HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ONTRUZANT safely and effectively. See full prescribing information for ONTRUZANT.

ONTRUZANT (trastuzumab-dttb) for injection, for intravenous use
Initial U.S. Approval: 2019

ONTRUZANT (trastuzumab-dttb) is biosimilar* to HERCEPTIN (trastuzumab)

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

See full prescribing information for complete boxed warning

Cardiomyopathy: trastuzumab products can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Ontruzant for cardiomyopathy. (2.3, 5.1)

Infusion Reactions, Pulmonary Toxicity: Discontinue Ontruzant for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

Embryo-Fetal Toxicity: Exposure to trastuzumab products during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.3)

----------INDICATIONS AND USAGE----------

Ontruzant is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer. (1.1, 1.2)
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. (1.3)

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product (1, 2.1).

----------DOSAGE AND ADMINISTRATION----------

For intravenous (IV) infusion only. Do not administer as an IV push or bolus. (2.2)

Do not substitute Ontruzant (trastuzumab-dttb) for or with ado-trastuzumab emtansine. (2.2)

Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1, 2.1)

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.2)

Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel and carboplatin). One week after the last weekly dose of Ontruzant, administer 6 mg/kg as an IV infusion over 30 to 90 minutes every three weeks to complete a total of 52 weeks of therapy, or
- Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30 to 90 minutes IV infusion every three weeks for 52 weeks.

Metastatic HER2-Overexpressing Breast Cancer (2.2)

- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.

Metastatic HER2-Overexpressing Gastric Cancer (2.2)

- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

----------DOSAGE FORMS AND STRENGTHS----------

- For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Exacerbation of Chemotherapy-Induced Neutropenia. (5.5, 6.1)

----------ADVERSE REACTIONS----------

Adjuvant Breast Cancer

- Most common adverse reactions (≥ 5%) are headache, diarrhea, nausea, and chills. (6.1)

Metastatic Breast Cancer

- Most common adverse reactions (≥ 10%) are fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash. (6.1)

Metastatic Gastric Cancer

- Most common adverse reactions (≥ 10%) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of Ontruzant (8.3).

See 17 for PATIENT COUNSELING INFORMATION.

* Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of Ontruzant has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 01/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

Cardiomyopathy

Administration of trastuzumab products can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Ontruzant. Discontinue Ontruzant treatment in patients receiving adjuvant therapy and withhold Ontruzant in patients with metastatic disease for clinically significant decrease in left ventricular function *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

Infusion Reactions; Pulmonary Toxicity

Administration of trastuzumab products can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of administration. Interrupt Ontruzant infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Ontruzant for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome *[see Warnings and Precautions (5.2, 5.4)]*.

Embryo-Fetal Toxicity

Exposure to trastuzumab products during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*.

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

Ontruzant is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature *[see Clinical Studies (14.1)]*) breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product *[see Dosage and Administration (2.1)]*.

1.2 Metastatic Breast Cancer

Ontruzant is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product *[see Dosage and Administration (2.1)]*.

1.3 Metastatic Gastric Cancer

Ontruzant is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens *[see Indications and Usage (1) and Clinical Studies (14)]*. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

2.2 Recommended Doses and Schedules

- **Do not administer as an intravenous push or bolus. Do not mix Ontruzant with other drugs.**
- **Do not substitute Ontruzant (trastuzumab-dttb) for or with ado-trastuzumab emtansine.**

Adjuvant Treatment, Breast Cancer:
Administer according to one of the following doses and schedules for a total of 52 weeks of Ontruzant therapy:
During and following paclitaxel, docetaxel, or docetaxel and carboplatin:

- Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an

intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel and carboplatin).
- One week following the last weekly dose of Ontruzant, administer Ontruzant at 6 mg/kg as an intravenous infusion over 30 to 90 minutes every three weeks.

As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens:
- Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
- Subsequent doses at 6 mg/kg as an intravenous infusion over 30 to 90 minutes every three weeks *[see Dosage and Administration (2.3)]*.
- Extending adjuvant treatment beyond one year is not recommended *[see Adverse Reactions (6.1)]*.

Metastatic Treatment, Breast Cancer:
- Administer Ontruzant, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as a 90-minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30-minute intravenous infusions until disease progression.

Metastatic Gastric Cancer:
- Administer Ontruzant at an initial dose of 8 mg/kg as a 90-minute intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30 to 90 minutes every three weeks until disease progression *[see Dosage and Administration (2.3)]*.

