An open-label, randomized phase II study of adecatumumab, a fully human anti-EpCAM antibody, as monotherapy in patients with metastatic breast cancer

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Background: High-level expression of epithelial cell adhesion molecule (EpCAM) is associated with unfavorable prognosis in breast cancer. This study was designed to investigate two doses of the fully human IgG1 anti-EpCAM antibody adecatumumab (MT201) in patients with metastatic breast cancer (MBC).

Methods: A total of 109 patients were stratified into high- and low-level EpCAM expression by immunohistochemical staining of primary tumors and subsequently randomly assigned to receive monotherapy with either high- (6 mg/kg every two weeks (q2w)) or low-dose adecatumumab (2 mg/kg/ q2w) until disease progression.

Results: No complete or partial tumor responses could be confirmed by central RECIST assessment. The probability for tumor progression was significantly lower in patients receiving high-dose adecatumumab and expressing high levels of EpCAM (hazard ratio 0.43; \(P = 0.0057\) versus low dose and low EpCAM). Three of 18 patients with highest EpCAM expression treated with adecatumumab developed new metastases up to week 6, compared with 14 of 29 patients with low EpCAM. Most frequent treatment-related adverse events (high dose/low dose) were chills (59%/20%), nausea (55%/18%), fatigue (39%/23%) and diarrhea (43%/7%).


Key words: adecatumumab, CD326, EpCAM, human mAb, metastatic breast cancer, MT201

introduction

The epithelial cell adhesion molecule (EpCAM, CD326) is a cell surface glycoprotein that is frequently expressed at high levels on most solid tumor types, including prostate, breast, colon, gastric, ovarian, pancreatic and lung cancer, making it a potential therapeutic target [1–4]. EpCAM appears to promote the proliferation, migration and invasiveness of breast cancer cells [5, 6]. Moreover, EpCAM is expressed on cancer stem cells from breast [7], colon [8, 9], prostate [10] and pancreatic cancers [11]. In breast cancer, only human tumor-derived cancer cells expressing EpCAM were tumorigenic in immunodeficient mice [7]. A functional role of EpCAM in tumorigenesis may also explain why overexpression of EpCAM is associated with reduced survival of patients with breast cancer [4, 12] and other solid tumors such as ovarian carcinoma [13], gallbladder cancer [14], pancreatic cancer [15] and squamous cell cancer of the esophagus [16].

Based on the experience in human epidermal growth factor receptor 2 (HER-2)-positive breast cancer [17, 18], it is conceivable that those targets that also carry a prognostic significance appear most promising for targeted therapies. This prompted us to investigate adecatumumab (MT201), a novel mAb targeting EpCAM, in metastatic breast cancer (MBC). To circumvent the toxic effects observed in earlier trials with high-affinity anti-EpCAM antibodies [19, 20], adecatumumab was designed as a fully human IgG1 antibody that binds with moderate affinity (\(k_d = 10^{-8}\) M) to EpCAM-positive cancer cells where it efficiently mediates both antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity [21–23]. A previous phase I trial in patients with hormone-refractory prostate cancer showed that adecatumumab is safe...
and well tolerated at a total dose up to 262 mg/m² given twice with a 2-week interval [24].

methods

This open-label, multicenter, randomized, phase II study was conducted in accordance with the amended recommendations of the Declaration of Helsinki, local drug laws and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice guideline. Approvals from regional ethics committees affiliated to the investigators were obtained before hand, and all patients provided written informed consent before.

patients

To be eligible, patients aged ≥18 years with Eastern Cooperative Oncology Group performance status of zero to one had to have MBC with histologically confirmed EpCAM expression, as determined by immunohistochemistry at screening, and at least one measurable metastatic lesion according to the RECIST. Major exclusion criteria were as follows: a history of central nervous system metastases; indication for and access to treatment for other antitumor treatments, including trastuzumab; any anticancer therapy within 4 weeks before study start except for hormonal treatment under other antitumor treatments; any anticancer therapy within 4 weeks before the start of therapy or during the study.

