

A Randomized Phase II Study of Anti-CSF-1 Monoclonal Antibody Lacnotuzumab (MCS110) Combined with Gemcitabine and Carboplatin in Advanced Triple-Negative Breast Cancer

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Translational Relevance

While first-line treatment options for TNBC have recently been extended to include PD-1/PD-L1 inhibitors, chemotherapy remains a mainstay in advanced disease and, for many patients efficacy is limited. Recent studies have shown how combining chemotherapy with novel immuno-oncology agents might improve efficacy for these patients. Preclinical studies in mouse models have demonstrated the utility of colony stimulating factor-1 (CSF-1) blockade in enhancing CD8+ tumor cell infiltration, depleting tumor-associated macrophages and slowing primary tumor development. The potential for adding CSF-1 inhibitors to a chemotherapeutic regimen is also under investigation. This phase II study explored the combination of the anti-CSF-1 monoclonal antibody lacnotuzumab with gemcitabine and carboplatin in patients with advanced TNBC. Whilst successful target engagement was achieved, the combination showed comparable antitumor activity to chemotherapy alone, with slightly poorer tolerability. These data may prove useful for investigators designing future studies exploring agents targeting the CSF-1–CSF-1 receptor pathway in TNBC.

Abstract

Background: This phase II study determined the efficacy of lacnotuzumab added to gemcitabine plus carboplatin (gem-carbo) in patients with advanced triple-negative breast cancer (TNBC).

Patients and Methods: Female patients with advanced TNBC, with high levels of tumor-associated macrophages, and not amenable to curative treatment by surgery or radiotherapy, were enrolled. Lacnotuzumab was dosed at 10 mg/kg every 3 weeks (Q3W), ± a dose on Cycle 1, Day 8. Gem and carbo were given at 1000 mg/m² and area under curve 2 dose in mg, respectively, Q3W. Treatment continued until unacceptable toxicity, disease progression, or discontinuation by physician/patient.

Results: Patients received lacnotuzumab+gem-carbo (*n*=34) or gem-carbo (*n*=15). Enrollment was halted due to recruitment challenges owing to rapid evolution of the therapeutic landscape; formal hypothesis testing of the primary endpoint, was therefore not performed. Median progression-free survival was 5.6 months (90% CI: 4.47, 8.64) in the lacnotuzumab+gem-carbo arm and 5.5 months (90% CI: 3.45, 7.46) in the gem-carbo arm. Hematologic adverse events were common in both treatment arms; however, patients treated with lacnotuzumab experienced more frequent aspartate aminotransferase, alanine aminotransferase, and creatine kinase elevations. Pharmacokinetic results showed that free lacnotuzumab at 10 mg/kg exhibited a typical IgG pharmacokinetic profile and target engagement of circulating CSF-1 ligand.

Conclusion: Despite successful target engagement and anticipated pharmacokinetic profile, lacnotuzumab+gem-carbo showed comparable antitumor activity to gem-carbo alone, with slightly poorer tolerability. However, the data presented in this manuscript would be informative for future studies testing agents targeting the CSF-1–CSF-1R pathway in TNBC.

Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 15% to 20% of all breast carcinomas (1). According to the American Society of Clinical Oncology/College of American Pathologists guidelines, TNBC is defined by $\leq 1\%$ expression of estrogen receptor (ER) and progesterone receptor (PgR) which is determined by immunohistochemistry (2). HER2 levels are either 0 to 1+ or 2+ according to immunohistochemistry and produce a negative result with FISH (3). Compared to other types of breast cancer, TNBC in general has greater metastatic potential and a more aggressive clinical course (1,4).

In advanced TNBC, chemotherapeutic agents such as gemcitabine and carboplatin (gem-carbo) are frequently used and are usually administered as the standard of care to patients who have previously been given anthracyclines and taxanes (5,6). However, TNBC remains a challenge to treat as efficacy of chemotherapy is often limited with poor survival outcomes (7).

In Europe, the chemotherapy combination of bevacizumab and paclitaxel is one of the options for first line of treatment (8). The median overall survival (OS) with current treatment options for metastatic TNBC is reportedly around 13–18 months (1). More recently, studies investigating the addition of immunotherapy agents (for example programmed cell death 1 [PD-1] or programmed cell death ligand 1 [PD-L1] inhibitors) to chemotherapy regimens have shown potential for significantly improving survival compared with chemotherapy alone (9,10).

Colony stimulating factor-1 (CSF-1) is crucial for the differentiation and survival of macrophages and other components in the mononuclear phagocyte system (11). Tumor secretion of CSF-1 is believed to recruit tumor-associated macrophages (TAMs) and to stimulate tumor growth, angiogenesis, invasion, and/or metastasis, and suppress antitumor immunity (12). Preclinical studies have shown that antibody-mediated blockade of CSF-1 did enhance CD8⁺ T-cell tumor infiltration and sensitivity to paclitaxel in xenograft models. CSF-1 blockade improved the survival of mammary tumor-bearing mice by slowing primary tumor development and reducing pulmonary metastasis (13). Furthermore, in a chemotherapy-resistant murine model of breast cancer, an anti-CSF-1 Fab fragment suppressed tissue CSF-1 expression and inhibited tumor growth by 40%. Notably, the combination of the CSF-1–targeting antibody in combination with chemotherapy suppressed tumor development by >50% and down-regulated the expression of chemoresistance genes (14). In patients with TNBC, tumors with high immunological infiltrates of TAMs (TAM high) have demonstrated a significantly worse outcome than tumors with low

TAM infiltrates (15). In addition, the TAM high subtype is also hypothesized to be more responsive to immunotherapy (16).