2.3 Important Dosing Considerations

If the patient has missed a dose of Ontruzant by one week or less, then the usual maintenance dose (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent Ontruzant maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of Ontruzant by more than one week, a re-loading dose of Ontruzant should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) as soon as possible. Subsequent Ontruzant maintenance doses (weekly schedule: 2 mg/kg; three-weekly schedule 6 mg/kg) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

Infusion Reactions

[see Boxed Warning, Warnings and Precautions (5.2)]
- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Discontinue Ontruzant for severe or life-threatening infusion reactions.

Cardiomyopathy

[see Boxed Warning, Warnings and Precautions (5.1)]

Assess left ventricular ejection fraction (LVEF) prior to initiation of Ontruzant and at regular intervals during treatment. Withhold Ontruzant dosing for at least 4 weeks for either of the following:
- ≥ 16% absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and ≥ 10% absolute decrease in LVEF from

pretreatment values.

Ontruzant may be resumed if, within 4 to 8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%.

Permanently discontinue Ontruzant for a persistent (> 8 weeks) LVEF decline or for suspension of Ontruzant dosing on more than 3 occasions for cardiomyopathy.

2.4 Preparation for Administration

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Ontruzant (trastuzumab-dttb) and not ado-trastuzumab emtansine.

150 mg Single-dose vial

Reconstitution: Reconstitute each 150 mg vial of Ontruzant with 7.4 mL of Sterile Water for Injection (SWFI) (not supplied) to yield a single-dose solution containing 21 mg/mL trastuzumab-dttb that delivers 7.15 mL (150 mg trastuzumab-dttb).

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject 7.4 mL of SWFI (not supplied) into the vial containing the lyophilized powder of Ontruzant, which has a cake-like appearance. The stream of diluent should be directed into the cake. The reconstituted vial yields a solution for single-dose use, containing 21 mg/mL trastuzumab-dttb.
- Gently swirl and invert the vial to aid reconstitution. **DO NOT SHAKE**.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Use the Ontruzant solution immediately following reconstitution with SWFI, as it contains no preservative and is intended for single-dose only. If not used immediately, store the reconstituted Ontruzant solution for up to 24 hours at 2° to 8°C (36° to 46°F); discard any unused Ontruzant after 24 hours. **Do not freeze.**

Dilution:

- Determine the dose (mg) of Ontruzant *[see Dosage and Administration (2.1)]*.
- Calculate the volume of the 21 mg/mL reconstituted Ontruzant solution needed
- Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- Gently invert the bag to mix the solution.
- The solution of Ontruzant for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2° to 8°C (36° to 46°F) for no more than 24 hours prior to use. Discard after 24 hours. This storage time is additional to the time allowed for the reconstituted vials. **Do not freeze**.

3 DOSAGE FORMS AND STRENGTHS

For injection: 150 mg of Ontruzant as a white to pale yellow, preservative-free lyophilized powder in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death *[see Boxed Warning: Cardiomyopathy]*. Trastuzumab products can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

There is a 4 to 6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving trastuzumab products as a single agent or in combination therapy compared with those not receiving trastuzumab products. The highest absolute incidence occurs when a trastuzumab product is administered with an anthracycline.

Withhold Ontruzant for ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values *[see Dosage and Administration (2.3)]*. The safety of continuation or resumption of Ontruzant in patients with trastuzumab product-induced left ventricular cardiac dysfunction has not been studied.

Patients who receive anthracycline after stopping Ontruzant may also be at increased risk of cardiac dysfunction *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

Cardiac Monitoring: Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:

- Baseline LVEF measurement immediately prior to initiation of Ontruzant
- LVEF measurements every 3 months during and upon completion of Ontruzant
- Repeat LVEF measurement at 4 week intervals if Ontruzant is withheld for significant left ventricular cardiac dysfunction *[see Dosage and Administration (2.3)]*
- LVEF measurements every 6 months for at least 2 years following completion of Ontruzant as a component of adjuvant therapy.

In Study 1, 15% (158/1031) of patients discontinued trastuzumab due to clinical evidence of myocardial dysfunction or significant decline in LVEF after a median follow-up duration of 8.7 years in the AC-TH (anthracycline, cyclophosphamide, paclitaxel, and trastuzumab) arm. In Study 3 (one-year trastuzumab treatment), the number of patients who discontinued trastuzumab due to cardiac toxicity at 12.6 months median duration of follow-up was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) of patients in the TCH (docetaxel, carboplatin, trastuzumab) arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) of

patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued trastuzumab due to cardiac toxicity.