reaction to treatment

Patients were randomly allocated to one of the two treatment groups: low-dose (2 mg/kg) or high-dose (6 mg/kg) treatment with i.v. adecatumumab diluted in 500 ml of 0.9% sodium chloride given every other week and administered over 60 min. Each patient was to receive a total of 14 infusions of adecatumumab over 24 weeks unless disease progression or treatment-limiting toxicity occurred. The dosage regimen and treatment duration selected for this study were based on pharmacokinetic modeling of the results of the phase I clinical study with adecatumumab in patients with prostate cancer [24]. The centralized randomization procedure stratified the treatment assignment by low- and high-level EpCAM expression on the primary tumors to ensure a balanced distribution of low- and high-dose treatments in both EpCAM strata.

clinical assessments

Patients were monitored for safety every 2 weeks until week 24 by physical examinations and laboratory tests. Tumor assessments were carried out by thoracic and abdominal computed tomography (CT) scan or magnetic resonance imaging at screening and regularly during the treatment phase (every 6 weeks until end of study). Bone scintigraphy was carried out at screening and at the final visit to assess the presence of bone metastases. Further bone scans were mandatory if bone metastases were present at screening or if clinically indicated (e.g., occurrence of pain and elevation of alkaline phosphatase). Pharmacokinetic measurements (serum trough and peak levels of adecatumumab) were determined at regular intervals during the study (days 1, 8, 15, 29 and 43 and at weeks 12, 18 and 24).

EpCAM testing

Analysis of EpCAM expression was carried out at a central laboratory by an immunohistochemical (IHC) staining assay using archived tumor material of the primary tumors. Expression levels were classified as ‘negative’, ‘low’ or ‘high’, according to published methodology [12]. For this, a composite immunostaining score, ranging from 0 to 12, was calculated taking into account the frequency and intensity scores of EpCAM expression.

end point assessments

Tumor response assessments based on RECIST were documented locally. CT scans from all patients with at least three assessments (including baseline) underwent a central assessment. Discrepancies in overall tumor response between central and local assessments were identified and adjudicated by an independent Response Assessment Board. Patients qualified as partial responders if at least a 30% decrease in the sum of the largest diameter (LD) of the target lesions, taking as reference the baseline sum LD, was detectable and was confirmed in at least two consecutive measurements.

The primary end point of the study was the clinical benefit rate (CBR). CBR was defined as the proportion of patients with partial response (PR) or complete response or stable disease (SD); neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started) up to week 24. Secondary outcomes included time to progression (TTP), defined as the duration between the date of first adecatumumab infusion and the date of clinical disease progression, safety and pharmacokinetics of the two dose levels of adecatumumab.

statistical analyses

Sample-size estimation and primary statistical analysis were based on standard single-stage single-arm phase II designs. The primary analysis was based on the full analysis (FA) population, which included all patients with EpCAM-positive (low or high expression) tumors who received at least one infusion of the study drug.

The CBR in each of the four analysis groups (low or high EpCAM expression within the low- or high-dose treatment groups) was evaluated separately. A 95% one-sided confidence interval (CI) was calculated for the CBR in each group at 24 weeks. The background CBR for best supportive care was estimated to be ≤5%. The future use of adecatumumab as monotherapy in the patient population investigated would be of considerable interest if the true CBR was ≥25%. Therefore, the following hypothesis was tested in each of the four analysis groups—H₂: the CBR observed for each EpCAM expression strata treated with each dose level is ≤5% against H₁: the CBR observed for each EpCAM expression strata treated with each dose level is ≥25%.

