Current and future landscape of targeted therapy in HER2-positive advanced breast cancer: redrawing the lines

Christine Simmons, Daniel Rayson, Anil Abraham Joy, Jan-Willem Henning, Julie Lemieux, Heather McArthur, Paul B. Card, Rebecca Dent and Christine Brezden-Masley

Abstract

Background: Evidence to date supports continued human epidermal growth factor receptor 2 (HER2) suppression beyond progression on HER2-directed therapy for advanced HER2-positive breast cancer. Data from several phase II and III trials evaluating HER2-directed therapy following second-line T-DM1 have recently become available.

Methods: We performed a systematic search of the published and presented literature to identify phase II and phase III trials assessing novel HER2-targeted agents as third-line therapy or beyond for HER2-positive advanced breast cancer using search terms 'breast cancer' AND 'HER2' AND 'advanced' AND ['phase II' OR 'phase III'].

Results: Eight clinical trials reporting efficacy outcomes on third-line or greater HER2-directed therapy for HER2-positive advanced breast cancer were identified. In phase III trials, margetuximab and neratinib combinations demonstrated significant 1.3-month (hazard ratio, HR = 0.71, p < 0.001) and 0.1-month (HR = 0.76, p = 0.006) net improvements in median progression-free survival (PFS), respectively, with no significant improvements in overall survival (OS). Tucatinib added to trastuzumab and capecitabine demonstrated a significant 2.7-month improvement in median PFS (HR = 0.57, p < 0.00001) and a 5.5-month improvement in median OS (HR = 0.73, p = 0.004) in a randomized phase II trial, including significant clinical benefit for patients with brain metastases. Finally, trastuzumab-deruxtecan, zenocutuzumab, and poziotinib demonstrated benefit in phase II trials with the most robust overall response rate (62.0%) and median duration of response (18.2 months) observed for trastuzumab-deruxtecan among heavily pretreated patients.

Conclusion: Tucatinib plus trastuzumab and capecitabine significantly prolongs OS, and promising preliminary response outcomes for trastuzumab-deruxtecan suggest that sequencing of these regimens following second-line therapy is reasonable.

Keywords: advanced disease, breast cancer, HER2-positive, neratinib, pertuzumab, T-DM1, T-DXdx, trastuzumab, tucatinib

Introduction

Globally, breast cancer (BC) remains one of the leading causes of morbidity and mortality among women. Approximately 15% to 20% of invasive BCs are characterized by human epidermal growth factor receptor 2 (HER2) gene amplification and/or HER2 protein overexpression, translating to an estimated global incidence of 340,000 to 450,000 new cases annually. Although often detected at an early stage, approximately one-third of HER2-positive BC patients present with or develop regional or distant metastatic disease. HER2-directed therapies for advanced HER2-positive disease have evolved dramatically over the past two decades with the advent of monoclonal
antibodies (MoAbs),6–7 small molecule tyrosine kinase inhibitors (TKIs),8–11 and antibody drug conjugates (ADCs).12,13 Improved systemic control has led to an increased prevalence of brain metastases, possibly due to variable penetrance of MoAbs across the blood–brain barrier.14 Patients with hormone receptor negative, HER2-positive BC are nearly three times more likely to present with brain metastases,15 and approximately half of patients with metastatic HER2-positive BC are expected to develop brain metastases over the course of their illness.16–18

Currently, the recommended first-line treatment for most patients with advanced HER2-positive BC is trastuzumab plus pertuzumab and a taxane based on results from CLEOPATRA,19–21 with the ADC trastuzumab emtansine (T-DM1) consisting of the humanized MoAb trastuzumab covalently linked to the cytotoxic agent DM1, a standard second-line option based on the EMILIA trial.12 The novel ADC trastuzumab-durvalumab (T-DXd), consisting of trastuzumab and a cleavable linker to a potent topoisomerase I inhibitor payload, has also demonstrated substantial activity in the second-line setting.22 Although evidence supports continued HER2 suppression after progression on HER2-directed therapy,11,23,24 no standardized treatment strategies have been established following T-DM1.20,21,25 Historically, candidate third-line and beyond regimens have included lapatinib with capecitabine, trastuzumab with capecitabine, or other chemo-therapeutics with continued trastuzumab.10,11

More recently, data from several trials assessing novel MoAbs, TKIs, and ADCs in the third-line and beyond setting for HER2-positive advanced BC have become available. The next generation HER2-specific MoAb margetuximab is a fragment crystallizable (Fc) engineered monoclonal anti-HER2 antibody which binds with greater affinity than trastuzumab to FcγRIIIa (CD16A) expressed on immune effector cells, thereby increasing antibody-dependent cellular cytotoxicity, with demonstrated activity in a phase III trial.26–29 Dual targeted bi-specific HER2 antibodies are also in development, including those targeting multiple HER2 epitopes, anti-HER2/CD3, and anti-HER2/human epidermal growth factor receptor 3 (HER3) MoAbs.29 While many of these are still in early phase studies, the anti-HER2/HER3 MoAb xenozotuzumab (MCLA-128) in addition to the ADC T-Dxd have demonstrated efficacy in phase II studies among heavily pretreated patients.25,30 Three novel HER2-targeted TKIs have also shown clinical benefit in heavily pretreated patients, including the irreversible pan-HER inhibitor neratinib in a phase III trial,31 the highly selective HER2-specific reversible inhibitor tucatinib in a randomized phase II study,32 and the potent epidermal growth factor receptor and HER2 exon 20 insertion inhibitor poziotinib in a phase II study.33 Biosimilars are also being developed that mimic existing biologic drugs to provide similarly active and potentially more cost-effective HER2-directed MoAb therapeutic options.34 This review will summarize the efficacy and safety outcomes of phase II and III trials evaluating novel third-line and beyond HER2-directed therapies for advanced HER2-positive BC and suggest guidance on treatment selection and sequencing.

Methods
A systematic search of published and presented literature was performed to identify phase II or III trials assessing novel third-line or beyond HER2-targeted therapy for HER2-positive advanced BC. PubMed (all time to February 10, 2021) and proceedings from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the San Antonio Breast Cancer Symposium (SABCS) 2019 and 2020 annual meetings were searched for phase II or III trials using the search terms ‘breast cancer’ AND ‘HER2’ AND ‘advanced’ AND (‘phase II’ OR ‘phase III’) OR respective aliases or using the respective filters when appropriate [Figure 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Supplemental File S1]. A supplemental bibliographic search of review articles and pooled/meta-analyses was also conducted, in addition to directed searches after the database search cutoff date to ensure that the most up-to-date reports of eligible studies were considered.

