Margetuximab for the treatment of HER2-positive metastatic breast cancer

Paolo Tarantino, Stefania Morganti, Jacopo Uliano, Federica Giugliano, Edoardo Crimini and Giuseppe Curigliano

*European Institute of Oncology IRCCS, Milan, Italy; †University of Milan, Milan, Italy

ABSTRACT

Introduction: No specific standard treatment is currently recommended for HER2-positive advanced breast cancer (BC) patients progressing to dual HER2 blockade and to trastuzumab emtansine (TDM-1). However, several novel anti-HER2 agents are emerging and rapidly revolutionizing this setting. Among these, the FC-engineered monoclonal antibody margetuximab has recently demonstrated to slightly improve progression-free survival (PFS) compared with trastuzumab, when combined with chemotherapy for pretreated HER2-positive advanced BC.

Areas covered: The present review article recapitulates the clinical development of margetuximab, critically discussing its implications in the current landscape of BC treatment algorithms.

Expert opinion: The clinical role of Margetuximab can only be interpreted in view of the rapidly evolving treatment landscape for pretreated HER2-positive advanced BC. Indeed, the recently approved anti-HER2 agents tucatinib and trastuzumab deruxtecan currently represent appealing options for the post-TDM1 setting, while margetuximab may have a role after progression to the abovementioned agents, in case of a future approval. Regardless of its clinical uptake, it should be noted that the development of margetuximab has relevantly improved our biological understanding of HER2-positive BC, highlighting the implication of patient’s genotype in determining treatment outcomes, as well as the relevance of antibody-dependent cellular cytotoxicity (ADCC) in the context of HER2-blockade.

1. Introduction

About 15–20% of breast cancers (BC) overexpress HER2 as consequence of ERBB2 gene amplification[1]. The discovery and clinical implementation of a wide variety of agents targeting the HER2 pathway has radically changed the prognosis of this subgroup of patients in the last decades, both in the early and advanced setting[2,3]. In particular, dual HER2 blockade with trastuzumab and pertuzumab combined with chemotherapy is currently considered the preferred first-line treatment for advanced HER2-positive BC, whereas the antibody-drug conjugate (ADC) trastuzumab-emtansine (TDM1) is currently considered a standard second-line choice[4]. Although no standard third-line treatment is recommended by current guidelines, multiple novel anti-HER2 compounds have recently emerged, rapidly revolutionizing this treatment setting. Indeed, the novel anti-HER2 ADC trastuzumab deruxtecan [5] and the anti-HER2 tyrosine kinase inhibitors (TKIs) tucatinib [6] and neratinib [7] were recently approved by FDA, enlarging the treatment arsenal of pretreated HER2-positive BC patients[4]. Among these emerging agents, the anti-HER2 monoclonal antibody (mAb) margetuximab has reached the advanced stage of development, thanks to the promising results shown in several early phase trials.

The purpose of this review is to recapitulate the clinical development of margetuximab, and to critically discuss its implications in the current landscape of BC treatment algorithms.

1.1. Current landscape in TDM-1 pretreated patients

As previously mentioned, a standard treatment strategy for BC patients pretreated with trastuzumab, pertuzumab and TDM-1 is yet to be determined. Several traditional options are suggested by current guidelines, including chemotherapy combined with trastuzumab, with lapatinib, or a chemo-free treatment with the two anti-HER2 agents[8]. More recently, a number of approvals have revolutionized the field, providing novel valuable options in this setting (Table 1). Indeed, the combination of tucatinib, trastuzumab and capecitabine was approved by the Food & Drugs Administration (FDA) for pretreated HER2-positive advanced BC patients, based on the overall survival (OS) benefit demonstrated in the phase III HER2CLIMB trial[6]. Tucatinib activity was particularly evident in the population of BC patients with brain metastasis, including those not previously treated with radiotherapy[9].

