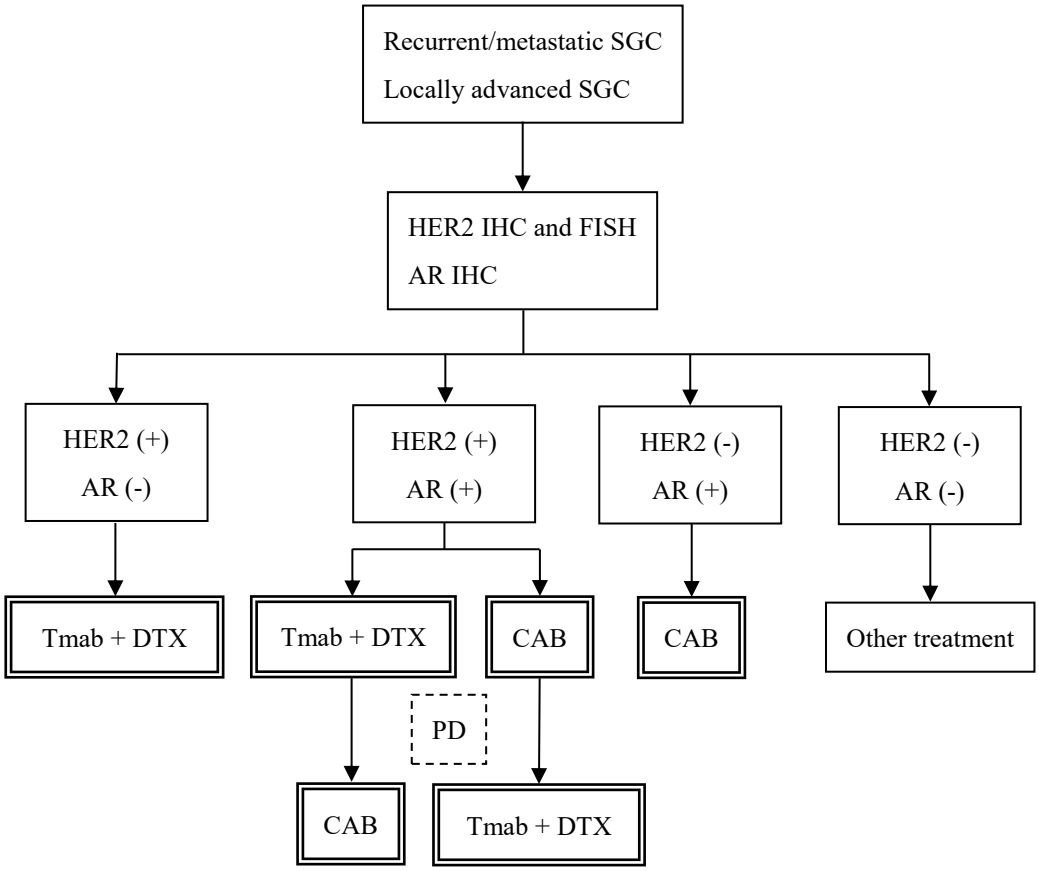
Study protocol

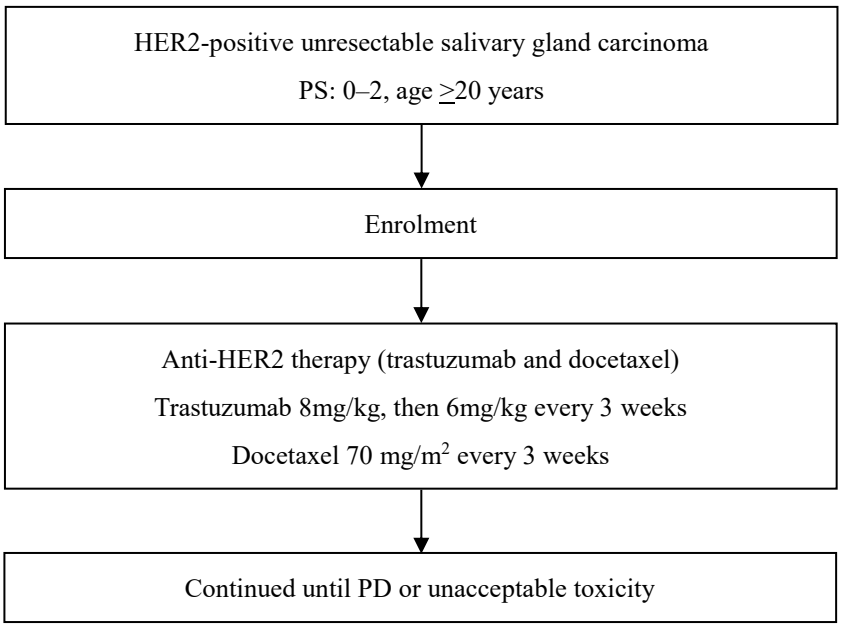
1 Summary (study ID: UMIN 000009437)

