Approval Date: on June 9, 2021

Instruction Manual of Disitamab Vedotin For Injection

This product is conditionally approved, please read the instructions carefully and use it under the guidance of your doctor

[Drug Name]

Product name: Aidix

English name: Disitamab Vedotin For Injection

Chinese Pinyin: Zhusheyong Weidixituo Dankang

[Ingredients]

Active ingredient: Disitamab Vedotin is an antibody-drug conjugate with a drug structure consisting of three parts: (1) Anti-human epidermal growth factor receptor 2 extracellular domain (HER2 ECD) antibody; (2) Linker (MC-Val-Cit-PAB, Linker); (3) Cytotoxic Monomethyl Auristatin E (Monomethyl Auristatin E, MMAE).

Excipients: histidine hydrochloride, mannitol, sucrose, polysorbate 80, sodium hydroxide.

[Properties]

This product is white to light yellow loose body, after reconstitution, it is colorless to light yellow clear liquid.

[Indications]

This product is suitable for patients with locally advanced or metastatic gastric cancer with overexpression of HER2 (including adenocarcinoma of gastroesophageal junction) who have received at least 2 systematic chemotherapy. HER2 overexpression is defined as 2 + or 3 + detected by HER2 immunohistochemistry.

This indication is based on the conditional approval given by the results of an II phase single arm clinical trial in patients with locally advanced or metastatic gastric cancer (including gastroesophageal junction adenocarcinoma) with overexpression of HER2. Full approval of this indication will depend on whether ongoing confirmatory randomized controlled clinical trials can confirm the clinical benefits of the product in this population.

[Specification]

Each vial contains Disitamab Vedotin 60 mg.

After reconstitution, each milliliter of solution contains 10 mg of Disitamab Vedotin.

This product is a lyophilized preparation.

[Usage and Dosage]

This product should be prescribed by doctors who are experienced in anti-tumor therapy.

Patient Selection

Patients treated with this product should be identified as HER2 overexpression tumors, and HER2 overexpression is defined as an immunohistochemical (IHC) score of 2 + or 3 +. The test must be carried out in a professional laboratory to ensure the reliability of the results. For a complete description of the test performance and explanation, please refer to the relevant HER2 test and analysis manual.

Recommended Dose

2.5 mg/kg, every two weeks, intravenous drip (intravenous injection or rapid intravenous administration is prohibited).

Drug Preparation

After taking out the product, it should be dissolved, diluted and administered at room temperature within 4 hours. The specific steps are as follows:

Re-dissolve: this product is a freeze-dried preparation. Each dose (60 mg) of this product is re-dissolved with 6 ml sterilized water for injection. The concentration of the solution is 10 mg Disitamab Vedotin per ml. During resuscitation, the flow of sterilized injection water should be directed toward one side of the bottle and added slowly along the bottle wall to minimize foam formation. During the period of resuscitation, place the bottle at room temperature and rotate slowly for about 60 seconds. Violent concussion is strictly prohibited and rest until the foam subsides. After the drug is dissolved, rotate gently again, and the liquid will be completely mixed. The re-dissolution is usually completed within 10 minutes after the addition of sterilized water for injection. After resuscitation, the solution is colorless to yellowish clear liquid.

Discard if visible particles are observed.

Because the product contains no preservatives, any remaining medicine in the vial should be discarded.

Required drug dose = body weight (kg) X2.5 (mg/kg)

Required number of drug sticks = required drug dose (mg) + 60 (mg/piece)

Note 1: 2.5 indicates that the subjects received a dose of 2.5mg/kg. If dose adjustment is needed, the dose is calculated according to the actual kg body weight after adjustment.

Note 2: if the calculated drug number is not an integer, the required number is the integer part of the calculation result + 1.

Example: The body weight is 70.0 kg, and the intended dose is 2.5 mg/kg, then the required dose is 70.0 kg X 2.5 mg/kg = 175.0 mg. The number of sticks required for calculation is 175 mg: 60 (mg/piece) = 2.9 pieces, and the whole number is 2 (the integer part of 2.9) + 1 = 3 pieces.

Dilution: the re-soluble solution obtained from the above steps, calculated according to the body weight, was added to 0. 9% sodium chloride injection or 5% glucose injection for dilution.