A second TKI was approved by FDA in the same setting, namely neratinib combined with capecitabine, although the regimen did not show to improve survival compared with lapatinib and capecitabine[7]. Finally, the novel ADC trastuzumab deruxtecan was granted an accelerated approval by FDA for TDM-1 pretreated patients, based on the impressive objective response rate (ORR) and progression-free survival (PFS) observed in the single-arm DESTINY-Breast01 trial[5]. The phase 3 DESTINY-Breast02 trial is currently ongoing, to confirm the role of trastuzumab deruxtecan after progression to TDM-1 (ClinicalTrials.gov ID: NCT03523585).
With a rapidly enlarging arsenal of anti-HER2 regimens for pretreated patients, guidelines are currently undergoing a wide revision, and may in the future lead to an improved tailoring of treatments based on patients’ characteristics and preferences. Furthermore, some of the abovementioned novel drugs are being tested in second-line against TDM-1 monotherapy (e.g. DESTINY-Breast03 phase 3 trial, HER2CLIMB-02 phase 3 trial), and ongoing immuno-oncology trials may also redefine current treatment algorithms in the future[10]. It should be noted, however, that none of the abovementioned novel drugs is yet approved by the European Medicine Agency (EMA).

1.2. Margetuximab: pharmacodynamics and pharmacokinetics

Margetuximab (also known as MGAH22) is a human/mouse chimeric IgG1 monoclonal antibody targeting HER2 receptor. Based on the murine precursor of trastuzumab, it has similar epitope binding properties, but with an engineered Fc domain: the substitution of five aminoacid into the IgG1 Fc domain improves binding to FcγRIIA (CD16A), a low-affinity stimulatory receptor found on macrophages and natural killer cells, and reduces binding to the inhibitory Fc receptor FcγRIIB (CD32B) (Figure 1) [11]. No difference in binding to the high-affinity activating FcγRI (CD64) was instead observed in preclinical studies[12].

More in detail, CD16A is encoded by two alleles differing in the codon for amino acid 158: a higher-affinity valine (V) variant and a lower-affinity phenylalanine (F) variant[13]. The increase in affinity to both the allotypes of CD16A ultimately leads to a greater antibody-dependent cellular cytotoxicity (ADCC) activation, namely the killing of targeted cells by activated effector cells (NK lymphocytes, macrophages, neutrophils), which has been previously demonstrated to be a relevant player in the context of targeting HER2 [14,15]. Preclinical studies demonstrate that the optimized Fc domain confers enhanced ADCC against all HER2+ tumor cell tested compared with trastuzumab, including in trastuzumab resistant and HER2 low expressing cells, defined as those with an HER2 immunohistochemical score of 1+ or 2+ with a negative in-situ hybridization test [12,16]. Of note, the greatest improvement in ADCC activation occurred in presence of the CD16A-158 F, the low-binding allele[12].

The phase 1 study [17] elucidates Margetuximab’s pharmacokinetics: a bi-compartment model and Michaelis – Menten elimination, with a terminal half-live estimated at 15.5 days (about half of that observed with trastuzumab [18]). The recommended dose, used for the subsequent studies, was 15 mg/kg Q3W or 6.0 mg/kg QW.

1.3. Early clinical development

The clinical development of Margetuximab started on 2010, when the first-in-human phase I trial was launched, sponsored by MacroGenics. The trial enrolled 66 patients affected by HER2-positive advanced solid tumors for whom no standard therapy was available, including mostly breast (27 patients) and gastro-esophageal (20 patients) adenocarcinomas. Interestingly, HER2 positivity was assessed only by immunohistochemistry, and patients scored 3+ or 2+ could be included, regardless of HER2 amplification status. Margetuximab demonstrated to be well tolerated, as the most frequent toxicities were grade 1 and grade 2, including especially pyrexia, nausea, anemia, diarrhea, and fatigue. The compound also showed antitumor activity, as 64% of the 60 patients who were evaluable for tumor response experienced a stability of disease (52%) or a partial response (12%). Noticeably, all the patients who obtained a response had HER2 expression assessed as 3+ at immunohistochemistry or harbored amplification at FISH test. Median PFS was 3.5 months among all the included patients and 4.5 months among BC patients[17].

Following the phase I study, several further early phase studies were initiated in various diseases.

A phase II trial (ClinicalTrials.gov ID NCT01828021) was designed and started enrollment in 2013, in order to explore the efficacy of Margetuximab in HER2-low BC patients, defined as those showing 2+ by immunohistochemistry without amplification at FISH test. A total of 25 patients affected by advanced BC and who received at least two lines of therapy were included, with efficacy results available for 22 patients. No responses were achieved in these patients, with only six disease stabilizations observed in the trial[19]. Furthermore, as a confirmation of the worldwide rising awareness of potentialities of this novel anti-HER2 compound, a phase I (NCT04398108) and a phase II (NCT04262804) studies are currently investigating safety and efficacy of Margetuximab in Chinese HER2-positive BC patients.