All secondary end points (efficacy and safety) were analyzed descriptively. TTP was estimated using Kaplan–Meier methodology.

exploratory analyses

The methodology used for the assignment of patients into categories of low and high EpCAM expression [12] has been shown to be of prognostic relevance but has not been tested for its predictive value. Therefore, exploratory analyses using modified criteria for EpCAM classification were carried out retrospectively. Amongst others, the following cut-offs for defining ‘high’ EpCAM expression were investigated: original evaluation (composite score > 4), EpCAM staining intensity 3 + when observed in any cancer cell, EpCAM expression with 2+ or 3+ intensity in >50% of cancer cells and EpCAM expression with 3+ intensity in >50% of cancer cells, respectively (Table 3).

results

Of 160 patients screened, a total of 117 patients at 24 sites in Germany [8], Austria [3], Belgium [4], Bulgaria [5] and Romania [2] were entered into a randomized study (five patients were entered into a randomized study erroneously); 112 patients were treated with adecatumumab (56 patients at high and low dose, respectively), of whom 109 were assessable for efficacy (FA population, since three patients finally turned
out to be EpCAM negative). The study was conducted from 26 March 2004 until 4 April 2006.

patients

All patients were Caucasian females, aged 38–81 years, with histologically confirmed MBC. Patient demographics and characteristics for the FA population were generally similar between the subgroups according to dose and EpCAM expression (Table 1).

A total of 88 of the 109 EpCAM-positive patients (81% of the FA set population) had previously received chemotherapy, most commonly anthracyclines (68%). One-third of the patients had been pretreated with both anthracyclines and taxanes (33%). Sixty-six patients (61%) had received hormonal therapies. Seventeen patients have been assessed as being HER-2/neu positive. Out of this group, six patients had previously been assessed as IHC 3+ or FISH positive. Of these six patients, three patients had been treated with trastuzumab before being included in the current trial. Overall, no significant differences in antitumor pretreatment or concomitant medications were found between the subgroups.

On an average, each patient received seven infusions of adecatumumab (range 1–26, median 5.0).

efficacy

Local investigators reported two patients with PRs (both in the high-EpCAM/high-dose group) and 10 patients with SD at week 24, according to RECIST criteria. However, a central radiology review failed to confirm the PRs; clinical benefit in terms of SD at 24 weeks was confirmed in six patients. Of those, five had high EpCAM expression, three in the low-dose group and two in the high-dose group (Table 2). As a result, the primary end point was not reached as the lower bound of the one-sided 95% CI of the CBR was not >5% in any of the four groups.

### Table 1. Patient demographics and characteristics

<table>
<thead>
<tr>
<th></th>
<th>Low-dose adecatumumab</th>
<th>High-dose adecatumumab</th>
<th>Total (N=55), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>60.3 ± 9.8</td>
<td>59.2 ± 9.6</td>
<td>59.5 ± 9.6</td>
</tr>
<tr>
<td>Tumor status at screening, n (%)</td>
<td>57.8 ± 11.5</td>
<td>59.1 ± 11.5</td>
<td>58.7 ± 11.4</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>18 (94.7)</td>
<td>35 (97.2)</td>
<td>53 (96.4)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (5.3)</td>
<td>1 (2.8)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Partial response</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>ECOG status at screening, n (%)</td>
<td>0 (63.2)</td>
<td>18 (50.0)</td>
<td>30 (54.5)</td>
</tr>
<tr>
<td>1</td>
<td>7 (36.8)</td>
<td>18 (50.0)</td>
<td>25 (45.5)</td>
</tr>
<tr>
<td>HER-2/neu status at screening, n (%)</td>
<td>10 (52.6)</td>
<td>19 (52.8)</td>
<td>29 (52.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>5 (26.4)</td>
<td>4 (11.2)</td>
<td>9 (16.4)</td>
</tr>
<tr>
<td>Positivea</td>
<td>4 (21.1)</td>
<td>13 (36.1)</td>
<td>17 (30.9)</td>
</tr>
<tr>
<td>Not known</td>
<td>3 (15.8)</td>
<td>11 (30.6)</td>
<td>14 (25.5)</td>
</tr>
<tr>
<td>Hormone receptor status—overall, n (%)</td>
<td>12 (63.2)</td>
<td>21 (58.3)</td>
<td>33 (60.0)</td>
</tr>
<tr>
<td>Positiveb</td>
<td>4 (21.1)</td>
<td>4 (11.1)</td>
<td>8 (14.5)</td>
</tr>
<tr>
<td>Negativec</td>
<td>5 (26.3)</td>
<td>9 (25.0)</td>
<td>14 (25.5)</td>
</tr>
<tr>
<td>Not known</td>
<td>14 (73.7)</td>
<td>32 (88.9)</td>
<td>46 (83.6)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>12 (63.2)</td>
<td>29 (80.6)</td>
<td>41 (74.5)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>7 (36.8)</td>
<td>13 (36.1)</td>
<td>20 (36.4)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>7 (36.8)</td>
<td>13 (36.1)</td>
<td>20 (36.4)</td>
</tr>
<tr>
<td>Both anthracyclines</td>
<td>5 (26.3)</td>
<td>9 (25.0)</td>
<td>14 (25.5)</td>
</tr>
<tr>
<td>and taxanes</td>
<td>14 (73.7)</td>
<td>32 (88.9)</td>
<td>46 (83.6)</td>
</tr>
<tr>
<td>Capecitabine, vinorelbine or gemcitabine</td>
<td>9 (47.4)</td>
<td>25 (69.4)</td>
<td>34 (61.8)</td>
</tr>
</tbody>
</table>