The dosage is calculated according to body weight as follows:

1) if the required dose is a multiple of the whole dose according to the body weight, use a syringe to remove all the re-soluble solution from the vial.

Example: if the body weight is 48.0 kg, the intended dose is 2.5mg/kg, the required dose is 120.0 mg, and the calculated number is 2. After dissolving with sterilized water for injection, use a syringe to extract the re-soluble solution from 2 vials and add it to 0.9% sodium chloride injection or 5% glucose injection for dilution.

2) If the required amount of medicine calculated according to the body weight is a non-integer multiple, it is recommended that the amount drawn from the non-integer bottle be rounded to the nearest 0.1 mL during the calculation, and the required amount is drawn with a syringe.

Example: If the body weight is 70.0 kg, the intended dose is 2.5 mg/kg, and the required dose is 175.0 mg, the required number of medicines is 2.9, and the whole number is 3, and the reconstituted solution is prepared.

The volume of the reconstituted solution to be drawn from the non-integer bottle is (175-60X2) +10mg/mL=5.5mL. Therefore, use a syringe to exhaust all the reconstituted solution in the two vials, and accurately extract 5.5 mL of the reconstituted

solution from the third vial and add it to 0.9% sodium chloride injection or 5% glucose injection for dilution. .

Dosing regimen:

The mode of administration is intravenous infusion, and intravenous bolus injection or rapid intravenous administration is prohibited. It takes 30-90 minutes (usually about 60 minutes is recommended). During infusion, if infusion-related reactions or hypersensitivity reactions occur, slow or interrupt infusion, and/or administer appropriate medical treatment. Discontinue medication immediately for life-threatening infusion-related reactions.

Dose adjustment

Hematological abnormalities

Hematological Abnormalities		
Common Adverse Events Terminology Evaluation Criteria (CTCAE) classification	Advice on treatment during treatment	Dosage Adjustment Recommendations
Level 1 - Level 2	Maintain the original dose	2.5 mg/kg
Level 3		
Appear for the first time	Suspend medication and treat symptomatically until recovery to Level 0-1 or pre-treatment level	2.5 mg/kg
Appear for the second time	Suspend medication and treat symptomatically until recovery to Level 0-1 or pre-treatment level	2.0 mg/kg
Appear for the third time	Suspend medication and treat symptomatically until recovery to Level 0-1 or pre-treatment level	1.5 mg/kg
Appear for the fourth time	Stop treatment or If the doctor believes that it is more beneficial for the patient to continue the treatment, the drug will be suspended, and the symptomatic treatment will be continued until the remission reaches Level 0-1 or the level before treatment.	NA
Level 4		
Appear for the first time	Suspend the drug and treat symptomatically until it recovers to Level 0-1 or the level before treatment.	2.0 mg/kg

Appear for the second time	Stop treatment or If the doctor believes that it is more beneficial for the patient to continue the treatment, the drug will be suspended and the symptomatic treatment will be continued until the remission reaches Level 0-1 or the level before starting the treatment.	NA

If the patient has drug-related ⩾Level 3 hematological abnormalities (such as: ⩾ Level 3 white blood cell count, ≥Level 3 neutrophil count decreased, etc.), it is recommended to perform hematological examinations twice a week. If the patient does not return to CTCAE < Level 1 or the level before the start of treatment after 28 days of discontinuation, treatment is recommended to be discontinued.

Elevated transaminase

Elevated transaminase		
CTCAE classification	Advice on treatment during treatment	Dosage Adjustment Recommendations
Level 1 - Level 2	Maintain the original dose	2.5 mg/kg
Level 3		
Appear for the first time	Suspend medication and treat symptomatically until recovery to Level 0-2 or pre-treatment level	2.0 mg/kg
Appear for the second time	Suspend the drug and treat symptomatically until it recovers to Level 0-2 or the level before treatment.	1.5mg/kg
Appear for the third time	Stop treatment or If the doctor believes that it is more beneficial for the patient to continue the treatment, the drug will be suspended, and the symptomatic treatment will be continued until the remission reaches Level 0-1 or the level before treatment.	NA
Level 4		
Appear for the first time	Stop treatment	NA

If the patient has drug-related ≥ Level 3 transaminase elevations, it is recommended to perform blood chemistry tests twice a week. If the patient does not return to CTCAE level 0-2 or the level before the start of treatment after 28 days of discontinuation,

treatment is recommended to be discontinued.