The compound was also explored in combination with immune checkpoint inhibitors (ICIs): a phase Ib/II study of margetuximab combined with pembrolizumab for gastric and gastroesophageal cancers with HER2 overexpression (HER2 3+ or amplification at FISH test) enrolled 95 patients pretreated with Trastuzumab. The results showed that the combination of anti-PD1 and anti-HER2 therapy is acceptably safe and discretely tolerated; the most frequent grade 3 or 4 adverse events related to the treatment were anemia (4%) and infusion-related reactions (3%), followed by autoimmune hepatitis (2%). Concerning efficacy analysis, median PFS was 2.7 months, with a median OS of 12 months; ORR was 18%, with a disease control rate of 53%. It is necessary to emphasize that PFS and OS were significantly longer for patients with HER2 3+ at immunohistochemistry. These results warranted further studies, taking into account the biological plausibility of synergic action of adaptive and natural immunity activation, respectively, due to PD1 blockade with...
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Trial type</th>
<th>Control Arm</th>
<th>N. of pts</th>
<th>Line of tx</th>
<th>Patient population</th>
<th>Outcomes in experimental arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib – capecitabine (EMILIA trial)</td>
<td>R – P3</td>
<td>TDM1</td>
<td>991</td>
<td>2nd line</td>
<td>HER2+ ABC pretreated with taxanes and trastuzumab</td>
<td>mPFS 6.4 months ORR 30.8% mOS 25.1 months</td>
</tr>
<tr>
<td>Lapatinib – trastuzumab</td>
<td>R – P3</td>
<td>Lapatinib</td>
<td>296</td>
<td>Late line</td>
<td>HER2+ ABC pretreated with anthracylines, taxanes and trastuzumab</td>
<td>ORR 10.3% mOS 13 months</td>
</tr>
<tr>
<td>Trastuzumab – capecitabine</td>
<td>R – P3</td>
<td>Lapatinib – capecitabine</td>
<td>540</td>
<td>Any line</td>
<td>HER2+ ABC pretreated with anthracylines, taxanes (previous trastuzumab not mandatory)</td>
<td>mPFS 8.1 months ORR 32% mOS 27.3 months</td>
</tr>
<tr>
<td>Trastuzumab deruxtecan</td>
<td>NR – P2</td>
<td>NA</td>
<td>184</td>
<td>3rd or later line</td>
<td>HER2+ ABC pretreated with trastuzumab and TDM1</td>
<td>mPFS 7.8 months ORR 40.6% mOS not reached</td>
</tr>
<tr>
<td>Tucatinib – trastuzumab – capecitabine</td>
<td>R – P2</td>
<td>Placebo – trastuzumab – capecitabine</td>
<td>612</td>
<td>3rd or later line</td>
<td>HER2+ ABC pretreated with trastuzumab, pertuzumab and TDM1</td>
<td>mPFS 8.3 months ORR 32.9% mOS 24.3 months</td>
</tr>
<tr>
<td>Abemaciclib – trastuzumab – fulvestrant</td>
<td>R – P2</td>
<td>Abemaciclib – trastuzumab OR CT</td>
<td>237</td>
<td>3rd or later line</td>
<td>HR + HER2+ ABC pretreated with taxane and TDM1</td>
<td>mPFS 5.7 months ORR 25% mOS 21.6 months PFS 37.8% at 1 year ORR 32.8% OS 72.5% at 1 year</td>
</tr>
<tr>
<td>Margetuximab – chemotherapy</td>
<td>R – P3</td>
<td>Trastuzumab – CT</td>
<td>536</td>
<td>3rd – 4th line</td>
<td>HER2+ ABC pretreated with pertuzumab</td>
<td>mPFS 4 months ORR 23.5% mOS 63% at 1 year mPFS 12.5 months ORR 67% mOS not reported</td>
</tr>
<tr>
<td>Neratinib – capecitabine</td>
<td>R – P3</td>
<td>Lapatinib – capecitabine</td>
<td>621</td>
<td>3rd or later line</td>
<td>HER2+ ABC pretreated with at least two prior Tx</td>
<td></td>
</tr>
<tr>
<td>Poziotinib – capecitabine</td>
<td>NR – P2</td>
<td>NA</td>
<td>106</td>
<td>3rd or later line</td>
<td>HER2+ ABC pretreated with trastuzumab</td>
<td></td>
</tr>
<tr>
<td>Pyrotinib – capecitabine</td>
<td>R – P3</td>
<td>Lapatinib – capecitabine</td>
<td>267</td>
<td>3rd line</td>
<td>HER2+ ABC pretreated with up to 2 prior lines including trastuzumab, taxanes and/or anthracylines</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** Several trials testing anti-HER2 compounds in pretreated HER2-positive advanced breast cancer patients have been conducted, identifying multiple potential strategies to improve outcomes in this setting. In this table, we summarize the results from the most relevant of these trials reported in the last decade.