aImmunohistochemical staining intensity 2+, 3+ or FISH+.
bHormone receptor status: estrogen and/or progesterone positive.
cHormone receptor status: estrogen negative and progesterone negative.

EpCAM, epithelial cell adhesion molecule; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; HER-2, human epidermal growth factor receptor 2.
Table 2. Primary efficacy results: clinical benefit rate (patients with SD at week 24, complete remission or partial remission; as assessed by the iRAB according to RECIST)

<table>
<thead>
<tr>
<th></th>
<th>Low-dose adecatumumab</th>
<th></th>
<th>High-dose adecatumumab</th>
<th></th>
<th>All patients (N = 109), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(X=19), n (%)</td>
<td>(X=36), n (%)</td>
<td>(X=55), n (%)</td>
<td>(X=38), n (%)</td>
<td>(X=54), n (%)</td>
</tr>
<tr>
<td>Clinical benefit rate(^a)</td>
<td>0 (0.0)</td>
<td>1 (6.3)</td>
<td>1 (6.3)</td>
<td>3 (5.6)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>No clinical benefit(^b)</td>
<td>19 (100.0)</td>
<td>32 (88.9)</td>
<td>51 (92.7)</td>
<td>34 (89.5)</td>
<td>49 (90.7)</td>
</tr>
<tr>
<td>Not evaluable(^c)</td>
<td>0 (0.0)</td>
<td>1 (2.8)</td>
<td>1 (1.8)</td>
<td>2 (5.3)</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>Lower 95% confidence interval for clinical benefit rate</td>
<td>0.0%</td>
<td>2.3%</td>
<td>0.3%</td>
<td>0.9%</td>
<td>3 (2.8)</td>
</tr>
</tbody>
</table>

\(^a\)All patients with clinical benefit had SD for at least 24 weeks as confirmed by the iRAB; no partial or complete response was confirmed by the iRAB.

\(^b\)Progressive disease or data not available.

\(^c\)Patients classified as ‘not assessable’ by the iRAB include the following patients: \#101-017 (low dose/high EpCAM): local assessment of SD at week 24 (reason for being not assessable: part of CT scans at week 24 not available for central review; as a consequence, despite SD of target lesions, iRAB considered assessment as not possible according to RECIST); \#403-005 (high dose/high EpCAM): local assessment of SD at week 24 (reason for being not assessable: iRAB considered PET scan used to monitor target lesions to be ‘not measurable’ according to RECIST); \#401-013 (high dose/high EpCAM): local assessment of SD at week 24 (reason for being not assessable: part of CT scans at week 24 not available for central review; as a consequence, despite SD of target lesions, iRAB considered SD according to RECIST).