Sensory abnormality

Sensory abnormality		
CTCAE classification	Advice on treatment during treatment	Dosage Adjustment Recommendations
Level 1	Maintain the original dose	2.5 mg/kg
Level 2	Suspend the drug and treat symptomatically until it recovers to Level 0-1 or the level before treatment.	2.0 mg/kg
Level 3		
Appear for the first time	Suspend the drug and treat symptomatically until it recovers to Level 0-1 or the level before treatment.	1.5 mg/kg
Appear for the second time	Stop treatment or If the doctor believes that it is more beneficial for the patient to continue the treatment, the drug will be suspended, and the symptomatic treatment will be continued until the remission reaches Level 0-1.	NA

If the patient has drug-related sensory abnormalities (such as numbness, etc.) and does not return to the level at which medication can be continued after 28 days of suspension, treatment is recommended.

Other Adverse Reactions

If patients have other drug-related adverse events and have significant clinical significance, and have not recovered to CTCAE < 1 before the next administration, they can suspend the use of drugs or reduce the dose. If it does not return to the level at which the medication can continue within 28 days (calculated according to the predetermined date of administration), the patient needs to stop treatment. "Significant clinical significance" and "correlation" are based on the doctor's judgment, for example, alopecia may be judged to be drug-related, but may not be evaluated as significant clinical significance.

Dose description for special population:

Patients with liver insufficiency: patients with mild liver function damage do not need to adjust the dose. At present, the effect of moderate and severe liver function damage

on the pharmacokinetics of this product has not been investigated.

Patients with renal insufficiency: patients with mild to moderate renal dysfunction do not need to adjust the dose. At present, the pharmacokinetics of patients with severe renal damage has not been evaluated, and there is no research data on patients with severe renal damage.

[Adverse Reactions]

Clinical Trial Experience

Clinical trials are conducted under different conditions, so the incidence of adverse reactions observed in one drug clinical trial cannot be directly compared with that in another drug clinical trial, and may not reflect the incidence in clinical practice.

Summary of security features

The safety of Disitamab Vedotin for Injection has been evaluated in 350 subjects with malignancies, including subjects who received Disitamab Vedotin for Injection in the pivotal gastric cancer clinical trial C008(N=127), the gastric cancer-based solid tumor phase I clinical trial C002 (N=57), and 3 clinical trials in other tumor types: 24 cases of C001 (all breast cancer patients), 43 cases of C005 (all urothelial carcinoma patients), and 99 cases of C006 (all breast cancer patients).

The median administration time of this product was 18.00 weeks (range: 2.00-99.86 weeks). 28.3% of the subjects were treated with this product for 26 months, and 9.1% of the subjects were treated with this product for 12 months.

Common laboratory adverse reactions include hematological abnormalities (decreased white blood cell count, decreased neutrophil count) and increased transaminase (aspartate aminotransferase, alanine aminotransferase). The common clinical symptoms and signs of adverse reactions include alopecia, fatigue, hypoesthesia, etc. The following table summarizes the common adverse reactions (≥5%) in 350 subjects in these five clinical trials according to CTCAE classification.

Table-1. Common (≥5%) Adverse Reactions Classified by CTCAE

System organ classification	Disitamab Vedotin For Injection (N=350)	
Preferred term	all levels n (%)	≥Level 3 n(%)
Various inspections	304 (86.9%)	91 (26.0%)