**Abbreviations:** LEGEND: ABC = advanced breast cancer; CT = chemotherapy; mPFS = median progression-free survival; ORR = objective response rate; mOS = median overall survival; N. OF PTS = number of patients, P2 = phase II, P3 = phase III, PERT = pertuzumab, Tx = treatment
pembrolizumab and ADCC eliciting via CD16a activation by margetuximab[20]. In this perspective, the MAHOGANY phase II/III trial is exploring the safety and efficacy of the combination of margetuximab and ICIs in the first-line setting for patients affected by HER2-positive gastro-esophageal adenocarcinoma, disclosing a possible chemo-free scenario for these patients.

Finally, the encouraging results achieved by the compound in advanced BC patients prompted the initiation of studies in the early setting. In particular, a newly-designed Phase II study (ClinicalTrials.gov ID: NCT04425018-MARGOT) is currently comparing the activity of margetuximab plus pertuzumab and paclitaxel to the standard of care treatment of trastuzumab, pertuzumab, and paclitaxel in the neoadjuvant setting for HER2-positive BC patients. The primary endpoint is pathological complete response and the estimated primary completion date is 2024.

On the whole, the attempt to expand margetuximab indications is actually supported by increasing data on its activity and safety in various cancers, as showed by the numerous completed and ongoing clinical trials.

1.4. Late clinical development: the SOPHIA trial

Based on the promising efficacy demonstrated by the antibody in early phase trials enrolling BC patients, a confirmatory phase III trial was initiated in 2015.

SOPHIA was a randomized, open-label phase III trial testing the combination of margetuximab plus chemotherapy versus trastuzumab plus chemotherapy in patients with HER2-positive metastatic BC. All patients were pretreated with at least 2 anti-HER2 regimens, including pertuzumab, and 1–3 lines of therapy of systemic therapy for HER2+ metastatic BC[21]. Patients enrolled were randomized 1:1 to receive margetuximab or trastuzumab along with capecitabine, eribulin, gemcitabine, or vinorelbine, as per investigator choice. Stratification factors included number of metastatic sites (≤2, >2), previous lines of treatment for metastatic BC (≤2, >2), and administered chemotherapy. Primary endpoints were PFS and OS.

536 patients were included in the intention-to-treat (ITT) population. Most patients received vinorelbine as combination chemotherapy (36%), followed by capecitabine (27%), eribulin (25%) and gemcitabine (12%). All patients received both trastuzumab and pertuzumab as previous anti-HER2 agents, along with T-DM1 in more than 90% of cases in both arms. Two-third of patients received ≤2 lines of therapy for metastatic disease. 62% had HR+/HER2- BC[22].

The first PFS analysis has been published in 2019 (data cutoff 10 October 2018). After 265 PFS events, margetuximab showed to significantly prolong PFS over trastuzumab (median 5.8 vs 4.9 months, HR 0.76; 95% CI 0.59–0.98; p 0.033). A benefit favoring margetuximab over trastuzumab was observed in all chemotherapy arms, and more pronounced
for patients receiving eribulin (HR 0.66; CI 0.42–1.05) and
gemcitabine (HR 0.58; CI 0.29–1.18), even if statistical signifi-
cance was not reached in any subgroup[21].