Among 64 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive heart failure, one patient died of cardiomyopathy, one patient died suddenly without documented etiology, and 33 patients were receiving cardiac medication at last follow-up. Approximately 24% of the surviving patients had recovery to a normal LVEF (defined as ≥ 50%) and no symptoms on continuing medical management at the time of last follow-up. Incidence of congestive heart failure (CHF) is presented in Table 1. The safety of continuation or resumption of Ontruzant in patients with trastuzumab product-induced left ventricular cardiac dysfunction has not been studied.

Table 1

Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

		Incidence of CHF	
Study	Regimen	Trastuzumab	Control
1 & 2[a]	AC[b] → Paclitaxel + Trastuzumab	3.2% (64/2000)[c]	1.3% (21/1655)
3[d]	Chemo → Trastuzumab	2% (30/1678)	0.3% (5/1708)
4	AC[b] → Docetaxel + Trastuzumab	2% (20/1068)	0.3% (3/1050)
4	Docetaxel + Carbo + Trastuzumab	0.4% (4/1056)	0.3% (3/1050)

[a] Median follow-up duration for studies 1 and 2 combined was 8.3 years in the AC → TH arm.
[b] Anthracycline (doxorubicin) and cyclophosphamide.
[c] Includes 1 patient with fatal cardiomyopathy and 1 patient with sudden death without documented etiology.
[d] Includes NYHA II-IV and cardiac death at 12.6 months median duration of follow-up in the one-year trastuzumab arm.

In Study 3 (one-year trastuzumab treatment), at a median follow-up duration of 8 years, the incidence of severe CHF (NYHA III & IV) was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Table 2

Incidence of Cardiac Dysfunction[a] in Metastatic Breast Cancer Studies

		Incidence			
		NYHA I-IV		NYHA III−IV	
Study	Event	Trastuzumab	Control	Trastuzumab	Control
5 (AC)[b]	Cardiac Dysfunction	28%	7%	19%	3%
5 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
6	Cardiac Dysfunction[c]	7%	N/A	5%	N/A

[a] Congestive heart failure or significant asymptomatic decrease in LVEF.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[c] Includes 1 patient with fatal cardiomyopathy.

In Study 4, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the trastuzumab containing regimens (AC-TH: 0.3% (3/1068) and TCH: 0.2% (2/1056)) as compared to none in AC-T.

5.2 Infusion Reactions

Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia *[see Adverse Reactions (6.1)]*.

In post-marketing reports, serious and fatal infusion reactions have been reported. Severe reactions, which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable, including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

Interrupt Ontruzant infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered (which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen). Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with trastuzumab products after experiencing a severe infusion reaction. Prior to resumption of trastuzumab infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated trastuzumab infusions, others had recurrent severe infusion reactions despite pre-medications.

5.3 Embryo-Fetal Toxicity

Trastuzumab products can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Verify the pregnancy status of females of reproductive potential prior to the initiation of Ontruzant. Advise pregnant women and females of reproductive potential that exposure to Ontruzant during pregnancy or within 7 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of Ontruzant *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.3)]*.

5.4 Pulmonary Toxicity

Trastuzumab product use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions *[see Warnings and Precautions (5.2)]*. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

5.5 Exacerbation of Chemotherapy-Induced Neutropenia

In randomized, controlled clinical trials, the per-patient incidences of NCI-CTC Grade 3 to 4 neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab and those who did not *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiomyopathy *[see Warnings and Precautions (5.1)]*
- Infusion Reactions *[see Warnings and Precautions (5.2)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.4)]*
- Exacerbation of Chemotherapy-induced Neutropenia *[see Warnings and Precautions (5.5)]*

The most common adverse reactions in patients receiving trastuzumab products in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of trastuzumab product treatment include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity *[see Dosage and Administration (2.3)]*.

In the metastatic gastric cancer setting, the most common adverse reactions ($\geq$ 10%) that were increased ($\geq$ 5% difference) in the patients receiving trastuzumab as compared to patients receiving chemotherapy alone were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most common adverse reactions which resulted in discontinuation of trastuzumab treatment in the absence of disease progression were infection, diarrhea, and febrile neutropenia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adjuvant Breast Cancer Studies

The data below reflect exposure to one-year trastuzumab therapy across three randomized, open-label studies, Studies 1, 2, and 3, with (n = 3678) or without (n = 3363) trastuzumab in the adjuvant treatment of breast cancer.