English language records were vetted at abstract level and confirmed at full text as needed. Non-original research, preclinical, correlative science, modeling or simulation, those in earlier stages of disease or without BC patients, case reports, retrospective, prospective studies of undefined design, phase I trials, and those that did not assess or report outcomes for HER2-directed therapies in HER2-positive BC were excluded (PRISMA, Figure 1). Trials with less than two prior lines of
HER2-directed treatment, those restricted to low HER2 expression levels, those with exclusively hormone receptor-positive populations, or those with fewer than 30 patients per cohort were also excluded. Phase II trials were only eligible if the majority of the patients were pretreated with two or more HER2-directed agents.

Findings beyond second-line HER2-directed therapy

The literature search identified a total of 1348 records. Selection criteria revealed eight phase II or III trials reporting efficacy outcomes on third-line or greater HER2-directed therapy for HER2-positive advanced BC, which excluded the phase I/II trial of ruxolitinib plus trastuzumab trial due to size (n = 26, PRISMA; Figure 1).

T-DM1

The phase III TH3RESA study randomized 602 patients treated with at least two prior lines of HER2-directed therapy consisting of trastuzumab and lapatinib [median 4 prior systemic therapies in experimental arm (range = 1–19) and no prior pertuzumab or T-DM1] 2:1 to receive either T-DM1 or treatment of physician’s choice (TPC; Figure 2). The co-primary endpoints were investigator-assessed, progression-free survival (PFS) and overall survival (OS). At a median follow-up of 7.2 months in the T-DM1 arm and 6.5 months in the TPC arm, significant improvements for T-DM1 versus TPC were observed in the co-primary endpoints of PFS – median 6.2 versus 3.3 months, hazard ratio (HR) = 0.53, 95% confidence interval (CI) = [0.42–0.66], p < 0.0001 – and OS – median 22.7 versus 15.8 months, HR = 0.68, 95% CI = [0.54–0.85], p = 0.0007 (Table 1). Among patients with measurable disease at baseline (n = 508), objective response rates (ORRs) were 31.3% versus 8.6% favoring T-DM1, with a median duration of response (DoR) of 9.7 months versus not yet reached (NYR). Adverse events (AEs) led to treatment withdrawal in 14.6% of patients receiving T-DM1 and 10.9% of TPC patients (Table 2). Grade ≥ 3 AEs of any cause occurred in 40.0% of patients receiving T-DM1 versus 47.3% on TPC, with thrombocytopenia (6.0%), anemia (3.5%), and both dyspnea and aspartate aminotransferase elevation (2.5% each) most commonly reported with T-DM1. Treatment-related deaths were reported in 2.2% and 1.6% of patients in the T-DM1 and TPC groups, respectively.

Margetuximab

The phase III SOPHIA trial randomized 536 patients with disease progression after at least two prior lines of HER2-directed therapy (34% with ≥3 lines) including pertuzumab (all patients except 1) and T-DM1 (91.2%) to receive margetuximab plus TPC or trastuzumab plus TPC (Figure 2). Preliminary findings at a median follow-up of 2.8 months showed a significant improvement in the co-primary endpoint of centrally assessed PFS for margetuximab plus TPC (median 5.8 versus 4.9 months, HR = 0.76, 95% CI = 0.59–0.98, p = 0.03) which did not translate into improved OS at the second planned interim analysis (median 21.6 versus 19.8 months, HR = 0.89, 95% CI = 0.69–1.13, p = 0.33) (Table 1), despite a lack of cross-over and longer follow-up (median 15.6 months). Investigator assessed ORRs were significantly greater for margetuximab versus trastuzumab (25.2% versus 13.7%, p = 0.0006), although median DoRs were comparable (6.9 versus 7.0 months, p = 0.74). Although data suggested that presence of a CD16A-158F allele predicted margetuximab benefit over trastuzumab, patients homozygous for the CD16A-158VV allele saw no benefit. AEs leading to treatment withdrawal (3.0% versus 2.6%) and grade ≥ 3 AEs of any cause (53.8% versus 52.6%) were similar (Table 2), with the most commonly reported grade ≥ 3 AEs for margetuximab versus trastuzumab being neutropenia (19.7% versus 12.4%), neutrophil count decrease (8.7% versus 10.5%), anemia (4.9% versus 6.4%), and fatigue (4.9% versus 3.0%). Any grade infusion-related reactions were more common in the margetuximab arm (13.3% versus 3.4%). No treatment-related deaths were reported.

Neratinib

The open label phase III NALA study randomized 621 patients previously treated with at least two prior lines of HER2-directed therapy (31% with ≥3 prior lines, 42% and 54% had received prior pertuzumab and T-DM1, respectively) to neratinib or lapatinib, both administered with capecitabine (Figure 2). The co-primary endpoints were centrally assessed PFS and OS. At a median follow-up of 29.9 months, PFS was significantly improved for patients receiving neratinib (median 5.6 versus 5.5 months, HR = 0.76, 95% CI = 0.63–0.93, p = 0.006) although no significant differences in OS were observed (median 21.0 versus 18.7 months, HR = 0.88, 95% CI = 0.72–1.07,
Median DoR was 8.5 versus 5.6 months, significantly favoring neratinib (HR = 0.50, 95% CI = 0.33–0.74, p = 0.004) and ORR was 32.8% versus 26.7% (p = 0.12). Treatment-emergent AEs (TEAEs) led to treatment withdrawal in 13.9% of patients receiving neratinib versus 18.0% in the lapatinib arm (Table 2). Grade ≥ 3 AEs of any cause occurred in 60.7% versus 60.5% of patients overall, with the most common grade 3/4 TEAEs in the neratinib versus lapatinib arms being diarrhea (24.4% versus 12.5%), palmar-plantar erythrodysesthesia (PPE, 9.6% versus 11.3%), hypokalemia (4.6% versus 6.4%), and nausea (4.3% versus 2.9%). Deaths due to TEAEs were reported in 2.6% and 3.2%
of patients in the neratinib and lapatinib combination arms, respectively.

