508      | 95           | 201                      | 126 |
| Mean/median age (years) | 56.0  | 55       | 59.5         | 51                       | 54  |
| Age <55 years (%) | 47.8    | –       | –            | –                       | –  |
| ECOG-PS = 0 (%) | 55.4  | 42.7*   | 40.9*        | 58.2                     | 43.7* |
| Prior hormone therapy = yes (%) | 48.9  | 85.0     | –            | –                       | –  |
| Mean prior lines | 6.6   | –       | –            | –                       | –  |
| Prior lines ≥3 (%) | 91.8  | –       | –            | 81.6                    | –  |
| Treatment lines prior to T-DM1 <2 (%) | 18.5  | –       | –            | –                       | –  |
| Prior chemo lines ≥3 (%) | –     | 87.0    | 64.6         | –                       | 45.2 |
| Visceral disease = yes (%) | 91.8  | –       | 59.4         | 78.6                    | –  |

*Missing data counted as no/negative in calculation of %.

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; MAIC, matching-adjusted indirect comparison; N, sample size; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician’s choice.
Results of the matching-adjusted indirect comparisons

All MAICs demonstrated that weighted patients receiving T-DXd had significantly longer PFS, and significant improvements in ORR versus eribulin, and capecitabine (Table S2).

To assess whether the proportional hazards (PH) assumption holds between treatments within each trial, two approaches were adopted: 1) production of a log-cumulative hazard plot – under proportional hazards, the curves will be parallel across different treatment groups [16]; 2) tests of non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on time, equivalent to testing that the relative hazard of progression is not constant over time – rejection of the null hypothesis of a zero slope indicates a deviation from the PH assumption (significance, p<0.05).

Log-hazard plots and Schoenfeld residuals tests support the PH assumption for the Barni 2019 (T-DXd vs eribulin) and EGF100151 (T-DXd vs capecitabine) comparisons, however Schoenfeld residual tests for the remaining two study comparisons suggested significant violation (p<0.05). However, in the case where non-PH is detected, the HR obtained still represents an average of the HRs at all event times [17].
### Table S2: Results of the MAICs

| Comparator | Study          | N    | Method                        | HR for T-DXd vs comparator (95% CI) | OR for T-DXd vs comparator (95% CI) |
|------------|----------------|------|-------------------------------|-----------------------------------|-------------------------------------|
| Eribulin   | Cortes 2011    | 508.0| Naïve unadjusted              | 0.18 (0.14, 0.24)                | 11.45 (7.68, 17.08)               |
|            | [3]a           |      | Weighted bootstrapped CI (HRs)/ | 0.22 (0.16, 0.29)                | 9.62 (5.74, 16.13)               |
|            |                |      | sandwich estimator (ORs)       |                                   |                                     |
| Barni 2019 | [1]           | 95.0 | Naïve unadjusted              | 0.12 (0.08, 0.18)                | 6.64 (4.62, 9.55)                |
|            |                |      | Weighted bootstrapped CI (HRs)/ | 0.08 (0.05, 0.14)                | 8.00 (4.17, 15.33)               |
|            |                |      | sandwich estimator (ORs)       |                                   |                                     |
| Capecitabine| EGF100151     | 165.0| Naïve unadjusted              | 0.16 (0.12, 0.22)                | 9.83 (5.98, 16.17)               |
|            | [7-9]a         |      | Weighted bootstrapped CI (HRs)/ | 0.15 (0.11, 0.20)                | 12.14 (6.96, 21.17)              |
|            |                |      | sandwich estimator (ORs)       |                                   |                                     |
|            | Fumoleau 2004  | 126.0| Naïve unadjusted              | 0.30 (0.22, 0.40)                | 4.14 (2.53, 6.78)                |
|            | [6]           |      | Weighted bootstrapped CI (HRs)/ | 0.25 (0.14, 0.38)                | 8.95 (4.73, 16.94)               |
|            |                |      | sandwich estimator (ORs)       |                                   |                                     |

*aThese studies were selected for the model base case.

Abbreviations: CI, confidence interval; HR, hazard ratio; MAIC matching-adjusted indirect comparison; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival; T-DXd; trastuzumab deruxtecan.

### Discussion of matching-adjusted indirect comparison results

The MAICs demonstrated that in patients with u/mBC in a third- or later-line setting, T-DXd is associated with significant improvements in PFS and ORR versus eribulin, and capecitabine. In the primary analysis of the Phase 3 study DESTINY-Breast03, T-DXd has also demonstrated superior PFS with a strong trend towards improved OS versus standard-of-care (trastuzumab emtansine [T-DM1]) in a second-line setting (patients with u/mBC previously treated with trastuzumab and a taxane) [18].
Fig. S1: Survival curves for (a) PFS and (b) TTD for T-DXd, eribulin, and capecitabine.