Decreased white blood cell count	194 (55.4%)	38 (10.9%)
Decreased neutrophil count	177 (50.6%)	59 (16.9%)
Elevated aspartate aminotransferase	174 (49.7%)	9 (16%)
Elevated alanine aminotransferase	150 (42.9%)	6 (1.7%)
Weight loss	66 (18.9%)	1 (0.3%)
Decreased platelet count	56 (16.0%)	4(1.1%)
Elevated gamma-glutamyltransferase	49 (14.0%)	13 (3.7%)
Decreased hemoglobin	42 (12.0%)	4 (1.1%)
Conjugated bilirubin rises	37 (10.6%)	6 (1.7%)
Elevated blood bilirubin	36 (10.3%)	2 (0.6%)
Elevated serum alkaline phosphatase	31 (8.9%)	0
Urine protein detection	24 (6.9%)	1 (0.3%)
Elevated blood lactate dehydrogenase	24 (6.9%)	0
Decreased lymphocyte count	20 (5.7%)	5(1.4%)
Skin and subcutaneous tissue diseases	231 (66.0%)	2 (0.6%)
Hair loss	191 (54.6%)	2 (0.6%)
Pruritus	51 (14.6%)	0
Rash	41 (11.7%)	0
Gastrointestinal diseases	200 (57.1%)	13 (3.7%)
Nausea	109 (31.1%)	1 (0.3%)
Vomit	64 (18.3%)	2 (0.6%)
Constipate	41 (11.7%)	0
Diarrhea	40(11.4%)	1 (0.3%)
Stomach ache	26 (7.4%)	0
Bloating	25 (7.1%)	0
Various neurological diseases	201 (574%)	50 (14.3%)
Hypoesthesia	143 (40.9%)	31 (8.9%)
Neurotoxicity	22 (6.3%)	9 (2.6%)
Dizziness	18 (5.1%)	0
Peripheral neuropathy	18 (5.1%)	4(1.1%)
Systemic disease and administration site reactions	197 (56.3%)	23 (6.6%)
Fatigue	162 (46.3%)	14 (4.0%)
Fever	39(11.1%)	1 (0.3%)
Pain	19(5.4%)	2 (0.6%)
Metabolic and nutritional diseases	150 (42.9%)	20 (5.7%)
Loss of appetite	85 (24.3%)	0
Hypertriglyceridemia	24 (6.9%)	10 (2.9%)
Hypokalemia	18 (5.1%)	3 (0.9%)
Various musculoskeletal and connective tissue disorders	85 (24.3%)	5 (1.4%)
Joint pain	31 (8.9%)	1 (0.3%)
Limb pain	27 (7.7%)	2 (0.6%)
Myalgia	19 (5.4%)	2 (0.6%)
Blood and Lymphatic System Disorders	81(23.1%)	11 (3.1%)

Anemia	79 (22.6%)	9 (2.6%)
Hepatobiliary disease	24 (6.9%)	4(1.1%)
Abnormal liver function	19 (5.4%)	4(1.1%)

Immunogenicity

All therapeutic protein drugs have the possibility of immunogenicity. The incidence of anti-drug antibody (ADA) is closely related to the sensitivity and specificity of the detection method, and is affected by many factors, including the method of analysis, the method of sample processing, the time of sample collection, the combination of drugs, and other basic diseases of the patients. Therefore, the incidence of ADA in different products should be carefully compared.

Based on the clinical studies of C001 CANCER and C002 CANCER, bridged electrochemiluminescence immunoassay (Bridging-ECLIA) was used to detect the production of ADA in serum of 80 patients with advanced solid tumor before and after intravenous administration of Disitamab Vedotin (dose range 0.5 mg/kg-3.0 mg/kg). A total of 19 patients showed ADA positive before and after administration of this product, with a total incidence of 23.8%. Of the 80 patients, 69 patients collected ADA data after administration, of which 3 patients (4.3%) were positive for baseline ADA, and the rest were baseline ADA negative. Among the patients with baseline ADA positive, 1 was ADA negative after administration, 2 were transient positive for ADA after administration, 11 (15.9%) were transient positive for ADA after administration of baseline ADA negative, and 4 (5.8%) were persistent positive for ADA after administration. The results showed that the incidence of persistent positive ADA was low, but due to the limited data available, it was not possible to judge the effect of ADA on the pharmacokinetics, safety and efficacy of this product.

[Taboo]

Those who are allergic to the active ingredients or excipients under [ingredients] in this manual are prohibited.

[Precautions]

Blood Toxicity

Patients treated with this product often have hematological abnormalities characterized

by granulocytopenia. Hematological adverse reactions in 350 patients included 55.4% of patients with leukocytopenia (10.9% ≥ Level 3), 50.6% of patients with neutrophil count (16.9% ≥ Level 3), 16.0% of patients with thrombocytopenia (1.1% ≥ Level 3), and 12.0% of the patients had a decrease in hemoglobin (1.1% of which was ≥ Level 3).