Observed antitumor responses were also higher in patients
in the experimental arm (ORR 22% vs 16%). Interestingly,
benefit was more pronounced in patients with a CD16A gen-
type containing a 158 F allele (median PFS 6.9 vs 5.1 months,
HR 0.68; 95% CI 0.52–0.90; p 0.005). [21]

A second interim analysis conducted after 270 deaths (70%)
confirmed the benefit in terms of both PFS (HR 0.71, p 0.0006) and
ORR (25.2 vs 13.7%, p 0.0006). However, no statistically significant
advantage was observed in terms of OS, with an absolute increase
of 1.8 months for the margetuximab versus trastuzumab (median
OS 21.6 vs 19.8, HR 0.89; p 0.326). An increased benefit was
observed for CD16A-185 F carriers in pre-specified exploratory
analysis, even if still not significant (mOS 23.7 vs 19.4, HR 0.79,
p 0.087). Of note, CD16A-185 F carriers represented the wide
majority of the enrolled population, accounting for about 85% of
the patients[22].

Overall, the combination of margetuximab plus chemother-
apy was relatively well tolerated, with toxicities comparable to
what observed in the standard arm in all chemotherapy
groups. Grade ≥3 AEs occurred in 53.8% and 52.6% of patients
receiving margetuximab and trastuzumab, respectively. Serious
AEs were recorded in 16.3% and 18.4% of patients.

More patients on margetuximab than trastuzumab discon-
tinued chemotherapy because of toxicity (11% vs 6.4%), while
serious AEs were recorded in 16.3% and 18.4% of patients.

Serious AEs were recorded in 16.3% and 18.4% of patients.

A second interim analysis conducted after 270 deaths (70%)
confirmed the benefit in terms of both PFS (HR 0.71, p 0.0006) and
ORR (25.2 vs 13.7%, p 0.0006). However, no statistically significant
advantage was observed in terms of OS, with an absolute increase
of 1.8 months for the margetuximab versus trastuzumab (median
OS 21.6 vs 19.8, HR 0.89; p 0.326). An increased benefit was
observed for CD16A-185 F carriers in pre-specified exploratory
analysis, even if still not significant (mOS 23.7 vs 19.4, HR 0.79,
p 0.087). Of note, CD16A-185 F carriers represented the wide
majority of the enrolled population, accounting for about 85% of
the patients[22].

Overall, the combination of margetuximab plus chemother-
apy was relatively well tolerated, with toxicities comparable to
what observed in the standard arm in all chemotherapy
groups. Grade ≥3 AEs occurred in 53.8% and 52.6% of patients
receiving margetuximab and trastuzumab, respectively. Serious
AEs were recorded in 16.3% and 18.4% of patients.

More patients on margetuximab than trastuzumab discon-
tinued chemotherapy because of toxicity (11% vs 6.4%), while
only 3 of them were considered probably or definitely related
to antibody therapy (seroma and infusion-related reaction for
margetuximab, pneumonia for trastuzumab) [22,23].

Extended publication of the SOPHIA trial is awaited.

1.5. Regulatory aspects

Although a biologics license application (BLA) for margetuximab
was submitted to the FDA in December 2019, the compound has
not yet been granted any approval for the treatment of BC, neither
for other cancer types. Based on the outcomes of the SOPHIA trial,
and based on FDA approval history in the same setting, a future
approval for margetuximab for pretreated HER2-positive
advanced BC patients may be hypothesized. Indeed, the TKI ner-
atinib was approved in the same setting on the basis of a relatively
small PFS benefit demonstrated in the NALA trial, without showing
any statistically significant OS improvement[7]. Less clear is if the
CD16A genotype analysis will impact regulatory decisions, when
a PFS benefit could be demonstrated in the intent-to-treat popula-
tion of the SOPHIA trial.

No application was instead submitted to date to the
European Medicine Agency to our knowledge.

2. Expert Opinion

The impact of the SOPHIA trial on current treatment algorithms
can only be interpreted in view of the rapidly evolving treatment
landscape for pretreated HER2-positive advanced BC[24]. Indeed,
although margetuximab could demonstrate a small PFS benefit
over trastuzumab when combined with chemotherapy, no
comparisons exist between this combo and the novel, recently
approved anti-HER2 regimens.