**Pertuzumab retreatment**

The phase III PRECIOUS trial randomized 217 patients previously treated with pertuzumab plus trastuzumab (99%) and T-DM1 (98%) 1:1 to receive retreatment with pertuzumab plus trastuzumab and TPC or trastuzumab plus TPC. With a median follow-up of 14.2 months, the primary endpoint of investigator-assessed PFS was significantly improved for the addition of pertuzumab to trastuzumab plus chemotherapy (median 5.3 versus 4.2 months, HR = 0.76, 95% CI = not reported, NR–0.97, p = 0.022). Median OS was 28.8 versus 23.4 months with the addition of pertuzumab versus the doublet (HR = 0.71, 95% CI = NR–1.03, p = 0.062) and ORRs were 18.9% versus 19.6%, respectively. AEs leading to treatment discontinuation were NR, with grade ≥ 3 AEs of any cause occurring in 61.9% versus 69.4% of patients (pertuzumab plus trastuzumab and TPC or trastuzumab plus TPC), and the most common in the pertuzumab arm were febrile neutropenia (15.2% versus 16.7%), anemia (13.3% versus 6.5%), infection (5.7% versus 1.9%), and diarrhea (2.9% versus 0.9%). Deaths due to AEs were reported in one patient receiving pertuzumab (1.0%) with none in the control arm.

**Tucatinib**

The phase II HER2CLIMB study involved 612 patients previously treated with both pertuzumab (99.7%) and T-DM1 (100%), including patients with brain metastases (47.5%). Patients were randomized in a 2:1 ratio to receive tucatinib (n = 410) or placebo (n = 202), in combination with trastuzumab and capecitabine (Figure 2). With a median follow-up of 14.0 months in the total population, the primary endpoint analysis conducted for the first 480 randomized patients observed a significant improvement in centrally assessed PFS favoring tucatinib over placebo (median PFS 7.8 versus 5.6 months, HR = 0.54, 95% CI = 0.42–0.71, p < 0.001) as well as a doubling of ORR (40.6% versus 22.8%, p < 0.001). At a longer follow-up of 29.6 months, tucatinib also demonstrated a statistically significant improvement in investigator-assessed PFS (median 7.6 versus 4.9 months, HR = 0.57, 95%
Table 1. Clinical trials assessing efficacy of later lines of therapy of HER2-directed therapy in HER2-positive breast cancer.

| Trial name (NCT number) | Study type | Line of therapy | Prior HER2-directed therapy | Regimen(s) | n   | Median follow-up (months) [range] | Overall response rate, % [95% CI] | Median DoR, months [95% CI] [range] | Median progression-free survival, months HR (95% CI) | Median overall survival, months HR (95% CI) |
|------------------------|------------|------------------|-----------------------------|------------|-----|-----------------------------------|-------------------------------------|-------------------------------------|---------------------------------------------|---------------------------------------------|
| TH3RESA²⁵,²⁶ (NCT01419197) | Phase III | ≤4th line (35%) >4th line (65%) | Prior Trastuzumab (100%) Prior lapatinib (100%) | Trastuzumab emtansine 3.6mg/kg q3w | 404 | 7.2³ [5.0–10.1] | 31.3 [16.2–29.2] | 9.7 [6.6–10.5] | 6.2 [0.42–0.66] | 22.7²³ [0.54–0.85] | 0.0007 |
| SOPHIA²⁶ (NCT02492711) | Phase III | ≤3rd line (65%) >3rd line (34%) | Prior Trastuzumab (100%) Prior Pertuzumab (100%) Prior T-DM1 (91%) Prior Lapatinib (15%) | Margetuximab 15 mg/kg q3w plus chemotherapy q3w | 266 | 15.6 | 25.2 [20.1–30.9] | 6.9 [5.45–7.49] | 5.7² [0.58–0.86] | 21.6 [0.69–1.13] | 0.33 |
| NALA²¹ (NCT01808573) | Phase III | ≤3rd line (69%) >3rd line (31%) | Prior trastuzumab (100%) Prior pertuzumab (42%) Prior T-DM1 (64%) | Neratinib 240mg, QD, q3w plus capecitabine 1500 mg/m² BID D1-14, q3w | 307 | 29.9 [21.9–40.6] | 32.8 [27.1–38.9] | 8.5 [0.33–0.74] | 5.6 [0.63–0.93] | 21.0 [0.72–1.07] | 0.21³ |
| PRECIOUS²⁷ (NCT02514681) | Phase III | Medium 3rd-line therapy Pertuzumab (99%) Trastuzumab (99%) T-DM1 (98%) Lapatinib (14%) Others (8%) | | Pertuzumab 840 mg loading then 420 mg IV q3w + Trastuzumab 8 mg/kg loading then 6 mg/kg q3w + Physician’s choice chemotherapy³ | 108 | 14.2 | 18.9 | NR | 5.3 [0.76 | NR | 0.022 | 28.8 [0.71 | NR | 0.062 | 0.062 |

(Continued)
### Table 1. (Continued)

| Trial name (NCT number) | Study type | Line of therapy | Prior HER2-directed therapy | Regimen(s) | n | Median follow-up (months) [range] | Overall response rate, % (95% CI) | Median DoR, months (95% CI) [range] | Median progression-free survival, months HR (95% CI) | Median overall survival, months HR (95% CI) |
|-------------------------|------------|-----------------|-----------------------------|------------|---|----------------------------------|-----------------------------------|--------------------------------|-------------------------------------------|------------------------------------------|
| HER2CLIMB (NCT02614794) | Randomized phase II | Median 4th-line therapy | Trastuzumab (100%) T-DM1 (100%) Pertuzumab (100%) Lapatinib (7%) | Tucatinib 300 mg BID plus trastuzumab 6 mg/kg q3w + capecitabine 100 mg/m² BID D1-14, q3w | 410 | 29.6 | 40.6 | NR | 7.6 | 24.7 |
|                        |            |                  |                             | Placebo BID plus trastuzumab 6 mg/kg q3w + capecitabine 100 mg/m² BID D1-14, q3w | 202 | 22.8 | NR | 4.9 | 19.2 |
| DESTINY-Breast01 (NCT03248492) | Phase II | Median 6th-line therapy | Trastuzumab (100%) T-DM1 (100%) Pertuzumab (66%) Other anti-HER2 therapy (54%) | Trastuzumab-deruxtecan 5.4 mg/kg q3w | 184 | 26.5 | 62.0 | 18.2 | 19.4 | 29.1 |
| MCLA-128-CL02 (NCT03321981) | Phase II [cohort 1] | Median 6th-line HER2-directed therapy | Trastuzumab (100%) T-DM1 (100%) | Zenocutuzumab 750 mg plus trastuzumab 8 mg/kg loading then 6 mg/kg and vinorelbine 25 mg/m², D1,8, q3w | 37 | NR | 18.9 | NR | NR | NR |
| SPI-POZ-201 (NCT02659514) | Phase II | Median 5th- to 8th-line therapy | Trastuzumab (100%) T-DM1 (97%) Lapatinib (37%) Pertuzumab (76%) Neratinib (3%) | Cohort 1: Poziotinib 24 mg QD D1–14 q3w | 33 | NR | 23.3 | 5.6 [range: 3.0–9.6] | 3.0 [range: 0.9–10.8] | NR |
|                        |            |                  |                             | Cohort 2: Poziotinib 16 mg QD q3w | 34 | 22.2 | 13.8 [range: 4.4–18.7] | 4.9 | 4.9 | 19.8 |