Lacnotuzumab (MCS110) is a neutralizing humanized IgG1 kappa monoclonal antibody, which binds to CSF-1, preventing CSF-1–mediated receptor activation (17). Here, we report a phase II, open-label, randomized trial designed to investigate whether lacnotuzumab improves the efficacy of gem-carbo combination in patients with advanced TNBC and a high TAM content.

Materials and Methods

Clinical study design

This was a phase II, two-arm, open-label, multicenter randomized study (ClinicalTrials.gov identifier: NCT02435680) of lacnotuzumab combined with gem-carbo in TNBC. The current study was designed and initiated prior to the introduction of PD-1/PD-L1 inhibitors as part of the treatment armamentarium in TNBC. Chemotherapy, such as gem-carbo, was a frequently used first-line regimen for metastatic breast cancer with demonstrated high efficacy and tolerability in first- to third-line metastatic settings at the time of study design (18,19), supporting the choice of the gem-carbo doublet as the backbone chemotherapy in this study. The data cut-off date was October 1, 2018. Although the study is still ongoing with one patient on treatment, recruitment was halted as of June 16, 2017, due to challenges in enrollment and the rapid evolution of the therapeutic landscape. Importantly, the recruitment for this study was not halted due to safety concerns and all patients benefiting on treatment were continued as per the protocol.

The study was sponsored by Novartis and performed according to the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice. The study protocol was approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) before the start of the study. Written informed consent was obtained from each patient.

Treatment plan and drug administration

All eligible patients were randomized 2:1 to Arm 1: lacnotuzumab with gem-carbo, or Arm 2: gem-carbo alone. The study was open label and no placebo was administered in the control arm. Lacnotuzumab was administered intravenously (I.V.) at a dose of 10 mg/kg on Day 1 and Day 8 of the first 21-day cycle, followed by Day 1 of subsequent 21-day cycles. The additional

Cycle 1, Day 8 (C1D8) lacnotuzumab dose was halted after the initial safety review, where individual patient safety and pharmacokinetic profiles were discussed and it was considered that an additional dose might increase the frequency of grade ≥ 3 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations. The omission of the Day 8 lacnotuzumab dose was not related to the decision to halt the study. Gem-carbo were both administered I.V. both on Day 1 and Day 8 of every 21-day cycle; gemcitabine at 1000 mg/m² and carboplatin at an area under curve (AUC) 2 dose in mg.

The AUC 2 dose was calculated by: $AUC \times (\text{glomerular filtration rate} + 25)$, according to Calvert's formula (20). The doses and treatment cycles of gem-carbo followed those of published regimens in phase II and phase III trials (18,21). This was considered to be a low to moderately emetogenic dosing regimen, which afforded minimal use of corticosteroids (thus avoiding the potential to activate TAMs). Treatment was administered until unacceptable toxicity, progressive disease defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, death, or patient/physician decision.

Study objectives

The primary objective was to assess antitumor activity of lacnotuzumab combined with gem-carbo compared to gem-carbo alone, measured by progression-free survival (PFS) by local investigator. Secondary objectives included assessing the antitumor activity of lacnotuzumab given in combination with gem-carbo, measured by tumor response per RECIST v1.1 (according to local investigator assessment), overall response rate (ORR; complete response [CR] + partial response [PR]), clinical benefit rate (CBR; CR + PR + stable disease lasting ≥ 6 months), duration of response (DOR), safety and tolerability of lacnotuzumab in combination with gem-carbo, the pharmacokinetic profile of lacnotuzumab, when combined with gem-carbo, the pharmacokinetic profile of gemcitabine and carboplatin in the absence of lacnotuzumab, the pharmacodynamic effect of lacnotuzumab when combined with gem-carbo, measured by total CSF-1 circulating levels, serum CTX-1, and circulating monocytes in blood and TAM and tumor-infiltrating lymphocyte (TIL) content in pre- and post-dose tumor biopsies. CD163 and CD8 were used to define TAMs and TILs by immunohistochemistry.

Statistical analysis

Available data on the efficacy of gem-carbo from a previous study (18) served to establish the clinically relevant efficacy expected from the addition of lacnotuzumab to gem-carbo as compared with gem-carbo alone. An estimated 30% reduction in the risk of a PFS event or correspondingly an estimated PFS hazard ratio ≤ 0.7 was considered clinically relevant. Furthermore, it was considered statistically significant if the upper bound of the one-sided 90% credible interval of hazard ratio was < 1 . Under the assumption that patient accrual would occur in the first 14 months, the study would last for 22 months with a uniform accrual pattern across months and the dropout rate with the assumption of censoring at time 0 would be equal to 10%, a sample size of 78 patients (52 in the lacnotuzumab + gem-carbo arm and 26 in the gem-carbo arm) was planned. For a one-sided log-rank test with a type-1 error equal to 10%, this was expected to achieve 72% power if the true hazard ratio was 0.6, and 90% power if the true hazard ratio was 0.5.