Abbreviations: PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation.
Table S3: Model diagnostics

| Model          | AIC      | BIC      |
|----------------|----------|----------|
| **TH3RESA OS** |          |          |
| Exponential    | 939.05   | 943.05   |
| Weibull        | 921.90   | 929.90   |
| Log-normal     | 935.65   | 943.65   |
| Log-logistic   | 917.34   | 925.35   |
| Gompertz       | 932.01   | 940.01   |
| Generalized gamma | 922.01 | 934.01   |
| **T-DXd OS**   |          |          |
| Exponential    | 362.22   | 329.44   |
| Weibull        | 311.21   | 317.64   |
| Log-normal     | 313.60   | 320.03   |
| Log-logistic   | 312.27   | 318.70   |
| Gompertz       | 312.95   | 319.38   |
| Generalized gamma | 312.27 | 318.70   |
| **Eribulin OS**|          |          |
| Exponential    | 1088.95  | 1093.18  |
| Weibull        | 1022.60  | 1031.06  |
| Log-normal     | 1023.71  | 1032.17  |
| Log-logistic   | 1017.85  | 1026.31  |
| Gompertz       | 1049.83  | 1058.29  |
| Generalized gamma | 1019.14 | 1031.83  |
| **Capecitabine OS** | | |
| Exponential    | 482.13   | 485.24   |
| Weibull        | 478.73   | 484.94   |
| Log-normal     | 487.88   | 494.10   |
| Log-logistic   | 480.39   | 486.61   |
| Gompertz       | 483.40   | 489.61   |
| Generalized gamma | 480.39 | 486.61   |
| **T-DXd PFS**  |          |          |
| Exponential    | 349.21   | 352.43   |
| Weibull        | 347.39   | 353.82   |
| Log-normal     | 336.52   | 342.95   |
| Log-logistic   | 341.91   | 348.34   |
| Gompertz       | 351.15   | 357.58   |
| Generalized gamma | 341.91 | 348.34   |
### Table S4: Progression-free, on treatment utility values

| T-DXd TTD | Exponential \(^a\) | 505.98 | 509.19 |
|-----------|---------------------|--------|--------|
|           | Weibull             | 496.27 | 502.70 |
|           | Log-normal          | 488.28 | 494.71 |
|           | Log-logistic        | 490.32 | 496.75 |
|           | Gompertz            | 503.86 | 510.29 |
|           | Generalized gamma   | 490.32 | 496.75 |

\(^a\)Used in the base case.

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival, PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TTD, time-to-discontinuation.

| Eribulin (95% CI) | Capecitabine (95% CI) | T-DXd (95% CI) |
|-------------------|-----------------------|----------------|
| **Baseline** \(^a\) | **0.704** (0.69, 0.72) | **0.704** (0.69, 0.72) |
| **Incremental utility of response** \(^a\) | **0.076** (0.051, 0.101) | **0.076** (0.051, 0.101) |
| **Tumor response rate** | **MAIC results based on:** | **MAIC results based on:** |
| Cortes 2011 [3]: 14.2\(^b\) | Cortes 2008 [8]: 11.6% |
| (9.0%, 21.7%) | (6.9%, 18.6%) \(^b\) |
| Barni 2019 [1]: 16.6% | Fumoleau 2004 [6]: 15.1% |
| (9.4%, 27.6%) | (8.6%, 25.2%) |
| Cortes 2010 [2]: 9.8% | Blum 2001 [5]: 22.2% |
| (6.0%, 15.6%) | (11.3%, 39.0%) |
| Gamucci 2014 [4]: 24.8% | **DESTINY-Breast01 [15]:** |
| (7.8%, 56.2%) | 61.4% |
| **Progression-free, on treatment utility value** \(^b\) | **Cortes 2011 [3]: 0.715** | **Cameron 2008 [8]: 0.713** |
| Barni 2019 [1]: 0.717 | **Fumoleau 2004 [6]: 0.715** |
| Cortes 2010 [2]: 0.711 | **Blum 2001 [5]: 0.721** |
| Gamucci 2014 [4]: 0.723 | **0.751** |

\(^b\)Baseline utility value and incremental utility of response were taken from NICE TA423 [19]; \(^c\)Progression-free, on treatment utility = baseline + ORR * incremental utility of response; \(^d\)Base-case.