BID, twice daily; CI, confidence interval; CT, chemotherapy; DoR, duration of response; Dx, day X; HER2, human epidermal growth factor 2; HER2i, HER2-inhibitor; HT, hormone therapy; IV, intravenous, mg/kg, milligrams/kilogram, n, number of patients; NE, not estimable; NR, not reported; NYR, not yet reached; QD, daily; q3w, every 3 weeks; T-DM1, trastuzumab emtansine.

Efficacy outcomes of phase II and III trials of later lines of HER2-directed therapy in advanced BC ordered by study type, then chronologically by release of primary analyses. Primary endpoints are in bold text.

aFinal OS analysis at a median follow-up of 30.5 months.

bPrimary endpoint was centrally assessed PFS at 2.8 months = HR = 0.76, 95% CI = 0.59–0.98, p = 0.03.

cRestricted analysis at 24 months.

dRestricted analysis at 48 months.

eChemotherapy was chosen from docetaxel, paclitaxel, nab-paclitaxel, vinorelbine, eribulin, capecitabine, or gemcitabine.

fAt an earlier median follow-up of 14.0 months.

gPrimary endpoint investigator-assessed clinical benefit rate at 24 weeks.
Table 2. Safety outcomes from clinical trials assessing later lines of HER2-directed therapy in HER2-positive BC.

| Trial phase | TH3RESA35,36 Phase III | SOPHIA26 Phase III | NALA31 Phase III | PRECIOUS37 Phase III | HER2CLIMB32 Rd Phase II | MCLA-128-CLB20 Phase II | DESTINY-Breast01 Phase II | SPI-POZ-2013 Phase II |
|-------------|------------------------|-------------------|-----------------|---------------------|------------------------|-------------------------|---------------------------|-----------------------|
| Treatment arms | T-DM1 | Physician’s choice (HER2i + CT) | Margetuximab + CT | Trastuzumab + CT | Neratinib + Capecitabine | Trastuzumab + Physician’s choice CT | Tucatinib + Capecitabine + Trastuzumab | Placebo + Capecitabine + Trastuzumab | Zenocutuzumab + Trastuzumab + Vinorelbine |
| Safety population (n) | 403 | 184 | 266 | 266 | 303 | 311 | 105 | 108 | 404 | 197 | 28 | 184 | 33 | 34 |
| Overall | | | | | | | | | | | | | | |
| Any grade AE | 377 (93.3) | 163 (88.6) | 260 (98.5) | 261 (98.1) | 302 (99.7) | 309 (99.4) | 91 (86.7) | 95 (88.0) | 401 (99.3) | 191 (97.0) | NR | 183 (99.5) | 33 (100.0) | 33 (97.1) |
| Grade ≥ 3 AEs | 161 (40.0) | 87 (47.3) | 142 (53.8) | 140 (52.6) | 184 (60.7) | 188 (60.5) | 65 (61.9) | 75 (69.4) | 223 (55.2) | 96 (48.7) | 15 (53.6) | 105 (57.1) | 22 (66.7) | 25 (73.5) |
| AEs leading to discontinuation of any treatment n (%) | 59 (14.6) | 20 (10.9) | 8 (3.0) | 7 (2.6) | 42 (13.9) | 56 (18.0) | NR | NR | 23 (5.7) | 6 (3.0) | NR | 28 (15.2) | 6 (18.2) | 10 (29.4) |
| AE or treatment-associated deaths n (%) | 9 (2.2) | 3 (1.6) | 3 (1.1) | 2 (0.8) | 8 (2.6) | 10 (3.2) | 1 (1.0) | 0 (0.0) | NR | NR | 1 (3.6) | 9 (4.9) | 3 (9.1) | 1 (2.9) |

Select grade ≥ 3 AEs

| Most common grade 3/4 AEs (%) | Neutropenia (15.8) | Diarrhea (4.4) | Febrile neutropenia (3.8) | Anemia (3.3) | Abdominal pain (2.7) | Neutropenia (19.7) | Decreased neutrophil count (8.7) | Anemia (4.9) | Fatigue (4.9) | Neutropenia (12.4) | Decreased neutrophil count (10.5) | Anemia (6.4) | Diarrhea (4.9) | Neutropenia (22.4) | PPE Syndrome (9.6) |
|------------------------------|-------------------|-----------------|---------------------|---------------|-----------------------|-------------------|--------------------------|-------------|----------------------|---------------------|-----------------------------|-------------|-------------------|------------------|------------------|
| (6.0) | (3.5) | (2.5) | (2.2) | (15.8) | (4.4) | (3.8) | (3.3) | (2.7) | (19.7) | (8.7) | (4.9) | (12.4) | (10.5) | (6.4) | (3.5) | (22.4) | (9.6) |

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate transaminase; BC, breast cancer; CT, chemotherapy; HER2i, human epidermal growth factor receptor 2 inhibitor; n, number of patients; NR, not reported; PPE, palmar-plantar erythrodysesthesia; T-DM1, trastuzumab emtansine.