The data summarized in Table 3 below, from Study 3, reflect exposure to trastuzumab in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18. Among the 3386 patients enrolled in the observation and one-year trastuzumab arms of Study 3 at a median duration of follow-up of 12.6 months in the trastuzumab arm, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil). All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients were also required to have adequate cardiac function (e.g., LVEF > 50%).

On the trastuzumab-containing arm, trastuzumab was administered as an IV infusion at an initial dose of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms cisplatin was administered at a dose of 80 mg/m^2 Day 1 every 3 weeks for 6 cycles as a 2 hour IV infusion. On both study arms, capecitabine was administered at 1000 mg/m^2 dose orally twice daily (total daily dose 2000 mg/m^2) for 14 days of each 21 day cycle for 6 cycles. Alternatively, continuous intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m^2/day from Day 1 through Day 5 every three weeks for 6 cycles.

The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1; 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant therapy, and 2% had received prior radiotherapy.

The main outcome measure of Study 7 was overall survival (OS), analyzed by the unstratified log-rank test. The final OS analysis based on 351 deaths was statistically significant (nominal significance level of 0.0193). An updated OS analysis was conducted at one year after the final analysis. The efficacy results of both the final and the updated analyses are summarized in Table 13 and Figure 7.

Table 13

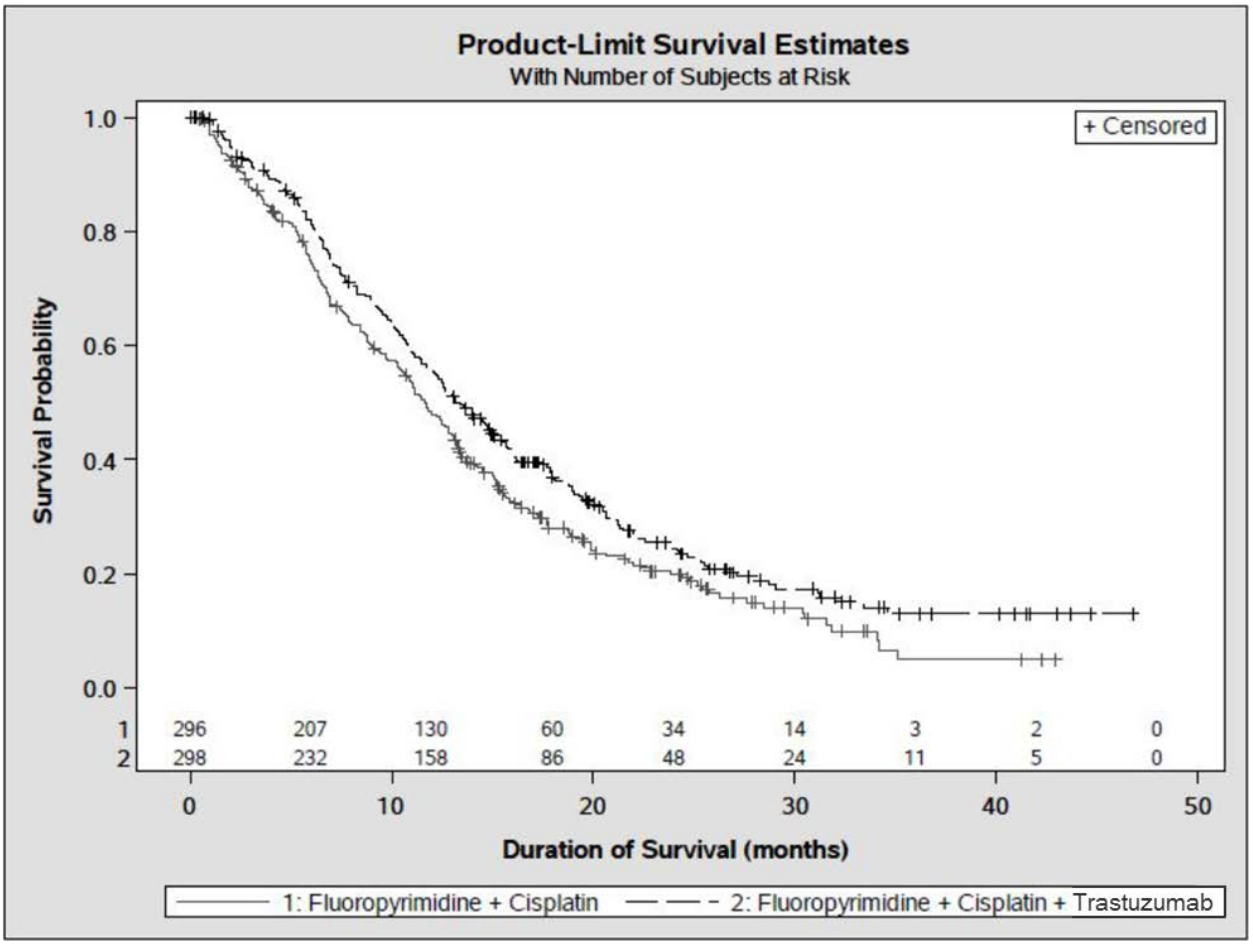
Study 7: Overall Survival in ITT Population