Abbreviations: CI, confidence interval; NICE, National Institute for Health and Care Excellence; MAIC, matching-adjusted indirect comparison; ORR, objective response rate; SoC, standard-of-care; T-DXd, trastuzumab deruxtecan.
Table S5: Adverse events, T-DXd (DESTINY-Breast01 June 2020 data-cut)

| Adverse event                          | Number of events | Proportion (n=184) |
|----------------------------------------|------------------|-------------------|
| Neutropenia                            | 46               | 25.00%            |
| Neutrophil count decreased             | 42               | 22.83%            |
| Anemia                                 | 30               | 16.30%            |
| Fatigue                                | 18               | 9.78%             |
| White blood cell count decreased       | 17               | 9.24%             |
| Anemia                                 | 30               | 16.30%            |
| Fatigue                                | 18               | 9.78%             |
| White blood cell count decreased       | 17               | 9.24%             |
| Neutropenia                            | 46               | 25.00%            |
| Neutrophil count decreased             | 42               | 22.83%            |
| Anemia                                 | 30               | 16.30%            |
| Fatigue                                | 18               | 9.78%             |
| White blood cell count decreased       | 17               | 9.24%             |
| Nausea                                 | 16               | 8.70%             |
| Electrocardiogram QT prolonged         | 4                | 2.17%             |
| Pneumonitis                            | 3                | 1.63%             |
| Dyspnea                                | 3                | 1.63%             |
| Febrile neutropenia                    | 3                | 1.63%             |
| Interstitial lung disease              | 2                | 1.09%             |
| Ejection fraction decreased            | 1                | 0.54%             |
| Vomiting                               | 0                | 0.00%             |

Abbreviations: T-DXd, trastuzumab deruxtecan.

Table S6: Adverse events, eribulin

| Adverse event                                      | Proportion of patients – Cortes 2011 [3] (EMBRACE), n=503 | Proportion of patients – Barni 2019 [1], n=574 | Proportion of patients – Cortes 2010 [2], n=291 | Weighted proportion |
|----------------------------------------------------|----------------------------------------------------------|-----------------------------------------------|-------------------------------------------------|---------------------|
| Neutropenia                                        | 14.51%                                                   | 0.33%                                        | 1.46%                                           | 5.78%               |
| Anemia                                             | 1.99%                                                    | 0.06%                                        | 0.15%                                           | 0.79%               |
| White blood cell count decreasedb                  | 4.17%                                                    | 0.00%                                        | 0.00%                                           | 1.53%               |
| Palmar-Plantar Erythro-Dysesthesia Syndrome        | 6.10%                                                    | 0.00%                                        | 0.00%                                           | 2.24%               |
| Nausea                                             | 1.19%                                                    | 0.07%                                        | 0.41%                                           | 0.55%               |
| Fatiguec                                           | 1.90%                                                    | 0.00%                                        | 0.00%                                           | 0.70%               |
| Dyspnea                                            | 3.38%                                                    | 0.00%                                        | 0.00%                                           | 1.24%               |
| Febrile neutropenia                                | 1.60%                                                    | 0.00%                                        | 0.00%                                           | 0.59%               |
| Electrocardiogram QT prolonged                     | 0.00%                                                    | 0.00%                                        | 0.00%                                           | 0.00%               |
| Interstitial lung disease                          | 0.00%                                                    | 0.00%                                        | 0.00%                                           | 0.00%               |
| Ejection fraction decreased                        | 0.00%                                                    | 0.00%                                        | 0.00%                                           | 0.00%               |
| Pneumonitis                                        | 0.00%                                                    | 0.00%                                        | 0.00%                                           | 0.00%               |
| Vomiting                                           | 0.00%                                                    | 0.00%                                        | 0.00%                                           | 0.00%               |
| Neutrophil count decreased                         | 0.00%                                                    | 0.00%                                        | 0.00%                                           | 0.00%               |

Adverse event frequencies were taken as a weighted average from all studies considered in the model that reported adverse events; bReported as ‘Leucopenia’/‘Leukopenia’; cFatigue and/or asthenia.
Table S7: Adverse events, capecitabine (Blum 2001 [5]*)

| Adverse event                                                   | Number of events | Proportion of patients (n=74) |
|----------------------------------------------------------------|------------------|-------------------------------|
| Palmar-Plantar Erythro-Dysesthesia Syndrome                     | 16               | 21.62%                        |
| Diarrhea                                                        | 14               | 18.92%                        |
| Stomatitis                                                      | 9                | 12.2%                         |
| Nausea                                                         | 7                | 9.5%                          |
| Fatigue                                                       | 6                | 8.1%                          |
| Dehydration                                                    | 5                | 6.8%                          |
| Neutropenia                                                    | 1                | 1.4%                          |
| White blood cell count decreased                                | 0                | 0.0%                          |
| Dyspnea                                                       | 0                | 0.0%                          |
| Febrile neutropenia                                            | 0                | 0.0%                          |
| Electrocardiogram QT prolonged                                 | 0                | 0.0%                          |
| Interstitial lung disease                                      | 0                | 0.0%                          |
| Ejection fraction decreased                                    | 0                | 0.0%                          |
| Pneumonitis                                                    | 0                | 0.0%                          |
| Vomiting                                                       | 0                | 0.00%                         |
| Neutrophil count decreased                                     | 0                | 0.0%                          |
| Anemia                                                         | 0                | 0.0%                          |

*Adverse event frequencies were taken from data reported in Blum 2001 [5] as data were not available from Fumoleau 2004 [6]; bFatigue and/or asthenia.

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