Safety outcomes of phase II and III trials of later lines of HER2-directed therapy ordered chronologically by release of primary analyses. Treatment-related AEs were summarized when available.

aFrom the earlier progression-free survival analysis.

bConsidered related to vinorelbine.

cMost common AEs among reported ‘AEs of special interest’.
CI = 0.47–0.70, \( p < 0.00001 \); Table 1) and OS (median 24.7 versus 19.2 months, HR = 0.73, 95% CI = 0.59–0.90, \( p = 0.004 \)) compared with placebo.\textsuperscript{38} AEs led to discontinuation of tucatinib versus placebo in 5.7% and 3.0% of patients, respectively (Table 2). Grade \( \geq 3 \) AEs of any cause occurred in 55.2% versus 48.7% (tucatinib versus placebo) with the most common grade \( \geq 3 \) AEs in the tucatinib arm being PPE (13.1% versus 9.1%), diarrhea (12.9% versus 8.6%), alanine transaminase increase (5.4% versus 0.5%), and fatigue (4.7% versus 4.1%).\textsuperscript{32} Deaths due to AEs were reported in 1.5% and 2.5% of patients in the tucatinib and placebo arms, respectively.

\textbf{T-DXd}

The single-arm phase II DESTINY-Breast01 trial assessed T-DXd in 184 heavily pretreated patients (100% prior T-DM1 and 66% prior pertuzumab; Figure 2).\textsuperscript{25} The primary endpoint was ORR by independent central review. Updated results at a median follow-up of 26.5 months observed an ORR of 62.0% (95% CI = 54.5–69.0%) with a median DoR of 18.2 months (95% CI = 15.0–not estimable, NE) (Table 1).\textsuperscript{39} Median PFS was 19.4 months (95% CI = 14.1–25.0) and at a median follow-up of 31.1 months, and median OS was 29.1 months (95% CI = 24.6–36.1). TEAEs led to T-DXd discontinuation in 15.2% of patients with grade \( \geq 3 \) TEAEs occurring in 57.1% (Table 2).\textsuperscript{25} The most common grade 3/4 TEAEs were decreased neutrophil count (23.7%), anemia (11.1%), and decreased white blood cell (8.7%) and platelet (6.3%) counts. Deaths due to TEAEs were reported in nine patients (4.9%). Overall, 15.2% of patients developed T-DXd-related interstitial lung disease (ILD), with one grade 3 event (0.5%) and five ILD-related deaths (2.7%).\textsuperscript{40}

\section*{Zenocutuzumab and poziotinib}

Zenocutuzumab and poziotinib were assessed in two phase II trials (MCLA-128-CL02 and SPI-POZ-201), both enrolling heavily pretreated patients (100% prior T-DM1 and pertuzumab in MCLA-128-CL02 and 76% and 97%, respectively, in SPI-POZ-201).\textsuperscript{30,33} The single-arm MCLA-128-CL02 study evaluated zenocutuzumab plus trastuzumab and vinorelbin in 37 evaluable patients, observing an ORR of 18.9% (secondary endpoint)\textsuperscript{30} and SPI-POZ-201 observed an ORR of 22.2% to 23.3% (primary endpoint) among 57 evaluable patients at the two different doses of poziotinib (Table 1).\textsuperscript{33} DoRs were not reported in MCLA-128-CL02 and were 5.6 to 13.8 months in SPI-POZ-201. Median PFS was not reported in MCLA-128-CL02 and were similar in both SPI-POZ-201 cohorts (3.0–4.9 months).\textsuperscript{30,33} Discontinuation due to vinorelbin-related AEs occurred in 7.1% of patients receiving the zenocutuzumab combination, which was more common for those receiving poziotinib (18.2%–29.4%; Table 2).

\section*{Discussion}

Two lines of HER2-directed therapy are currently approved in many jurisdictions for HER2-positive advanced BC. Data on novel HER2-directed agents in the third-line and beyond setting highlight the importance of continuing HER2-targeting beyond second-line treatment. Although additional research is needed to determine optimal sequencing of these agents, a proposed approach informed by current data is outlined.

\section*{What is the clinical impact of HER2-directed therapy for third-line line treatment and beyond in HER2-positive advanced BC?}

The phase III EMILIA study led to the US Food and Drug Administration (FDA) approval of T-DM1 as second-line therapy following trastuzumab and a taxane in February 2013 (Table 3).\textsuperscript{12,41} Continued HER2 targeting beyond second-line therapy is standard of care for HER2-positive advanced BC, with multiple lines of HER2-directed agents common.\textsuperscript{20,21,42} Available data, however, suggest that outcomes vary between HER2-targeted strategies and optimal options are beginning to evolve for third-line treatment and beyond.

Studies addressing HER2-directed therapy in the third-line setting and beyond include TH3RESA, which reported a 32% reduced risk of death\textsuperscript{10} and 47% reduced risk of progression\textsuperscript{15} for T-DM1 among patients with prior trastuzumab, lapatinib, and taxane exposure (Table 1). A second trial, PRECIOUS, observed limited clinical benefit from doublet re-challenge using pertuzumab added to trastuzumab and chemotherapy for patients with prior pertuzumab and trastuzumab exposure (Table 1).\textsuperscript{37} The open label SOPHIA and NALA trials assessed the benefit of replacing established agents with novel HER2-directed therapies, both combined with chemotherapy.\textsuperscript{26,31}
trastuzumab in SOPHIA and the pan-HER TKI neratinib replaced lapatinib in NALA. These trials enrolled more than 500 and 600 patients, respectively, and included similar proportions of patients with baseline central nervous system (CNS) metastases (13%–16%) and with Eastern Cooperative Oncology Group Performance Status 1 (42%–46%) (Figure 2), although patients in SOPHIA were more heavily pretreated.26 Both agents demonstrated statistically significant PFS improvements versus established comparators, with discontinuation rates due to toxicities of 3.0% for margetuximab and 13.9% for neratinib.26,31 Substitution of margetuximab for trastuzumab resulted in a 1.3-month improvement in median PFS (29% reduced risk of progression, \( p < 0.001 \)) with a 0.1-month median PFS improvement observed for neratinib when substituted for lapatinib (24% reduced risk of progression, \( p = 0.006 \)) (Table 1).26 Neratinib significantly reduced the cumulative incidence of CNS interventions compared with lapatinib (\( n = 621, 22.8\% \) versus 29.2%, \( p = 0.043 \)),31 consistent with prior neratinib trial data.43,44 Neither agent resulted in a statistically significant OS benefit (HR = 0.89, \( p = 0.33 \) and HR = 0.88, \( p = 0.21 \)) at median follow-ups of 15.6 and 29.9 months, respectively,26,31 remaining non-significant for margetuximab at the final OS analysis (HR = 0.95, \( p = 0.62 \)).43 The phase III landscape is rapidly changing with data on new agents continually emerging, including recently presented results.