Before each treatment of this product, or when there is a clinical indication, the patient's blood routine should be monitored. When hematological abnormalities occur, the dose should be adjusted and symptomatic treatment should be given according to the degree of hematological abnormalities. For the method of dose adjustment, please refer to the chapter [Usage and Dosage].

Elevated Transaminase

Among the patients treated with this product, elevation of transaminase was common in 0350 patients, 49.7% of the patients had an increase in drug-related aspartate aminotransferase (2.6% ≥ Level 3), and 42.9% of patients had an increase in drug-related alanine aminotransferase (1.7% ≥ Level 3).

Before each treatment of this product, or when there is a clinical indication, the patient's liver function index should be monitored. When there is an increase in transaminase, the dose should be adjusted and symptomatic treatment should be given according to the degree of transaminase. The method of dose adjustment refers to the chapter [Usage and Dosage].

Sensory abnormality.

The sensory abnormalities related to this product are mainly manifested as hypoesthesia (numbness), and most of the parts are found in the hands and feet.

Of the 350 patients, 40.9% had drug-related hypoesthesia and 8.9% had Level 3 or more. During treatment, patients should be monitored for new or aggravated sensory abnormal symptoms and signs, and dose adjustment and symptomatic treatment should be given according to the degree of neurotoxicity. For the method of dose adjustment, please refer to the section of [Usage and Dosage]. If necessary, a neurologist should be asked to make differential diagnosis and treatment.

Reproductive Toxicity

Based on the results of animal experiments, this product may be potentially toxic to male reproductive system and embryo-fetal development.

Female patients should have a pregnancy test before they begin to receive treatment with this product. Female patients who are likely to give birth are advised to use appropriate methods of contraception during treatment and within at least 180 days after treatment. It is recommended that male patients whose spouses are likely to have children during treatment and within at least 180 days after treatment.

Use appropriate methods of contraception.

[Medication For Pregnant and Lactating Women]

The safety and efficacy of this product in pregnant women have not been established. Spouses of women or men of childbearing age should be advised to avoid pregnancy during treatment with this product. If the drug is used during pregnancy, or during pregnancy, the doctor should inform the patient of the potential harm to the fetus. Appropriate methods of contraception should be used during treatment and at least 180 days after the end of treatment.

It is not clear whether this product and its metabolites are excreted by human milk.

[Medicine for Children]

The safety and efficacy of this product in children and adolescents under the age of 18 have not been established.

[Medication for the Elderly]

Among the 350 patients treated with this product, 77 (22%) were more than 65 years old. There was no significant difference in effectiveness and safety between these patients and the whole population.

[Medicine Interactions]

The drug-drug interaction of this product has not been formally studied in patients. In order to characterize the potential drug-drug interaction of free MMAE, another drug-drug interaction study of ADC, which is coupled with the same cytotoxin monomethylolastatin E (MMAE), is described below.

Effects of other drugs on Disitamab Vedotin for Injection:

CYP3A4 potent inhibitors: other ADC drugs coupled with MMAE combined with

ketoconazole (a potent inhibitor of CYP3A4) will increase the exposure of free MMAE, as shown by a 25% increase in Cmax and a 34% increase in AUC; there is no effect on ADC exposure. It is speculated that when this product is combined with CYP3A4 strong inhibitory preparation, the effect on the exposure of free MMAE and binding antibody is the same as that of this ADC drug.

CYP3A4 potent inducer: other ADC drugs coupled with MMAE combined with rifampicin (a potent inducer of CYP3A4) will reduce the exposure of free MMAE, as shown by a 44% reduction in Cmax and a 46% reduction in AUC; there is no effect on ADC exposure. It is speculated that when this product is combined with CYP3A4 strong inducer, the effect on the exposure of free MMAE and binding antibody is the same as that of this ADC drug.

Effects of Disitamab Vedotin for Injection on other drugs:

Substrate of CYP3A4: other MMAE-coupled ADC drugs combined with midazolam (a sensitive substrate of CYP3A4) did not affect midazolam exposure. It is speculated that this product will not affect the exposure of drugs metabolized by CYP3A4 enzyme.