Analyses of secondary end points revealed lower probability for tumor progression in patients receiving high-dose adecatumumab compared with low-dose adecatumumab [hazard ratio (HR) 0.67; P = 0.0465] (Figure 1A). Patients with high EpCAM expression showed a tendency toward a lower probability for tumor progression compared with patients with low EpCAM scores [HR 0.71; P = 0.1157] (Figure 1B). The lowest probability for tumor progression was seen in patients expressing high levels of EpCAM and receiving high-dose adecatumumab (HR 0.43; P = 0.0057 versus low EpCAM expression and low-dose adecatumumab) (Figure 1C).

As described in the ‘Methods’ section, we carried out additional exploratory analyses to better understand the presumably target- and dose-dependent activity of adecatumumab. As shown in Table 3, the tendency toward a decreased probability of tumor progression was more prominent when more tumor cells expressed EpCAM. For example, the percentage of patients without signs of progression after 24 weeks (3% and 12% in the original low- and high-EpCAM groups, respectively) was as high as 22% in those patients who expressed EpCAM at >50% intensity in >50% of cancer cells. Of those, patients receiving high-dose adecatumumab had a 30% chance of being progression free after 24 weeks.

We also analyzed the underlying cause for disease progression in relation to EpCAM expression. Figure 2A shows patients with >50% of tumor cells expressing EpCAM (which was only observed in patients with IHC 2+ and 3+ staining intensity) versus all others indicating a significantly longer TTP in patients with >50% EpCAM expression. While the rate of progression due to increase of known lesions did not appear to be different between groups (Figure 2B), a distinct pattern was observed in the rate of occurrence of new lesions. Whereas almost half of the patients with non-high EpCAM presented with new metastases at week 6 (48%; 14 of 29 assessable patients), this rate was decreased to only 17% in the patients with high EpCAM levels (3 of 18 assessable patients; P = 0.034 in two-sided Fisher’s exact test; Figure 2C). Notably, administration of high-dose adecatumumab resulted in improved outcome, i.e. only 10% of high-EpCAM patients treated with the higher adecatumumab dose showed development of new lesions (Figure 2D).

**safety**

Overall, drug-related adverse events were reported in 85% of patients, with a higher incidence in patients who received high-dose adecatumumab (Table 4). Although about twice as many adverse events have been reported in the high-dose adecatumumab group compared with low-dose treatment, no increase in grade 3 and 4 toxic effects was observed (Table 4). EpCAM expression did not appear to correlate with the incidence of adverse events in either treatment group (data not shown).

General symptoms, such as chills, fatigue, headache and gastrointestinal side-effects, like nausea, vomiting, diarrhea and constipation, were the most commonly reported clinical adverse events (Table 4). Transient pancreas enzyme abnormalities (increases up to Common Terminology Criteria Adverse Events grade 4 in levels of lipase and/or amylase) were recorded in seven patients (13%) in the low-dose group and five patients (9%) in the high-dose group. However, no clinical signs of pancreatitis were reported and increased enzymes normalized without interruption of treatment. Other grade 3/4 adverse events observed at both dose levels included increases in C-reactive protein, elevated serum levels for alkaline phosphatase and lactate dehydrogenase (subsumed as ‘enzyme abnormalities’ in Table 4) and abnormal hepatic function.

Human antibodies against adecatumumab (HAHA) were not detected in a single patient. No case of death was reported as potentially caused by adecatumumab treatment.