### Table 3. Regulatory status of later lines and beyond HER2-directed therapy for HER2-positive advanced breast cancer.

| Regulatory agency (search date) | Indication | Level of data (primary outcome) | Type of approval | Date of approval |
|-------------------------------|------------|--------------------------------|-----------------|-----------------|
| Trastuzumab-emtansine monotherapy | FDA – HER2-positive metastatic breast cancer following trastuzumab and a taxane used separately or in combination | Phase III (PFS and OS) | Approved | February 2013 |
| | EMA – HER2-positive advanced breast cancer following trastuzumab and a taxane used separately or in combination | Phase III (PFS and OS) | Approved | September 2013 |
| Margetuximab plus chemotherapy | FDA – HER2-positive metastatic breast cancer following two or more prior HER2-directed therapies, with at least one for metastatic disease | Phase III (PFS and OS) | Approved | December 2020 |
| | EMA – Not approved |
| Neratinib plus capecitabine | FDA – HER2-positive advanced breast cancer following two or more prior anti-HER2 regimens for metastatic disease | Phase III (PFS and OS) | Approved | February 2020 |
| | EMA – Not approved |
| Tucatinib plus trastuzumab and capecitabine | FDA – HER2-positive advanced breast cancer following one or more prior anti-HER2 regimens for metastatic disease | Rd Phase II (PFS) | Approved | April 2020 |
| | EMA – In combination with trastuzumab and capecitabine for HER2-positive advanced breast cancer following at least two prior anti-HER2 regimens | Phase III (PFS) | Approved | December 2020 |
| Trastuzumab-deruxtecan monotherapy | FDA – HER2-positive advanced breast cancer following two or more anti-HER2-based regimens in metastatic setting | Phase II (ORR) | Accelerated approval | December 2019 |
| | EMA – HER2-positive advanced breast cancer following two or more prior anti-HER2 regimens | Phase II (ORR) | Approved with conditions | December 2020 |

EMA, European Medicines Agency; FDA, US Food and Drug Administration; HER2, human epidermal growth factor 2; NA, not approved; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Rd, randomized. Regulatory data were collected through review of FDA and EMA news bulletins and product monographs.
from the TULIP trial which demonstrated a PFS benefit for the novel ADC SYD985 compared with physician’s choice of therapy in heavily pretreated patients (87.6% prior T-DM1, HR = 0.64, 95% CI = 0.49–0.84, p = 0.002).46

Four phase II trials assessed novel HER2-directed therapies beyond second line,25,30,32,33 with notable benefits seen for tucatinib and T-DXd (Table 1).38,39 The randomized phase II placebo-controlled HER2CLIMB study evaluating tucatinib added to trastuzumab and capecitabine showed a statistically significant 46% reduced risk of progression in the primary endpoint population (n = 480, p < 0.001)12 and a 27% reduction in risk of death in the overall trial population with longer follow-up (n = 612, p = 0.004).38 Tucatinib and its metabolites have been shown to effectively distribute to the cerebrospinal fluid47 and resulted in a 68% reduced risk of intracranial progression or death (p < 0.0001), a 42% reduced risk of death (p = 0.005), and a 47.3% confirmed intracranial ORR in patients with measurable active brain metastases at baseline (n = 55).48 The phase II DESTINY-Breast01 study (n = 184) reported a high ORR (62.0%), an estimated 85% 1-year OS rate, and an 18.2-month median DoR for T-DXd (Table 2).32 Any grade diarrhea and PPE occurred as common AEs in both arms of HER2CLIMB, with diarrhea and PPE being the most frequent for tucatinib compared with neratinib across the relevant trials (12.9% versus control arm for both toxicities (Table 2). Importantly, the chemotherapy backbone in both arms was capecitabine which may also have contributed to the higher rates of these two clinically relevant toxicities. Grade ≥ 3 diarrhea was less frequent for tucatinib compared with neratinib across the relevant trials (12.9% versus 24.4%) even with more active mandatory primary prophylaxis for neratinib in NALA, with both agents requiring proactive patient education and early intervention to optimize quality of life (QoL).31,32 T-DXd was associated with substantial hair loss in DESTINY-Breast01,25 with nearly half of patients experiencing alopecia of any grade. ILD was a rare but potentially life-threatening treatment complication of T-DXd, which was associated with any grade ILD in 13.6% of patients including four with grade 5 events (2.2%). Subsequent analyses on ILD time course have observed a
### Table 4. Ongoing phase III clinical trials of HER2-directed therapy in advanced HER2-positive breast cancer.

| Experimental agent(s) | Trial ID (NCT#) | Key eligibility criteria | Experimental regimen | Comparator | Primary end point(s) | Estimated PCD |
|-----------------------|-----------------|--------------------------|----------------------|------------|----------------------|---------------|
| Early breast cancer   |                 |                          |                      |            |                      |               |
| Neoadjuvant           |                 |                          |                      |            |                      |               |
| QL1209                | QL1209-301      | Early or locally advanced ER/PR negative disease | QL1209 + trastuzumab + docetaxel | Trastuzumab + pertuzumab + docetaxel | tpCR | October 2022 |
| Pyrotinib             | HRHB-CB001      | Early breast cancer      | Pyrotinib + epirubicin + cyclophosphamide → taxanes + trastuzumab | Epirubicin + cyclophosphamide → taxanes + trastuzumab | pCR | March 2022 |
| HS627/Pertuzumab      | HS627-III       | Early or locally advanced disease | HS627 + trastuzumab + docetaxel | Trastuzumab + pertuzumab + docetaxel | pCR | November 2021 |
| SIBP-01               | SIBP-01-3       | Early or locally advanced disease | SIBP-01 + docetaxel + carboplatin | Herceptin + docetaxel + carboplatin | tpCR | May 2021 |
| TX05                  | TX05-03         | Early breast cancer      | TX05                 | Herceptin  | pCR | November 2020 |
| EG12014               | EGC002          | Early or locally advanced disease | EG12014              | Herceptin  | pCR | November 2020 |
| Apatinib              | HebeiMUFH       | Stage IIb-IIIc breast cancer | Apatinib + paclitaxel + cisplatin | Paclitaxel + cisplatin | pCR | May 2020 |
| Residual disease post-NAC/adjuvant | | | | | | |
| Tucatinib, T-DM1      | CompassHER2 RD  | High-risk residual disease after HER2-directed NAT | T-DM1 + tucatinib    | T-DM1 + placebo | iDFS | January 2028 |
| T-DXd                 | DESTINY-Breast05 | High-risk residual invasive disease after NAT | T-DXd                | T-DM1      | iDFS | December 2025 |
| Pyrotinib             | ATP             | Residual invasive disease after NAT | Pyrotinib            | Observation | iDFS | August 2023 |
| Pertuzumab            | BOLD-1          | Moderate/high risk early breast cancer | Pertuzumab + trastuzumab + docetaxel | Trastuzumab + docetaxel | iDFS | December 2022 |