[Drug Overdose]

No cases of overdose have been reported in clinical trials. In the event of overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment should be administered promptly.

[Clinical Trials]

Gastric cancer (including gastroesophageal junction adenocarcinoma): Study C008

The C008 study is an open, multicenter, single-arm II phase clinical trial conducted in patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the gastroesophageal junction) with overexpression of HER2 (defined as 2 + or 3 + by HER2 immunohistochemistry) who have received at least 2 systematic chemotherapy. The primary endpoint of the study was objective response rate (ORR) as assessed by the Independent Response Review Committee (IRC) according to RECIST 1.1 criteria. Secondary endpoints were investigator-assessed ORR, Progression Free Survival (PFS), Overall Survival (OS), Duration of Response (DOR), Time to Progression (TTP), Disease Control Rate (DCR). The safety index is adverse

events, etc.

A total of 127 patients were enrolled and received Disitamab Vedotin For Injection 2.5 mg/kg, intravenous infusion, every 2 weeks until disease progression, intolerable toxicity, death or withdrawal of informed consent. The ratio of male to female was 93: 34, the median age was 58 years (range: 24-70 years), and the median course of disease was 17.1 months (range: 3.8-94.5 months). More than half of the patients (71 cases, 55.9%) had liver metastasis and 57 cases (44.9%) had lung metastasis. Nearly half of the patients (60 cases, 47.2%) had received 3 or more lines of treatment in the past, and most of them had an ECOG score of 1 (98 cases, 77.2%). The number of patients with 2 + and 3 + results of HER2 immunohistochemical examination (IHC) was equal, 61 cases (48.0%) and 64 cases (50.4%), respectively.

The 0RR of IRC evaluation was 24.4% (95% confidence interval: 17.2%, 32.8%), the median duration of remission (DOR) was 4.7 months (95% confidence interval: 33.0%, 50.8%), the disease control rate (DCR) was 41.7% (95% confidence interval: 33.0%, 50.8%), and the ORR evaluated by the researchers was 23.6% (95% confidence interval: 16.5%, 32.0%). The median PFS of the total population was 4.1 months (95% confidence interval: 3.5,4.8), and the median OS was 7.9 months (95% confidence interval: 6.7,9.6).

Table-2. IRC-Assessed Efficacy Outcomes (FAS Set)

	Disitamab Vedotin For Injection (N = 127)
Objective response rate (ORR) n (%) (95% CI)	31 (24.4) (17.2, 32.8)
Best Response Evaluation (BOR) n (%):	
Complete remission (CR)	0 (0.0)
Partial remission (PR)	31 (24.4)
Stable disease (SD)	22 (17.3)
disease progression (PD)	38 (29.9)
Not Evaluable (NE)	36 (28.3)
Disease Control Rate (DCR) n (%)	53 (41.7) (33.0,50.8)
(95% CI)	4.7 (3.4, 6.9)
Median duration of response (months) (95% CI)	
Progression Free Survival (PFS)	109 (85.8)
Number of events, n (%)	4.1 (3.5,4.8)

Median (months) (95% CI)	25.8 (18.0, 34.2)
6-month PFS rate (%) (95% CI)	
Overall survival (OS)	99 (78.0)
Number of events, n (%)	7.9 (6.7, 9.6)
Median overall survival (months) (95% CI)	63.9 (54.8, 71.6)
6-month OS rate (%) (95% CI)	32.8 (24.6, 41.3)

Subgroup population analysis (IRC assessment).

According to the expression level of HER2 at baseline:

Immunohistochemical method was used to analyze the expression of HER2 in tumor tissue samples at baseline, including 61 subjects with IHC2+, ORR of 23.0% (95% confidence interval: 13.2% 35.5%) and 64 subjects with IHC3+, ORR of 26.6% (95% confidence interval: 16.3%, 39.1%). The results of IHC detection of HER2 in tumor tissues of 2 subjects were unknown (but the results of FISH were positive), and the corresponding therapeutic results were not combined and analyzed.