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**original article**

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pharmacokinetics

The anticipated trough target level of 10 µg/ml for the low-dose group (based on previous phase I data) was reached over the entire study period (mean trough concentration 10.2 ± 4.33 µg/ml; range 8.2 ± 4.65 µg/ml to 12.7 ± 3.28 µg/ml at each visit). The anticipated trough level of 30 µg/ml for the high-dose group was not reached over the entire study period (mean trough value 26.5 ± 8.65 µg/ml) but could be reached at visit 4 after the third loading dose (mean trough value 33.5 ± 9.83 µg/ml). The lowest mean trough value of the higher dosage was 23.3 ± 6.10 µg/ml.

The mean peak concentration over the evaluated period of time was 138.2 ± 38.92 µg/ml (range 121.8 ± 37.29 µg/ml to 156.1 ± 35.94 µg/ml per visit) in the high-dose group and 48.6 ± 16.19 µg/ml (range 40.6 ± 16.80 µg/ml to 55.5 ± 8.06 µg/ml per visit) in the low-dose group (data not presented).

discussion

This phase II trial was designed to investigate the clinical activity of single-agent adecatumab, a novel antibody against EpCAM, in MBC patients and to explore the influence of EpCAM expression levels on clinical outcome. Whereas objective clinical responses could not be confirmed, analyses of secondary end points such as TTP indicated that treatment with adecatumab is biologically active. Longer time to disease progression was observed in patients with high EpCAM expression despite the fact that EpCAM overexpression is associated with a negative prognosis in breast cancer [4, 12, 25].

Figure 1. Kaplan–Meier curve of time to progression (A) by treatment group, (B) by EpCAM expression and (C) for low-dose adecatumab/low EpCAM versus high-dose adecatumab/high EpCAM expression.
The relevance of this finding is emphasized by additional exploratory analyses indicating a correlation between clinical outcome and the intensity of EpCAM expression. Whereas all but one patient with low EpCAM expression progressed early during the study, up to 30% of patients with highest EpCAM expression levels did not show signs of progressive disease (at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions) by week 24. Based on the clinical experience in patients with HER-2-positive disease, our observations further support the hypothesis that those targets are especially suitable for therapeutic intervention, which also carry a prognostic significance, i.e. the tumor has a disadvantage if these antigens are targeted.

Whereas limited clinical activity of this single-agent approach in patients with advanced disease might have been expected, it is still remarkable that the incidence of new lesions was significantly reduced in patients with high EpCAM-expressing tumors. This and the observation of an increased TTP in patients of the high-dose group might also indicate that traditional phase II methodologies and end points, such as tumor shrinkage, may not be applicable for assessing the single-agent activity of biological agents [26]. However, due to the limited patient number within these subgroups, these results need to be assessed with adequate carefulness.

Table 3. Retrospective analyses of efficacy variables in relation to various cut-offs for the definition of high EpCAM expression

<table>
<thead>
<tr>
<th></th>
<th>Low EpCAM (n = 35)</th>
<th>High EpCAM (n = 74)</th>
<th>IHC 3+ (in &gt;10% of cells) (n = 63)</th>
<th>IHC 2+3+ (in &gt;50% of cells) (n = 29)</th>
<th>IHC 3+ (in &gt;50% of cells) (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PRb (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CBRb at week 24 (%)</td>
<td>2.9</td>
<td>6.8</td>
<td>7.9</td>
<td>6.9</td>
<td>11.1</td>
</tr>
<tr>
<td>CBRb at week 12 (%)</td>
<td>8.6</td>
<td>18.9</td>
<td>19.0</td>
<td>24.1</td>
<td>27.8</td>
</tr>
<tr>
<td>Progression freea at week 24 (%)</td>
<td>2.9</td>
<td>12.2</td>
<td>12.7</td>
<td>17.2</td>
<td>22.2</td>
</tr>
<tr>
<td>Progression freea at week 12 (%)</td>
<td>14.3</td>
<td>31.1</td>
<td>31.7</td>
<td>34.5</td>
<td>38.9</td>
</tr>
</tbody>
</table>

Table shows data irrespective of dose (i.e. pooled data from 2 mg/kg and 6 mg/kg groups).

aLow and high EpCAM according to the original definitions, which were applied for all other analyses [12].
bCR, PR and CBR depict values confirmed by the independent Response Assessment Board (i.e. patients assigned as not assessable or with missing scans were handled as if they had progressive disease).

cProgression free denotes all patients in whom no evidence of progression, either from local sites or central assessments, was available.