The full analysis set (FAS), which comprised all patients to whom study treatment was assigned by randomization, was used to summarize patients' baseline characteristics, and analyze all the efficacy endpoints. The analysis was performed according to the randomized treatment assignment. Formal statistical hypothesis testing was not performed for the primary endpoint of PFS because of the insufficient sample size. Instead, the median PFS, including 90% confidence intervals (CIs) were computed using Kaplan–Meier method by treatment arms. In addition, the ORR and CBR were summarized and exact (Clopper–Pearson) 90% CIs were estimated by treatment arms. Additional statistical analysis information is stated in Supplementary Text 1. No OS data are available for the study, as a result of a protocol amendment after the enrollment halt, where survival follow-up was removed.

Patients

Eligible patients were females aged ≥ 18 years with advanced TNBC (metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy), whose tumors contain a high content of TAMs. TAM content was determined centrally, by immunohistochemistry on a pre-treatment tumor biopsy (further details are presented in the pharmacokinetic, pharmacodynamic, and biomarker section). All patients had confirmation of ER-negative (ER–), PgR-negative (PgR–), and HER2-negative (HER2–) tumors, based on local laboratory testing on the patient's last available tumor tissue. For the ER–/PgR– reports, local guidelines were used and all cases scoring HER2 2+ by immunohistochemistry required a negative fluorescent *in situ* hybridization test. Patients had radiological/objective evidence of

disease progression prior to enrollment and at least one measurable lesion per RECIST v1.1 (includes lytic or mixed [lytic + blastic] bone lesions with an identifiable soft tissue component that meets the measurability criteria). All patients had an Eastern Cooperative Oncology Group (ECOG) performance status 0–2. Patients with treated CNS metastases and stable neurological symptoms were eligible.

Patients enrolled in this study were not allowed to have prior chemotherapy for advanced breast cancer, although previous adjuvant/neoadjuvant chemotherapy was permitted irrespective of disease-free interval. Other exclusion criteria are described in Supplementary Text 2.

Assessments

Efficacy was evaluated by local investigator assessment using RECIST v1.1, every 6 weeks for Cycles 1–8, then every 9 weeks after Cycle 8 until disease progression, and at the end-of-treatment visit. Following a protocol amendment after the enrolment halt, the frequency of post Cycle 8 assessments was reduced from every 9 weeks to a minimum of every 12 weeks until disease progression, and at the end-of-treatment visit. All CRs and PRs were confirmed by a second assessment, no earlier than 28 days after the criteria for response were first met.

Regular safety assessments were performed, based on physical examination, ECOG performance status, laboratory parameters, and cardiac assessments. Adverse events (AEs) were assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (22).

Pharmacokinetic, pharmacodynamic, and biomarker analysis

In the first 15 patients treated with lacnotuzumab plus gem-carbo, serial blood samples were collected in Cycles 1 and 4, and pre-dose and limited post-dose samples were collected in Cycles 2, 3, and 5–8. In the lacnotuzumab arm, samples were collected to determine free lacnotuzumab concentration in serum, total CSF-1 levels in plasma, and anti-drug antibodies levels in serum. Serial blood samples were collected in Cycles 1 and 4 to determine plasma concentrations of gem-carbo and any metabolites in both treatment arms. If medically feasible, pre- and post-dose biopsies were performed between C2D8 and C3D1 to assess TAM content (CD163+ expression) and TIL counts (CD8+ expression), by immunohistochemistry.

An immunohistochemistry assay, CD163, for evaluating TAMs in TNBC was initially established where a TAM content of $\geq 15\%$ of the tumor area identified 40% of TNBC as TAM high and the rest as TAM low. Thereafter, an external lab was contracted for the central testing of TAMs. A correlation study was performed at the external lab to ensure that the same patient population

was identified using the two different assay platforms. The TAM cut-off determined during assay validation at the external lab for identifying patients with a high TAM content (40% of TNBC) differed from the one determined initially, which can be explained by well-known technical differences between assay platforms. The different cut-off values were strongly and significantly correlated and thus, both assay platforms identified the same patient population.

Following local IEC/IRB approval of Protocol amendment 6, which reduced the schedule of assessments after the recruitment halt, biomarker sample collections were no longer required. Pharmacokinetic sample collections for lacnotuzumab and gem-carbo were no longer needed and CSF-1 and anti-drug antibody (ADA) samples were no longer collected.

Results

Patient population and treatment

A total of 50 female patients were enrolled in the study across 27 sites with 34 patients randomized to the lacnotuzumab plus gem-carbo arm and 16 patients to the gem-carbo arm. At the time of data cut-off (October 1, 2018), 34 patients had received lacnotuzumab at 10 mg/kg Q3W and of these, 15 patients had received the C1D8 dose. Overall, 49 patients received gem-carbo, of which 15 patients received gem-carbo alone; one patient was randomized to the gem-carbo arm but never received study treatment (Supplementary Figure S1).

Patient demographics and baseline characteristics were similar across both arms (Table 1). Median patient age was 57 years (range 32–78) and 56 years (range 29–77) in the lacnotuzumab plus gem-carbo arm and the gem-carbo arm, respectively. All patients had an ECOG performance status between 0 and 2 across both arms and overall, the majority ($n=32$; 64.0%) had an ECOG performance status of 0. More than 50% of tumors were poorly differentiated; 19 (56.0%) patients in the lacnotuzumab and gem-carbo arm and 12 (75.0%) patients in the gem-carbo arm. Patient data on prior radiotherapy are presented in Supplementary Table S1.