Analysis based on previous treatment with Herceptin ®(trastuzumab):

74 subjects had previously received Herceptin ®treatment, the ORR was 27.0% (95% confidence interval: 17.4%, 38.6%); 53 subjects had not received Herceptin ®treatment, the ORR was 20.8% (95% confidence zone: 10.8%, 34.1%).

Table-3. Efficacy Outcomes in Key Subgroups Evaluated by IRC (FAS Set)

	Disitamab Vedotin For Injection (N=127)			
	HER2 expression level*		Have received Herceptin® in the past	
	IHC2+ (n=61)	IHC3+ (n=64)	Yes (n=74)	No (n=53)
Objective response rate (ORR) n (%) (95% CI)	14 (23.0) (13.2, 35.5)	17 (26.6) (163, 39.1)	20 (27.0%) (17.4, 38.6)	11 (20.8%) (10.8, 34.1)
Best Response Evaluation (BOR) n(%):				
Complete remission (CR)	0	0	0	0
Partial remission (PR)	14 (23.0)	17(26.6)	20 (27.0%)	11 (20.8%)
Stable disease (SD)	11 (18.0)	11 (17.2)	13 (17.6%)	9 (17.0%)
disease progression (PD)	17 (27.9)	19 (29.7)	26 (35.1%)	12 (22.6%)
Not Evaluable (NE)	19(31.1)	17 (26.6)	15 (20.3%)	21 (39.6%)
Disease Control Rate (DCR) n (%) (95% CI)	25 (41.0) (28.6, 54.3)	28 (43.8) (31.4, 56.7)	33 (44.6%) (33.0, 56.6)	20 (37.7%) (24.8, 52.1)
Median Duration of Response	4.7 (2.4, 6.9)	4.2	5.6 (2.9, 8.3)	4.1 (2.4,

(months) (95% CI)		(2.8,14.6)		5.2)
Progression Free Survival (PFS)				
Number of events, n(%)	53 (86.9%)	54 (84.4%)	62 (83.8%)	47 (88.7%)
Median (months) (95% CI)	4.0 (2.7, 4.9)	41(2.8,5.4)	4.1 (2.8,5.4)	4.0 (2.7, 4.8)
6-month PFS rate (95% CI)	0.228 (0.125, 0.350)	0.294 (0182, 0.415)	0.296 (0.190, 0.410)	0.204 (0.102, 0.331)
Overall survival (OS)				
Number of events, n(%)	49 (80.3%)	48 (75.0%)	56 (75.7%)	43 (81.1%)
Median overall survival (months) (95% CI)	7.1 (5.3, 9.5)	9.0 (7.2,11.3)	7.9 (7.1, 9.5)	7.5 (4.8, 12.1)
6-month OS rate (95% CI)	0.578 (0.443, 0.692)	0.699 (0.570, 0.797)	0.709 (0.590, 0.800)	0.540 (0.396, 0.664)
12-month OS rate (95% CI)	0.312 (0,198, 0.434)	0.354 (0.236, 0.473)	0.289 (0.187, 0.399)	0.381 (0.250, 0.511)

* Since the IHC test results of 2 subjects' HER2 are unknown (but the FISH results are positive), the corresponding curative effect results are not included in the above table for analysis.

[Pharmacology and Toxicology]

Pharmacological Action

Disitamab Vedotin is a new type of antibody coupling drug targeting HER2 (ADC), which is formed by coupling the recombinant humanized HER2 IgGl monoclonal antibody with the microtubule inhibitor monomethylolastatin E (MMAE) through the linker. After the antibody of Disitamab Vedotin partially binds to the extracellular domain of HER2 on the cell surface, the ADC complex is swallowed and transported to the lysosome, and the linker is digested to release the microtubule inhibitor MMAE, which destroys the intracellular microtubule network and leads to mitotic cell cycle arrest and cell apoptosis. In addition, in vitro studies have shown that Disitamab Vedotin can inhibit HER2 receptor signal and has antibody dependent cell-mediated cytotoxicity (ADCC).

Toxicology Study

Genotoxicity:

The small molecule of Disitamab Vedotin is microtubule inhibitor MMAE. MMAE Ames test in vitro and L5178Y mouse lymphoma mutation test were negative, but bone marrow micronucleus test in rats was positive.