	FC Arm N = 296	FC + T Arm N = 298
Definitive (Second Interim) Overall Survival		
No. Deaths (%)	184 (62.2%)	167 (56.0%)
Median	11.0	13.5
95% CI (mos.)	(9.4, 12.5)	(11.7, 15.7)
Hazard Ratio	0.73	
95% CI	(0.60, 0.91)	
p-value*, two-sided	0.0038	
Updated Overall Survival		
No. Deaths (%)	227 (76.7%)	221 (74.2%)
Median	11.7	13.1
95% CI (mos.)	(10.3, 13.0)	(11.9, 15.1)
Hazard Ratio	0.80	
95% CI	(0.67, 0.97)	

*Comparing with the nominal significance level of 0.0193.

Figure 7

Updated Overall Survival in Patients with Metastatic Gastric Cancer (Study 7)



An exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein overexpression (IHC) testing is summarized in Table 14.

Table 14

Exploratory Analyses by HER2 Status Using Updated Overall Survival Results

	FC (N = 296)[a]	FC+T (N = 298)[b]
FISH+ / IHC 0, 1+ subgroup (N=133)		
No. Deaths (%) / n (%)	57/71 (80%)	56/62 (90%)
Median OS Duration (mos.)	8.8	8.3
95% CI (mos.)	(6.4, 11.7)	(6.2, 10.7)
Hazard ratio (95% CI)	1.33 (0.92, 1.92)	
FISH+ / IHC2+ subgroup (N=160)		
No. Deaths (%) / n (%)	65/80 (81%)	64/80 (80%)
Median OS Duration (mos.)	10.8	12.3
95% CI (mos.)	(6.8, 12.8)	(9.5, 15.7)
Hazard ratio (95% CI)	0.78 (0.55, 1.10)	
FISH+ or FISH- / IHC3+[c] subgroup (N=294)		
No. Deaths (%) / n (%)	104/143 (73%)	96/151 (64%)
Median OS Duration (mos.)	13.2	18.0
95% CI (mos.)	(11.5, 15.2)	(15.5, 21.2)
Hazard ratio (95% CI)	0.66 (0.50, 0.87)	

[a] Two patients on the FC arm who were FISH+ but IHC status unknown were excluded from the exploratory subgroup analyses.

[b] Five patients on the trastuzumab-containing arm who were FISH+, but IHC status unknown were excluded from the exploratory subgroup analyses.

[c] Includes 6 patients on chemotherapy arm, 10 patients on trastuzumab arm with FISH–, IHC3+ and 8 patients on chemotherapy arm, 8 patients on trastuzumab arm with FISH status unknown, IHC 3+.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Ontruzant (trastuzumab-dttb) for injection 150 mg/vial is supplied in a single-dose vial as a white to pale yellow lyophilized sterile powder, under vacuum. Each carton contains one single-dose vial of Ontruzant.

NDC 0006-5033-02.

16.2 Storage

Store Ontruzant vials in the refrigerator at 2° to 8°C (36° to 46°F) until time of reconstitution.

17 PATIENT COUNSELING INFORMATION

Cardiomyopathy

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness *[see Boxed Warning: Cardiomyopathy]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential that Ontruzant exposure during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of Ontruzant *[see Use in Specific Populations (8.3)]*.

Ontruzant [trastuzumab-dttb]

SAMSUNG
BIOEPIS

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