At the data cut-off date, in the lacnotuzumab and gem-carbo combination arm, 33 patients (97.1%) had discontinued from the study, mainly due to disease progression. All patients who received treatment ($n=15$; 93.8%) in the gem-carbo arm had discontinued from the study due to disease progression (Supplementary Table S2). One patient in the lacnotuzumab plus gem-carbo arm was ongoing (as of the data cut-off date of October 1, 2018) with a confirmed PR. The DOR was 810 days (26.6 months).

Efficacy

The primary endpoint was not met in the study, PFS was comparable between the lacnotuzumab plus gem-carbo arm and the gem-carbo arm (Figure 1). Median PFS was 5.6 months (90% CI: 4.47, 8.64) in patients treated with lacnotuzumab plus gem-carbo ($n=34$) compared with 5.5 months (90% CI: 3.45, 7.46) in the gem-carbo arm ($n=16$). The ORR in the lacnotuzumab plus gem-carbo arm was 23.5% (90% CI: 12.3, 38.5) and in the gem-carbo arm it was 37.5% (90% CI: 17.8, 60.9) (Table 2). The median Kaplan–Meier-estimated DOR was 9.6 months (90% CI: 3.61, not estimable) in the lacnotuzumab plus gem-carbo arm ($n=8$) and 5.0 months (90% CI: 2.66, 13.27) in the gem-carbo arm ($n=6$); however, due to small sample size, no conclusions can be drawn from these data. The observed DOR in patients treated with lacnotuzumab with and without gem-carbo is shown in Figure 2.

Exposure and dose intensity

The median duration of exposure was 17.4 weeks (range 3.0–125.3) for all patients treated with lacnotuzumab. In the lacnotuzumab plus gem-carbo arm, the median dose exposure was 18.1 weeks (min-max: 3.0–104.0) for carboplatin and 18.7 weeks (min-max: 3.0–126.3) for gemcitabine. In comparison, in the gem-carbo arm, the median dose exposure was 17.4 weeks (min-max: 4.1–63.0) for both carboplatin and gemcitabine. For all patients treated with lacnotuzumab, the median relative dose intensity (RDI) was 75%. The RDI of gemcitabine and carboplatin was similar between the lacnotuzumab plus gem-carbo and gem-carbo arms.

Safety

All patients experienced at least one AE regardless of relationship to study treatment (Table 3) and at least one AE suspected to be related to study treatment (Supplementary Table S3). In the lacnotuzumab plus gem-carbo arm, the most frequently reported (>40%) AEs of any grade regardless of study treatment were AST increased ($n=28$; 82.4%), neutropenia ($n=26$; 76.5%), ALT increased, anemia ($n=23$ each; 67.6%), nausea ($n=22$; 64.7%), thrombocytopenia ($n=16$; 47.1%), blood creatinine phosphokinase (CPK) increased ($n=16$; 47.1%), fatigue ($n=15$; 44.1%), and periorbital edema ($n=14$; 41.2%). In the gem-carbo arm, the most frequent (>40%) AEs were neutropenia ($n=12$; 80.0%), anemia ($n=10$; 66.7%), thrombocytopenia ($n=8$; 53.3%), and nausea ($n=8$; 53.3%) (Table 3).

The most frequently reported (>30%) AEs of grade ≥ 3 suspected to be related to study treatment in the lacnotuzumab plus gem-carbo arm were neutropenia ($n=25$; 73.5%), and AST increased ($n=15$; 44.1%). Neutropenia ($n=12$; 80.0%) was the most common grade ≥ 3 AE

suspected to be related to study treatment in the gem-carbo arm (Supplementary Table S3 and S4). Overall, hematologic AEs were common in both treatment arms, but patients treated with lacnotuzumab had higher frequencies of AST, ALT, and CPK elevations. No formal analyses of the association between drug exposure and hepatic toxicity were performed; however, data suggested that more patients treated with lacnotuzumab plus gem-carbo experienced grade 2 or higher ALT and/or AST elevations compared with those receiving gem-carbo alone (Supplementary Table S5).

In total, 17 patients (50.0%) in the lacnotuzumab plus gem-carbo arm and one patient (6.7%) in the gem-carbo arm experienced at least one serious AE (SAE), regardless of study treatment; the most frequently reported (≥ 2 patients) in the lacnotuzumab plus gem-carbo arm were dyspnea ($n=3$; 8.8%), thrombocytopenia ($n=3$; 8.8%), renal failure ($n=2$; 5.9%), and vomiting ($n=2$; 5.9%) (Table 3). In the gem-carbo arm, only one SAE (mastitis), was reported. Overall, eight patients (16.3%) experienced at least one SAE suspected to be related to study treatment, all of which occurred in the lacnotuzumab plus gem-carbo arm; the most frequent (≥ 2 patients) were thrombocytopenia ($n=3$; 8.8%) and renal failure ($n=2$; 5.9%).