EpCAM, epithelial cell adhesion molecule; IHC, immunohistochemical; CR, complete response; PR, partial response; CBR, clinical benefit rate.

Figure 2. Kaplan–Meier curve of time to progression of (A) all events qualifying for progressive disease according to RECIST, (B) events resulting from progression of target and nontarget lesions only, (C) events resulting from development of new lesions, (D) as (C) but analysis of patients treated with high-dose adecatumumab only.

The relevance of this finding is emphasized by additional exploratory analyses indicating a correlation between clinical outcome and the intensity of EpCAM expression. Whereas all but one patient with low EpCAM expression progressed early during the study, up to 30% of patients with highest EpCAM expression levels did not show signs of progressive disease (at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions) by week 24. Based on the clinical experience in patients with HER-2-positive disease, our observations further support the hypothesis that those targets are especially suitable for therapeutic intervention, which also carry a prognostic significance, i.e. the tumor has a disadvantage if these antigens are targeted.

Whereas limited clinical activity of this single-agent approach in patients with advanced disease might have been expected, it is still remarkable that the incidence of new lesions was significantly reduced in patients with high EpCAM-expressing tumors. This and the observation of an increased TTP in patients of the high-dose group might also indicate that traditional phase II methodologies and end points, such as tumor shrinkage, may not be applicable for assessing the single-agent activity of biological agents [26]. However, due to the limited patient number within these subgroups, these results need to be assessed with adequate carefulness.
Overall, adecatumumab showed an acceptable safety profile. More patients in the high-dose group (98%) than the low-dose group (71%) experienced treatment-related adverse events; however, no increase in severe toxic effects was found with the higher dose. Although side-effects such as chills and diarrhea are commonly reported also with other mAb therapies [20], for adecatumumab, an EpCAM-specific binding to normal tissue as causative mechanism cannot be excluded. Two other anti-EpCAM antibodies, ING-1 and 3622W94, both with high-affinity binding to EpCAM, were reported to cause acute pancreatitis as dose-limiting toxicity in phase I studies [19, 20]. Although an increase in pancreatic enzymes was recorded in our trial, these elevations were transient, fully reversible and not associated with clinical signs of pancreatitis.

Additional studies are currently going on to evaluate the safety and efficacy of adecatumumab in combination with standard chemotherapy regimens, as this approach has been shown to be advantageous with other biological agents in patients with MBC, such as trastuzumab [18, 27, 28] and bevacizumab [29, 30]. Combination therapy with cytotoxic agents might help to bridge the initial time interval when the onset of an immunological effector mechanism is counterbalanced by exponential tumor growth kinetics. This delayed onset of immunological action could also explain that a significant percentage of patients in our trial had already progressed at week 6 and why TTP curves in this trial diverge mainly thereafter.

HAHA were not detected in a single patient, indicating that long-term treatment with adecatumumab should not be impaired by immunogenicity.

In conclusion, this randomized study in patients with MBC confirmed the overall safety and feasibility of single-agent treatment with the anti-EpCAM antibody adecatumumab. The inhibitory effect on development of new metastatic lesions and the longer TTP in patients with high EpCAM-expressing tumors support further investigation of adecatumumab in patients with EpCAM-overexpressing tumors and lower tumor burden. Assessment of combining adecatumumab with standard chemotherapeutic regimens for patients suffering from advanced breast cancer is currently going on. Preliminary results indicate that combining adecatumumab with docetaxel is safe and feasible in patients with extensively pretreated MBC. The apparent target-dependent activity of adecatumumab observed in the current trial seems to find confirmation in the going on combination study [31].

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**references**