(Continued)
### Table 4. (Continued)

| Experimental agent(s) | Trial ID (NCT#) | Key eligibility criteria | Experimental regimen | Comparator | Primary end point(s) | Estimated PCD |
|-----------------------|-----------------|-------------------------|----------------------|------------|----------------------|--------------|
| Trastuzumab           | TMH Project-982 [NCT01785420] | Resectable early breast cancer | Trastuzumab | Placebo | DFS | April 2025 |
|                       | TX05 [NCT04109391] | Early disease following NAT and SR in protocol TX05-03 | TX05 | Herceptin | RAE, IA, DFS, OS | January 2022 |
| Pyrotinib             | HR-BLTN-III-EBC [NCT03980054] | Early breast cancer | Pyrotinib | Placebo | iDFS | July 2022 |
| Advanced breast cancer | HER2-naive | T-DXd DESTINY-Breast09 [NCT04784715] | Metastatic disease | T-DXd + pertuzumab or placebo | SOC taxane + trastuzumab + pertuzumab | PFS | July 2025 |
|                       | Pyrotinib HR-BLTN-III-MBC-C [NCT03863223] | Metastatic disease | Pyrotinib + trastuzumab + docetaxel | Placebo + trastuzumab + docetaxel | PFS | July 2022 |
| TQ-B211 TQB211-III-01 [NCT04385563] | Metastatic disease | TQB211 + docetaxel | Herceptin + docetaxel | ORR | February 2021 |
| GB221 GENOR GB221-003 [NCT04166615] | Advanced disease with at least one measurable target lesion | GB221 + capecitabine | Placebo + capecitabine | PFS | July 2020 |
| HER2-pretreated ≥1 prior regimen | Tucatinib HER2CLIMB-02 [NCT03975647] | Prior trastuzumab-based and taxane-based therapy | Tucatinib + T-DM1 | Placebo + T-DM1 | PFS | April 2024 |
|                       | Inetetamab IR-1.1 [NCT04736589] | Abnormal activation of PI3K/Akt/mTOR pathway after progression on trastuzumab | Inetetamab + rapamycin + chemotherapy | Pyrotinib + chemotherapy | PFS | February 2024 |
| T-DXd DESTINY-Breast03 [NCT03529110] | Prior trastuzumab-based and taxane-based therapy | T-DXd | T-DM1 | PFS | February 2022 |
| T-DM1 BO29919 [NCT03084939] | Prior trastuzumab-based and taxane-based therapy | T-DM1 | Lapatinib + capecitabine | PFS | September 2021 |
What is the optimal place in therapy of novel HER2-directed agents?

First-line pertuzumab plus trastuzumab and chemotherapy and second-line T-DM1 have been standard of care for metastatic disease since 2013,\(^{12,58-60}\) and are now being considered as (neo)adjuvant therapies based on results of the randomized phase II TRYPHAENA and NeoSphere studies as well as the phase III APHINITY (BIG 4-11) and KATHERINE trials.\(^{61-64}\) Rapidly evolving data are quickly changing standards of care, making treatment comparisons difficult, and highlighting the importance of clinical insight to navigate treatment selection for advanced disease. Based on the eligibility criteria for the phase III CLEOPATRA trial,\(^{60}\) appropriate patients with a disease-free interval beyond 6 to 12 months following adjuvant HER2-directed therapy should be offered trastuzumab plus pertuzumab and a taxane (Figure 3). T-DM1 was established as second-line therapy, although recent results from the phase III DESTINY-Breast03 trial (49% \(\leq\) 1 prior line of therapy) have shown an unprecedented statistically significant improvement in PFS for T-DXd \textit{versus} T-DM1 (median NYR versus 6.8 months, HR = 0.28, 95% CI = 0.22–0.37, \(p < 0.000001\)),\(^{22}\) supporting it as a new standard of second-line therapy. The tucatinib combination is a good option following second-line T-DM1 based on improved survival outcomes, favorable toxicity profile, and CNS activity.\(^{32,48}\) There are currently no data to inform optimal third-line therapy following second-line T-Dxd. Following progression on the tucatinib combination, neratinib plus capecitabine or other forms of continued HER2 targeting could be considered.

For patients that progress within 6 months of completing standard adjuvant HER2-directed therapy, T-DM1 remains a reasonable option based on EMELIA entry criteria.\(^{12}\) Patients with median time of onset of 5.6 months, with 97% of events occurring within the first year.\(^{54-56}\) Potential risk factors may include dose >5.4 mg/kg and Japanese ethnicity.\(^{57}\) Patient education, close monitoring, multidisciplinary collaboration, and prompt intervention with glucocorticoids are essential to avoid poor outcomes. Optimized treatment algorithms are needed, and further refinement of risk factors is awaited for further elucidation.
relapsed disease following adjuvant TDM-1 as a strategy indicated by results from the KATHERINE trial, as well as patients with disease progression on first-line TDM-1, could be candidates for the tucatinib combination or T-Dxd. Results from the QoL components of these trials and formal cost-utility analyses have not yet been completed and will be important to adjudicate optimal treatment decisions.

What upcoming trials will further our understanding of novel HER2-directed therapy in BC?

There are many exciting areas of ongoing HER2-directed research, including novel ADCs (ARX788 and RC48), bi-specific antibodies, and chimeric antigen receptor T-cells. A number of phase III trials exploring the role of new HER2-directed agents for advanced and earlier stage BC are also underway (Table 4). In the advanced setting, a number of novel agents are being assessed for patients with progressive disease on prior HER2-directed therapy, including tucatinib combined with T-DM1 (HER2CLIMB-02, NCT03975647), T-Dxd (DESTINY-Breast02, NCT03523585), and the trastuzumab ADC BAT8001 (NCT04185649). For HER2-therapy naïve advanced disease, T-DXd with or without pertuzumab (DESTINY-Breast09, NCT04784715), trastuzumab biosimilars (TQ-B211 (NCT04385563) and GB221 (NCT04164615)), and pyrotinib (HR-BLTN-III-MBC-C, NCT03863223) are also being evaluated. The rapidity of early drug and clinical development in this area suggests that promising agents like bi-specific antibodies and chimeric antigen receptor T-cells may become clinically relevant in the near future.