The most frequently reported ($>20\%$) AEs of any grade regardless of study treatment requiring dose adjustment or study drug interruption in the lacnotuzumab plus gem-carbo arm were neutropenia ($n=24$; 70.6%), anemia ($n=8$; 23.5%), thrombocytopenia ($n=7$; 20.6%), and AST increased ($n=7$; 20.6%). In the gem-carbo arm, the most frequently reported ($>20\%$) AEs requiring dose adjustment or study drug interruption were neutropenia ($n=12$; 80.0%), thrombocytopenia ($n=5$; 33.3%), and anemia ($n=4$; 26.7%) (Supplementary Table S6). All of these AEs, requiring dose adjustment or interruption in both treatment arms, were considered treatment related, with the exception of one event of anemia in the lacnotuzumab plus gem-carbo arm. Patients treated with lacnotuzumab plus gem-carbo exhibited more frequent elevations in AST, ALT, and CPK leading to dose adjustment or interruption compared with patients treated with gem-carbo alone (AST increased: 20.6% vs. 0%; ALT increased: 17.6% vs. 6.7%; CPK increased: 8.8% vs. 0%) (Supplementary Table S6). On-treatment deaths were reported for three patients (6.1%). Two of the deaths were due to renal failure and occurred in patients treated with lacnotuzumab plus gem-carbo. Both cases assessed as related to study treatment. In the control arm, one patient died on treatment due to disease progression.

Pharmacokinetics and immunogenicity

Free lacnotuzumab exhibited pharmacokinetics of a typical human/humanized IgG, presumably due to saturable target mediated drug disposition at 10 mg/kg. Following a 1-hour IV infusion, mean lacnotuzumab plasma exposure (AUC for 21-day Cycle 1) was approximately 2-fold higher in patients receiving the additional dose on C1D8 compared with patients without the additional dose (mean AUC from 0 to end of dosing period [AUC_{tau}]: 3020 versus 1470 day $\times$ μ g/mL). After repeated Q3W dosing, free lacnotuzumab plasma exposure increased only slightly from Cycle 1 to Cycle 4. The half-life ranged from 6.28 to 19 days after single administration (Cycle 1), and 5.65 to 16.7 days after repeated administration (Cycle 4). The geometric mean for clearance was 0.3 mL/h/kg (coefficient of variation [CV]:17.7%) and the volume of distribution was approximately 91 mL/kg (CV: 19.8%), which is consistent with a limited extravascular distribution.

Carboplatin plasma exposure (AUC and maximum serum concentration [C_{max}]) was comparable in both the arms during Cycle 1 and Cycle 4; overall there appeared to be no obvious pharmacokinetic interaction with lacnotuzumab. Gemcitabine plasma exposure (AUC and C_{max}) was comparable in both the arms during Cycle 1 but approximately 2- to 3-fold lower in the lacnotuzumab plus gem-carbo arm compared with the gem-carbo arm, during Cycle 4. This difference in observed exposure between the two arms was believed to be related to inter-patient variability, rather than a pharmacokinetic drug–drug interaction.

Notably, lacnotuzumab was not immunogenic in this population; all evaluable post-baseline samples tested were negative for anti-lacnotuzumab antibodies.

Pharmacodynamics and biomarkers

Following lacnotuzumab treatment, a rapid and time-dependent accumulation of total CSF-1 was seen in the plasma. This indicated a slow clearance of the lacnotuzumab–CSF-1 complex, relative to the known high turnover rate of free circulating CSF-1 (Figure 3). This suggested a successful target engagement. Total plasma CSF-1 levels remained elevated above baseline between administrations of lacnotuzumab, indicating a sustained target saturation and therefore supporting the selection of Q3W dosing. A trend towards an overall decrease in cluster of differentiation 163 (CD163)+ TAMs was observed upon treatment with lacnotuzumab; however, inter-patient variability was high. In addition, no obvious treatment-induced changes from baseline were seen in CD8+ TIL counts.

Discussion

Early study termination leading to a significantly reduced sample size prevented conduct of the primary analysis. Nonetheless, data from the enrolled 50 patients with TNBC were analyzed in order to determine whether lacnotuzumab is associated with any added beneficial effects when combined with chemotherapy. Efficacy results did not demonstrate any significant difference in median PFS between the lacnotuzumab plus gem-carbo and the gem-carbo arms. Observed ORR and CBR was higher in the gem-carbo arm, whereas median DOR was higher in the lacnotuzumab plus gem-carbo arm compared with the gem-carbo combination. However, patient numbers are small and none of the observed ORR, CBR, and DOR demonstrate any statistically significant difference between the arms.

Serious adverse events, grade ≥ 3 AEs, and AEs leading to treatment discontinuation were more frequent in patients treated with lacnotuzumab plus gem-carbo versus gem-carbo alone. Furthermore, treatment-related AEs leading to dose reductions and interruptions occurred in 97% of patients treated with lacnotuzumab plus gem-carbo compared with 80% of patients treated with gem-carbo alone. Of note, patients treated with the lacnotuzumab + gem-carbo combination exhibited a higher frequency of AST, ALT, and CPK elevations resulting in dose reductions and interruptions than patients treated with gem-carbo alone. Dose reductions and interruptions with a resulting lower dose intensity of chemotherapy could have been a possible explanation for the lack of benefit seen with the addition of lacnotuzumab. However, no significant differences were reported in the exposure to gem-carbo between the treatment arms.