1.1 Study overview



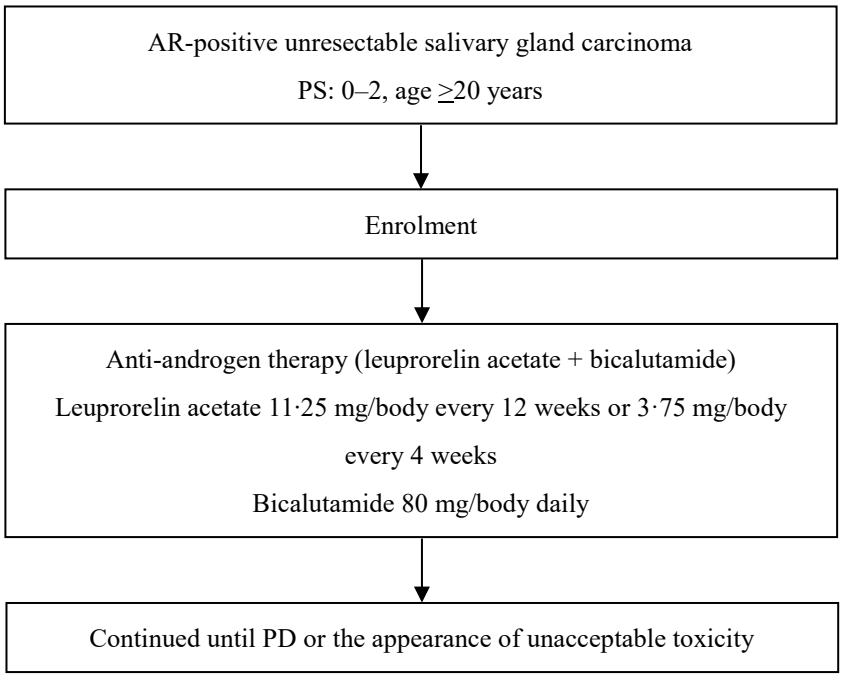
AR = androgen receptor; CAB = combined androgen blockade; DTX = docetaxel; FISH = fluorescence *in situ* hybridisation; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PD = progressive disease; SGC = salivary gland carcinoma; Tmab = trastuzumab

1.2 Regimen for HER2-positive salivary gland carcinoma



HER2 = human epidermal growth factor receptor 2; PD = progressive disease; PS = performance status

1.3 Regimen for androgen receptor-positive salivary gland carcinoma



AR = androgen receptor; PD = progressive disease; PS = performance status

2 Trastuzumab and docetaxel study

2.1 Objective

To evaluate the effectiveness and safety of trastuzumab plus docetaxel combination therapy in HER2-positive, unresectable, locally advanced and/or recurrent/metastatic salivary gland carcinoma.

2.2 Patient selection

2.2.1 Inclusion criteria

1) Histologically confirmed salivary gland carcinoma
2) Confirmed HER2 overexpression by either a score of 3 in immunohistochemistry or amplification of the *HER2* gene using fluorescence *in situ* hybridisation in tissue from the primary tumour or metastases
3) Eastern Cooperative Oncology Group (ECOG) performance status 0–2
4) Age ≥20 years
5) Survival expectancy ≥3 months
6) At least two weeks must have passed since the end of prior treatment (if administered).
7) Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, measurable disease
8) Adequately maintained functions of the main organs and screening laboratory values meeting the following criteria: haemoglobin ≥9.0 g/dL, white blood cell count ≥3,000/mm^3 and ≤12,000/mm^3, neutrophil count ≥2,000/mm^3, platelet count ≥75,000/mm^3, serum total bilirubin level at or below the upper limit of normal (ULN), aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤1.5 × ULN or alkaline phosphatase (ALP) level <2.5 × ULN, serum creatinine levels ≤1.5 × ULN
9) Written consent after a sufficient explanation of the study