In the (neo)adjuvant setting, pyrotinib, HER2 biosimilars, and a number of novel HER2-directed agents are being assessed alone or in combination with chemotherapy with or without trastuzumab (Table 4). Neoadjuvant pyrotinib (NCT04290793) and the highly selective vascular endothelial growth factor receptor 2 TKI apatinib (NCT03580395) are being assessed and HER2-directed biosimilars under development in this setting include those of trastuzumab (EG12014, NCT03433313 and SIBP-01, NCT03989037) and pertuzumab (HS627, NCT04514419 and QL1209, NCT04629846). Agents being evaluated in patients with residual invasive disease...
following neoadjuvant treatment include T-DXd (DESTINY-Breast05, NCT04622319), pyrotinib (ATP, NCT04254263), and tucatinib added to T-DM1 following HER2-directed neoadjuvant therapy (CompassHER2 RD, NCT04457596). Neoadjuvant HER2-directed therapy in combination with immune checkpoint blockade is also being explored in a phase II trial (neoHIP, NCT03747120).

Finally, we must acknowledge that there is substantial heterogeneity of BC which may include variable HER2 expression within metastatic deposits and possible changes in HER2 expression over time. Studies are underway to explore treatment options for patients with advanced BC and low HER2 expression with or without co-expression of hormone receptors (NCT03734029, NCT04494425, and NCT04400695).

**Summary**

The development of efficacious and generally well-tolerated HER2-directed therapies has led to clinically meaningful benefits for patients with advanced HER2-positive BC and evidence continues to support continued HER2 suppression beyond disease progression. Based on the OS benefit in favor of the tucatinib plus trastuzumab and capecitabine regimen in HER2CLIMB and the magnitude of response observed in the DESTINY-Breast01 study of T-DXd, either regimen is an appropriate consideration for third- and/or fourth-line treatment, with important consideration for proactive toxicity management. Further information on QoL and cost-effectiveness, as well as optimal sequencing and toxicity management strategies are awaited. Ongoing randomized trials and real-world evidence will further clarify the role of these agents in this rapidly evolving field.

**Acknowledgements**

We would like to thank Ilidio Martins and Deanna McLeod from Kaleidoscope Strategic, Inc., AstraZeneca Global, Inc., Hoffmann La-Roche Canada, Knight Therapeutics, Inc., Viatris, Inc. (Mylan Pharmaceuticals), and Pfizer Canada, Inc., for their support.

**Author contributions**

Christine Simmons: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Resources; Supervision; Validation; Writing – review & editing

Daniel Rayson: Conceptualization; Data curation; Resources; Supervision; Validation; Writing – review & editing

Anil Abraham Joy: Resources; Supervision; Validation; Writing – review & editing

Jan-Willem Henning: Resources; Validation; Writing – review & editing

Julie Lemieux: Resources; Validation; Writing – review & editing

Heather McArthur: Resources; Validation; Writing – review & editing

Paul B Card: Data curation; Formal analysis; Project administration; Resources; Validation; Writing – original draft; Writing – review & editing

Rebecca Dent: Resources; Validation; Writing – review & editing

Christine Brezden-Masley: Conceptualization; Data curation; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing

**Conflict of interest statement**

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Christine Simmons has served in a consultancy or advisory role and received honorarium from Pfizer, Eli Lilly, Roche, and Mylan, and has received research funding from AstraZeneca Global, Roche, Knight Therapeutics, Viatris, and Pfizer. Daniel Rayson has served in a consultancy or advisory role and received honorarium from AstraZeneca, Pfizer, Eli Lilly, Merck, Gilead, Novartis, and Seagen. Anil Abraham Joy has served in a consultancy or advisory role and received honorarium from AstraZeneca, Pfizer, Novartis, Pfizer, Mylan, and Teva. Jan-Willem Henning has served in a consultancy or advisory role and received honorarium from AstraZeneca, Pfizer, Novartis, Eli Lilly, Roche, Knight Therapeutics, Viatris, and Pfizer. Julie Lemieux has served in a consultancy or advisory role and received honorarium from AstraZeneca, Pfizer, Eli Lilly, Merck, Gilead, Novartis, and Seagen. Anil Abraham Joy has served in a consultancy or advisory role and received honorarium from AstraZeneca, Pfizer, Novartis, Eli Lilly, Gilead, Pfizer, and AstraZeneca, and has received research funding from Celgene, Genentech, GlaxoSmithKline, Roche, Millennium, Novartis, Merck Gilead, Abbvie, Acerta, Bayer, Pfizer, BMS, Esai, Sanofi, Janssen, Osmotys, Sierra AstraZeneca, and Takeda. Heather McArthur has
served in a consultancy or advisory role and received honorarium from Bristol-Myers Squibb, AstraZeneca, Genentech/Roche, Puma Biotechnology, Daiichi-Sankyo, Seattle Genetics, Merck, and Lilly, and has received research funding from Bristol-Myers Squibb, MedImmune, LLC/AstraZenica, BTG, and Merck. Paul B. Card has nothing to declare. Rebecca Dent has served in a consultancy or advisory role and received honorarium from AstraZeneca, Viatris, Pfizer, Eisai, Merck, Eli Lilly, Novartis, and Roche, and has received research funding from AstraZeneca. Christine Brezden-Masley has served in a consultancy or advisory role and received honorarium from AstraZeneca, Eli Lilly, Knight Therapeutics, Mylan, Gilead, Roche, Amgen, Seagen, and Novartis, and has received research funding from Eli Lilly and AstraZeneca.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Funding for this review was provided through unrestricted educational grants from AstraZeneca Global, Inc., Hoffmann La-Roche Canada, Knight Therapeutics, Inc., Viatris Inc. (Mylan Pharmaceuticals), and Pfizer Canada, Inc. No discussion or viewing of review content was permitted with sponsors at any stage of review development.

Disclaimer
This review was prepared according to ICMJE standards with editorial assistance from Kaleidoscope Strategic, Inc.

ORCID iDs
Christine Simmons https://orcid.org/0000-0002-6571-4587
Anil Abraham Joy https://orcid.org/0000-0003-4201-8930
Paul B. Card https://orcid.org/0000-0003-0612-0380

Supplemental material
Supplemental material for this article is available online.

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