Pharmacokinetic results showed that free CSF-1 was dramatically depleted in plasma (demonstrated by the rapid time-dependent accumulation of total CSF-1 following lacnotuzumab treatment at 10 mg/kg). However, a similar sustained depletion of free CSF-1 in the tumor microenvironment is unlikely. Tumor cells are known to overly express and secrete CSF-1, promoting an anti-inflammatory and pro-tumor environment (23). High CSF-1 concentrations, in addition to an expected high CSF-1 turnover rate, would require a local drug concentration threshold which can be sustained throughout the dosing interval. Therefore, it is plausible that a 10 mg/kg dose level of lacnotuzumab may not be a high enough concentration to saturate and maintain a depleted state of CSF-1 in the tumor microenvironment. An effective drug concentration would be potent enough to promote an antitumor environment, resulting in tumor shrinkage that is clinically relevant. In tumor-bearing mice, a study of tissue distribution and tumor penetration of an anti-PD-L1 monoclonal antibody (mAb), showed the minimum tumor

interstitial to plasma radioactivity ratio was ~ 0.3 , and the distribution of the anti-PD-L1 antibody into tumors was dose and time dependent (24). This limited biodistribution and tumor penetration for mAbs suggests that the estimated lacnotuzumab dose based on serum pharmacokinetics and pharmacodynamics may not accurately reflect the tumor microenvironment concentrations required to produce a clinical effect. In addition, due to the overlapping toxicities seen with the study treatments, it was not always possible to combine lacnotuzumab at the recommended dose with the chemotherapy doublet, leading to frequent dose interruptions and reductions of lacnotuzumab. It is possible that efficacy may have been improved with higher and more consistent dosing of lacnotuzumab; however, toxicity was dose limiting.

It is also possible that only targeting circulating CSF-1 ligand (or M-CSF) may not be enough to suppress CSF-1-mediated effects via its target receptor CSF-1R. The activation of CSF-1R can also be achieved independently by interleukin 34 (IL-34), and no obvious differences in the downstream signaling pathways triggered by both ligands in monocytes have been reported to date. In cancer, similar to CSF-1, IL-34 promotes the recruitment of M2-polarized TAMs by having a direct effect on CSF-1R, promoting new vessel formation and the extravasation of immune cells (25). A recent study also showed that IL-34 and M-CSF expression correlated with poor survival in lung cancer patients (26). Interestingly, the poorest survival was associated with the highest co-expression of IL-34 and M-CSF, compared with cancers that showed a weak or completely absent expression of IL-34 and M-CSF (26).

Finally, CD163 expression by immunohistochemistry in primary tumor samples was chosen to select patients with high TAM content in this study. Upon treatment with lacnotuzumab, an expected decrease in CD163+ TAMs were observed. Despite this, no additional benefit in terms of neither increased ORR nor prolonged PFS was seen in the triple combination arm. This may be due to multiple reasons. Firstly, inter-patient variability in CD163 changes upon treatment was high. CD163 is also a pan-macrophage and monocyte marker and is currently not considered as a very specific marker of M2 macrophages. As it is now possible to precisely identify TAMs through the use of multiple markers in addition to CD163, such as Sialic Acid Binding Ig Like Lectin 1 (SIGLEC1) (27), cluster of differentiation 204 (CD204) (28) and CSF1R (26), it is possible that the use of a multiplex strategy to identify TAMs may have resulted in a better selection of patients with high TAM content. This may have led to better response rates in this patient population. Overall, patient selection will be an important inclusion criterion to consider for future studies of anti-CSF-1R agents in TNBC. Therapeutic strategies involving

TAMs continue to be investigated with a wide range of agents including those that aim to activate antitumor activity as well as those aiming to inhibit survival, recruitment, and function related to tumor promotion (29).

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Figures/tables

Table 1. Patient demographics and characteristics.

	Arm 1: Lacnotuzumab + gem-carbo n=34	Arm 2: Gem-carbo n=16	All patients N=50
Median age, years (range)	56.5 (32–78)	56.0 (29–77)	56.0 (29–78)
Race, n (%)			
Caucasian	25 (73.5)	11 (68.8)	36 (72.0)
Asian	4 (11.8)	3 (18.8)	7 (14.0)
Unknown	4 (11.8)	1 (6.3)	5 (10.0)
Other	1 (2.9)	1 (6.3)	2 (4.0)
ECOG performance status, n (%)			
0	21 (61.8)	11 (68.8)	32 (64.0)
1	12 (35.3)	5 (31.3)	17 (34.0)
2	1 (2.9)	0	1 (2.0)
Histologic grade, n (%)			
Well differentiated	1 (2.9)	0	1 (2.0)
Moderately differentiated	7 (20.6)	2 (12.5)	9 (18.0)
Poorly differentiated	19 (55.9)	12 (75.0)	31 (62.0)
Undifferentiated	0	0	0
Unknown	7 (20.6)	2 (12.5)	9 (18.0)
Stage at initial diagnosis, n (%)			
I	3 (8.8)	2 (12.5)	5 (10.0)
II	12 (35.3)	5 (31.3)	17 (34.0)
III	11 (32.4)	5 (31.3)	16 (32.0)
IV	7 (20.6)	3 (18.8)	10 (20.0)
Unknown ^a	1 (2.9)	1 (6.3)	2 (4.0)
Prior antineoplastic therapy			
Yes	34 (100)	16 (100)	50 (100)
Surgery			
Yes	34 (100)	16 (100)	50 (100)
Radiotherapy			
No	10 (29.4)	8 (50.0)	18 (36.0)
Yes	24 (70.6)	8 (50.0)	32 (64.0)
Medication: other therapy setting^b			
Adjuvant	9 (26.5)	7 (43.8)	16 (32.0)
Neoadjuvant	13 (38.2)	6 (37.5)	19 (38.0)
Therapeutic ^c	1 (2.9)	0	1 (2.0)

^aThis is due to no additional information from the study sites.