In this regard, the tucatinib triplet demonstrated to improve OS
over standard-of-care [25], while trastuzumab deruxtecan showed
unprecedented activity in highly pretreated patients [5]; both regi-
mens, thus, currently represent more appealing choices in patients
pretreated with TDM-1, and are recommended as treatment
options by the latest guidelines[4]. More in detail, the ORR (60.9%), duration of response (14.8 months) and PFS (16.4 months)
demonstrated by trastuzumab deruxtecan appear as the highest
ever achieved in this setting [5]; although these results were
obtained in a non-randomized trial, various randomized phase 3
trials are ongoing to confirm the finding[3]. Tucatinib instead was
formally compared to standard-of-care in a well-designed rando-
mized trial, demonstrating to double ORR (40.6% vs 22.8%),
improve OS by 4.5 months (21.9 vs 17.4 months) as well as achieve
a very relevant activity in patients with treated and untreated brain
metastasis [6,26].

Nonetheless, both these regimens also harbor significant toxic-
ities, including gastrointestinal toxicity and fatigue for both, pal-
mar-plantar erythrodysesthesia for tucatinib triplet and alopecia
for trastuzumab deruxtecan. The same applies to the recently
approved neratinib, which showed relatively high rates of diarrhea,
nausea and vomiting in the NALA trial[7]. Conversely, margetux-
imab showed an optimal safety profile, comparable with that of
trastuzumab, a factor that may influence its future impact on
treatment algorithms[22].

Based on abovementioned considerations, a role for marge-
tuximab may be hypothesized in the future for advanced HER2-
positive BC patients progressing following standard first-
and second-line regimens, as well as tucatinib and/or trastuzu-
mar deruxtecan, although current guidelines do not yet recom-
mend treatment with margetuximab in any setting[4]. Notably,
the differential activity of the compound based on CD16A allele
may lead to its preference in the subgroup carrying the
CD16A-158 F allele (about 85% of the patients) [22], despite the
determination of CD16A allele could likely add non-negligible
time and costs to the management of patients, possibly repre-
senting a barrier to the implementation of the compound in low-
and middle-income countries. Similar considerations regarding
financial toxicity applies to the potential costs of the drug com-
pared with trastuzumab. Indeed, the price of newly approved
cancer drugs is progressively increasing, with no apparent rela-
tionship with the efficacy demonstrated in clinical trials[27]. In
this perspective, with the availability of relatively affordable
biosimilars of trastuzumab, the modest improvement in PFS
demonstrated in the SOPHIA trial may not justify the difference
in price required for the use of margetuximab, particularly in
those countries with a public-based healthcare system.

Ultimately, a better picture of the clinical role of margetux-
imab will require updated efficacy data, to determine if the
compound is able to improve OS or if its benefit is restricted
to a modest prolongation of PFS. In the latter case, less costly
combinations of chemotherapy and trastuzumab may be pre-
ferred after pretreatment with the standard-of-care.
3. Conclusion

The PFS improvement demonstrated in the SOPHIA trial has launched margetuximab on the crowded field of novel anti-HER2 agents demonstrating to improve outcomes in pretreated HER2-positive advanced BC. Updated efficacy data will be needed to clarify the impact of margetuximab on OS, as well as to indirectly compare its activity with other anti-HER2 agents which currently appear as the optimal treatment choices in TDM1-pretreated patients, including tucatinib and trastuzumab deruxtecan. Regardless of the clinical implementation of margetuximab, the improved biological understanding derived from its development is expected to fuel new paradigms in BC treatment, with the purpose of optimally tailoring treatments based on patients’ characteristics and exploiting the immune-mediated effects of anti-HER2 compounds.

**Drug Summary Box**

**Drug name:** Margetuximab  
**Phase:** III  
**Indication:** pretreated HER2-positive advanced breast cancer  
**Mechanism of action:** HER2 pathway disruption; antibody-dependent cellular cytotoxicity activation, through an engineered FC domain improving binding to the activating receptor FcγRIIIA  
**Chemical structure:** HER2-targeting monoclonal antibody  
**Pivotal trials:** phase 3 “SOPHIA” trial [21]

**Funding**

This paper is not funded.

**Declaration of interest**

G Curigliano received honoraria for speaker, consultancy or advisory roles from Roche, Pfizer, Novartis, Seattle Genetics, Lilly, Ellipses Pharma, Foundation Medicine and Samsung. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

**Reviewer disclosures**

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

**References**