Reproductive toxicity:

The fertility studies and embryo-fetal development studies have not been conducted with Disitamab Vedotin. In the 12-week toxicity test, when Disitamab Vedotin was injected intravenously every 2 weeks, the testes and epididymis atrophied when the dose was more than 6mg/kg (in terms of body surface area dose, about 0.39 times of the recommended clinical dose of 2.5 mg/kg). After 6 weeks of recovery, the testes and epididymis did not recover completely. The literature of ADC drugs with small molecular weight MMAE shows that embryo-fetal toxicity can be seen in pregnant rats treated with CD30-MMAE, including increased early absorption and loss after implantation, and appearance deformities (i.e. umbilical hernia and abnormal transposition of hindlimbs).

Carcinogenicity:

Carcinogenicity studies have not been conducted with Disitamab Vedotin or MMAE.

[Pharmacokinetics]

The pharmacokinetic characteristics of Disitamab Vedotin for Injection were evaluated through a phase I clinical study C002 CANCER and a Population Pharmacokinetics (PopPK) analysis of 88 patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the gastroesophageal junction). Study C002 CANCER enrolled 57 patients who received intravenous Disitamab Vedotin for Injection at doses ranging from 0.1 mg/kg to 3.0 mg/kg. After administration, three forms of analytes can be detected in serum: Bound antibody, total antibody and free MMAE that bind at least one MMAE. The pharmacokinetic results of this product are summarized below.

<u>Absorption</u>

After intravenous administration of Disitamab Vedotin for Injection, the concentration of drug in serum increased rapidly, and the concentration of binding antibody and total antibody reached the peak before and after infusion, while the concentration of free MMAE in serum reached the peak about 2 days after infusion. The peak concentrations

of binding antibody, total antibody and free MMAE were dose-dependent.

Distribution

In steady state, the average apparent distribution volume of total antibody was 72.09-87.18 mL/kg, and the apparent distribution volume of binding antibody was 124.71-340.81 mL/kg. According to the results of population pharmacokinetics, the apparent distribution volumes (VMc and VMp) of central and peripheral chambers of MMAE were estimated to be 29.0L and 59.3L, respectively.

Metabolism

In clinical studies, the exposure of free MMAE in serum has been at a low level. MMAE is not only the substrate of CYP3A4, but also the substrate of CYP2D6. In vitro data show that MMAE is mainly metabolized by CYP3A4/5.

Elimination

After a single dose of 2.0 mg/kg (Q2W) and 2.5 mg/kg (Q2W), the clearance rates of binding antibodies in serum were 2.80 ±0.65 mL/h/kg and 2.36 ±0.16mL/h/kg, respectively, and the half-lives of free MMAE were 33.07 + 11.66h and 45.69 + 17.62h, respectively, and the half-lives of free IgM were 66.51 ±45.12h and 63.97 ±17.59h, respectively. The median values of Ra ($_{cmax}$) and Ra ($_{AUC}$) in serum of subjects in 2. 0 mg/kg (Q2W) group and 2.5mg/kg (Q2W) group were close to 1. 0 after repeated administration, and no accumulation of binding antibody was observed after repeated administration. At the same time, there was no accumulation of free MMAE in serum after repeated administration.

The results of population pharmacokinetic model showed that age and muscle clearance rate (CrCL) had no effect on the pharmacokinetic characteristics of binding antibody and free MMAE. The effect of body weight on the distribution and clearance of binding antibodies and free MMAE has clinical significance. When the body weight of the patient was the median body weight of the study population, the clearance rates of conjugated antibody and free MMAE in serum were 0.178 L and 1.01 L, respectively, and the estimated elimination half-decay period was about 1.3d (31h) and 2.6d (62h), respectively.

[Storage]

Store and transport at 2~8°C away from light.

[Package]

1/box

Use medium borosilicate glass controlled injection bottles with bromide butyl rubber stoppers, each containing 60 mg of Disitamab Vedotin.

[Expiration Date]

24 months

[Execution Standard]

YBS00502021

[Approval Number]

Chinese medicine approved character S20210017

[Marketing Authorization Holder]

Name: Rongchang Biopharmaceutical (Yantai) Co., Ltd.

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[Manufacturer]

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To request drug information and to report adverse events, please call toll free 4001110266.