^bA patient may have had multiple settings.

^cAny antineoplastic agent given to treat cancer except in the adjuvant and neoadjuvant setting.

Table 2. Best overall response (investigator assessed according to RECIST v1.1), by treatment arm.

<i>N</i> (%)	Arm 1: Lacnotuzumab + gem-carbo <i>n</i> =34	Arm 2: Gem-carbo <i>n</i> =16
Best overall response		
CR	0	0
PR	8 (23.5)	6 (37.5)
Non-CR/Non-PD	1 (2.9)	0
SD	19 (55.9)	7 (43.8)
PD	4 (11.8)	1 (6.3)
Unknown ^a	2 (5.9)	2 (12.5)
ORR: CR+PR	8 (23.5)	6 (37.5)
90% exact CI	12.3, 38.5	17.8, 60.9
CBR: CR+PR+SD ≥6 mo	10 (29.4)	7 (43.8)
90% exact CI	16.9, 44.8	22.7, 66.7

^aTarget lesion biopsied or patients not treated or discontinued from study treatment before evaluation.mo, months; PD, progressive disease; SD, stable disease.

Table 3. Adverse events (in ≥20% of all patients) and serious adverse events (in ≥2 patients) regardless of study drug relationship.

Preferred term, <i>n</i> (%)	Arm 1: Lacnotuzumab + gem-carbo <i>n</i> =34		Arm 2: Gem-carbo <i>n</i> =15		All patients <i>N</i> =49	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	34 (100)	34 (100)	15 (100)	12 (80.0)	49 (100)	46 (93.9)
Hepatotoxicity						
AST increased	28 (82.4)	16 (47.1)	4 (26.7)	1 (6.7)	32 (65.3)	17 (34.7)
ALT increased	23 (67.6)	9 (26.5)	2 (13.3)	1 (6.7)	25 (51.0)	10 (20.4)
Hematologic toxicity						
Anemia	23 (67.6)	9 (26.5)	10 (66.7)	5 (33.3)	33 (67.3)	14 (28.6)
Neutropenia ^b	18 (52.9)	18 (52.9)	8 (53.3)	8 (53.3)	26 (53.1)	26 (53.1)
Thrombocytopenia	16 (47.1)	10 (29.4)	8 (53.3)	1 (6.7)	24 (49.0)	11 (22.4)
Neutrophil count decreased ^b	11 (32.4)	11 (32.4)	5 (33.3)	4 (26.7)	16 (32.7)	15 (30.6)
Platelet count decreased	6 (17.6)	2 (5.9)	6 (40.0)	3 (20.0)	12 (24.5)	5 (10.2)
Gastrointestinal toxicity						
Nausea	22 (64.7)	1 (2.9)	8 (53.3)	0	30 (61.2)	1 (2.0)
Vomiting	8 (23.5)	2 (5.9)	2 (13.3)	0	10 (20.4)	2 (4.1)
Constipation	8 (23.5)	0	2 (13.3)	0	10 (20.4)	0
Diarrhea	7 (20.6)	0	3 (20.0)	0	10 (20.4)	0
Other						
Fatigue	15 (44.1)	2 (5.9)	4 (26.7)	0	19 (38.8)	2 (4.1)
CPK increased	16 (47.1)	10 (29.4)	0	0	16 (32.7)	10 (20.4)
Periorbital edema	14 (41.2)	1 (2.9)	0	0	14 (28.6)	1 (2.0)
Rash	10 (29.4)	0	4 (26.7)	0	14 (28.6)	0
Dyspnea	11 (32.4)	3 (8.8)	2 (13.3)	0	13 (26.5)	3 (6.1)
Asthenia	7 (20.6)	0	4 (26.7)	0	11 (22.4)	0
Headache	7 (20.6)	0	4 (26.7)	0	11 (22.4)	0
Any SAE	17 (50.0)	15 (44.1)	1 (6.7)	1 (6.7)	18 (36.7)	16 (32.7)
Dyspnea	3 (8.8)	3 (8.8)	0	0	3 (6.1)	3 (6.1)
Thrombocytopenia	3 (8.8)	3 (8.8)	0	0	3 (6.1)	3 (6.1)
Renal failure	2 (5.9)	2 (5.9)	0	0	2 (4.1)	2 (4.1)
Vomiting	2 (5.9)	1 (2.9)	0	0	2 (4.1)	1 (2.0)

^aA patient with multiple severity grades for an AE was only counted under the maximum grade.

^bCombined numbers of patients with MedDRA preferred terms of “neutropenia” and “neutrophil count decreased” were calculated from listings and are reported in the text of the Safety section.

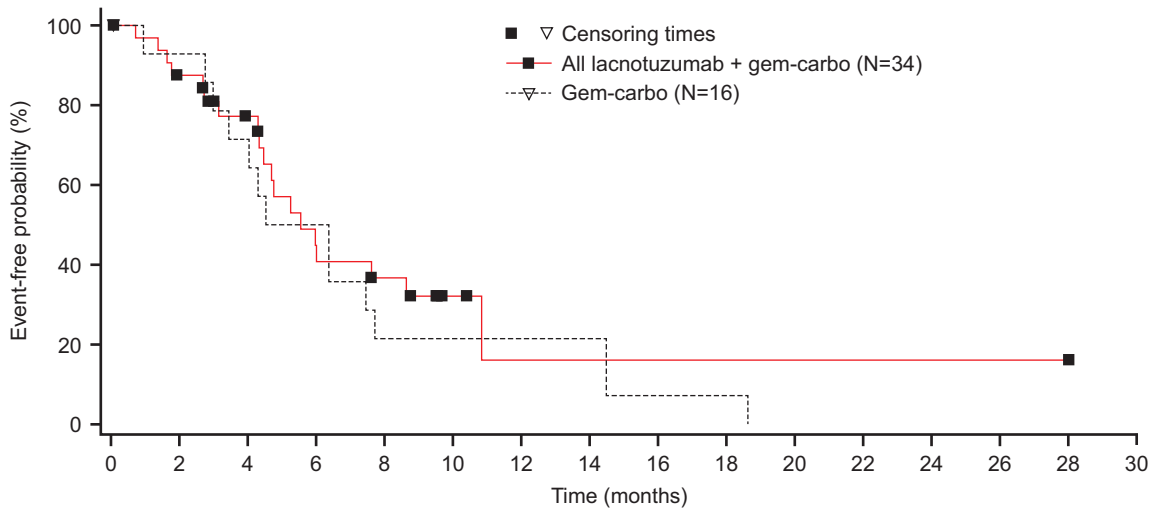
Figure legends

Figure 1. Progression-free survival (PFS). Kaplan–Meier plot of PFS in patients treated with lacnotuzumab plus gem-carbo (n=34) versus gem-carbo alone (n=16).

Figure 2. Duration of response. Duration of response in responding patients treated with lacnotuzumab plus gem-carbo (n=8) versus gem-carbo (n=6). PD, progressive disease.

Figure 3. Mean CSF-1 concentration profile. Linear plot of mean CSF-1 concentration profiles for lacnotuzumab plus gem-carbo with and without the additional dose of lacnotuzumab on Day 8 of Cycle 1.

Figure 1



Number of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
All lacnotuzumab + gem-carbo	34	27	20	11	8	3	1	1	1	1	1	1	1	1	1	0
Gem-carbo	16	13	10	7	3	3	3	3	1	1	0	0	0	0	0	0

Figure 2

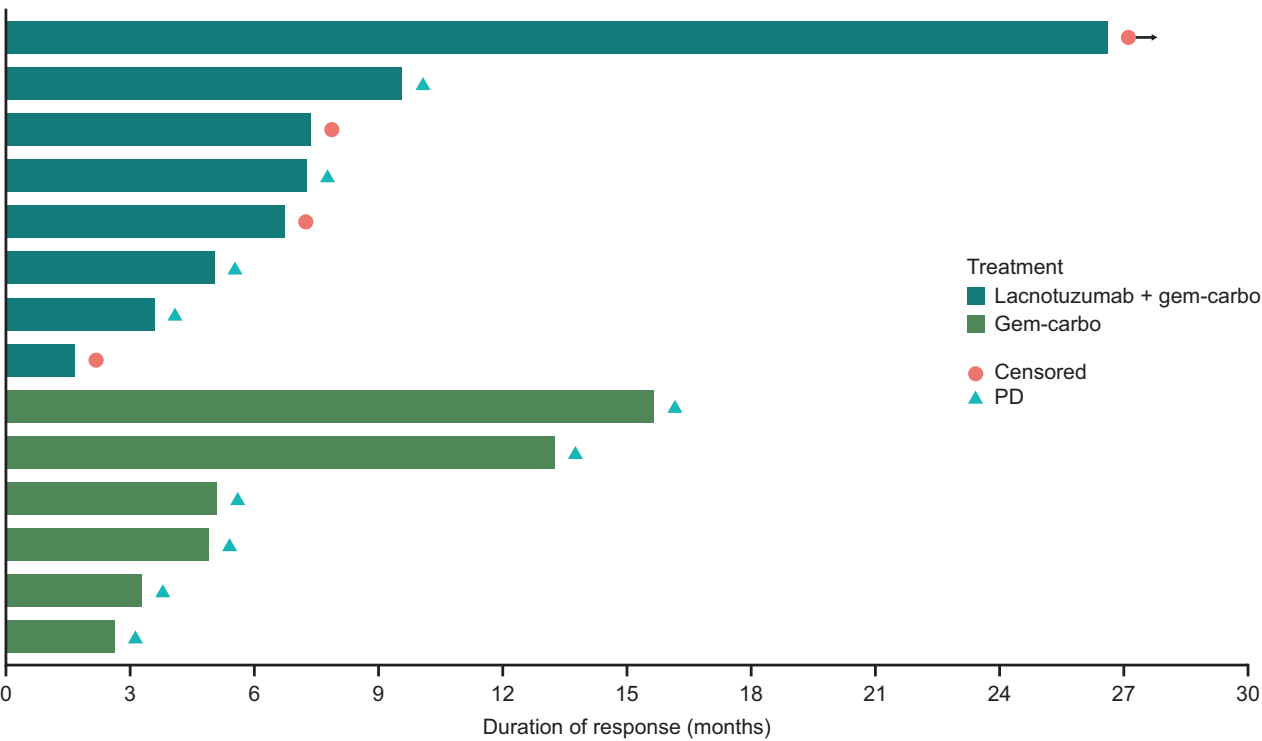


Figure 3