2.2.2 Exclusion criteria

1) Cumulative dose of anthracycline derivatives >360 mg/m^2 (converted into a dose of doxorubicin)
2) Known history of drug allergies that may interfere with the study treatment
3) Known history of an allergy to polysorbate 80
4) Severe complications that cannot be controlled
5) Active double cancers/multiple primary cancers
6) Previous trastuzumab treatment
7) Known history of myocardial infarction, clinically significant cardiovascular disease, a left ventricular ejection fraction (LVEF) <50% or below the lower limit of normal (LLN), or heart failure according to the New York Heart Association (NYHA) functional classification II to IV
8) Fever, active, or suspected infection
9) Motor paralysis or peripheral neuropathy
10) Pleural effusion requiring treatment or pericardial fluid accumulation
11) Symptomatic brain metastasis

12) Oedema of Grade 2 or higher
13) Interstitial pneumonia or pulmonary fibrosis
14) Known history of psychological diseases or treatment for psychological diseases
15) (Possibly) pregnant women
16) Other conditions assessed as inappropriate for enrolment by the examining physician

2.3 Study design

Open-label, single-arm, single-centre, phase 2 trial

2.4 Treatment

2.4.1 Drug dosing

Docetaxel: 70 mg/m^2, intravenous injection, day 1, then every 3 weeks; 55 mg/m^2 for patients aged ≥75 years

Trastuzumab: 8 mg/kg (loading dose), then 6 mg/kg (maintenance dose), intravenous injection, day 1, then every 3 weeks

Patients are scheduled to receive six cycles of the combined treatment.

Docetaxel and trastuzumab are continued until progressive disease (PD) or unacceptable toxicity.

2.4.2 Dose modifications

2.4.2.1 Trastuzumab

2.4.2.1.1 Dose reduction

The trastuzumab dose will be recalculated in cases of changes in body weight greater than 10% (increase or decrease compared to the body weight before the start of the trial).

The dose will not be adjusted in response to toxicity. If the participant cannot tolerate trastuzumab, its administration will be discontinued. If the administration of trastuzumab is extended past the period detailed in the regulations for the administration of trastuzumab for any reason, the following procedure will be followed. In such a case, it is possible to administer both trastuzumab and docetaxel on the same days.

2.4.2.1.2 Postponed administration of trastuzumab

If the trastuzumab administration period is extended by ≤7 days (≤28 days since the last administration), 6 mg/kg of the drug will be administered after the extension without waiting for the next planned administration date. Thereafter, the patient will return to receiving 6 mg/kg every three weeks, in accordance with the previous schedule.

If the period is extended by ≥8 days (≥29 days or more since the last administration), 8 mg/kg of the drug will be administered over a 90-minute period after the extension without waiting for the next planned administration date. Three weeks thereafter, the patient will again begin to receive 6 mg/kg every three weeks.

In cases in which the physician in charge judges that there will be clinical benefits to trastuzumab treatment, patients who discontinue chemotherapy will be able to continue trastuzumab treatment. Moreover, trastuzumab administration will not be postponed, even if the administration of the chemotherapy agents is

postponed due to toxicity.

2.4.2.1.3 Postponement (temporary cessation) and discontinuation

In the events of asymptomatic/symptomatic decreased LVEF other adverse events, the physician responsible for the clinical trial can suspend the administration of trastuzumab from the scheduled date in units of 1 week, for up to 2 weeks (2 administrations total). However, if the administration is discontinued for >2 weeks, the patient will be withdrawn from this trial. In this case, the date of withdrawal from the trial will be two weeks after the date of the postponement initiation.

Participants with postponed trastuzumab administration may receive continuous docetaxel during the extension period; however, if the patient receives any other antitumour drugs, he/she will be withdrawn from the study.

1) Asymptomatic decreased left ventricular ejection fraction

To ensure the safety of the participants, trastuzumab administration will be postponed (temporarily ceased) or discontinued in participants with asymptomatic decreased LVEF in accordance with the standards for discontinuation due to symptomatic decreased LVEF fraction (see below) or the standards for resuming treatment (2.4.2.1.4).

2) Symptomatic decreased left ventricular ejection fraction

In cases of symptomatic decreased LVEF (such as shortness of breath, chest pain, fatigue, respiratory distress, or wheezing), the trastuzumab administration period will be postponed according to the following regulations.

The administration of trastuzumab will be discontinued in the event of a class III or IV heart failure, as defined by the NYHA functional classification. Moreover, trastuzumab administration will be postponed (ceased temporarily) in the event of class II heart failure, and the LVEF will be evaluated. A re-evaluation of the participant's LVEF will be conducted within three weeks of the final administration. If the LVEF is ≤44%, 45–49% and has decreased ≤10% from its value before administration, or if the event has not improved to class I heart failure, trastuzumab administration and the trial will be discontinued for this patient.

2.4.2.1.4 Standards for resuming treatment

After trastuzumab administration is postponed (temporarily ceased) due to asymptomatic or symptomatic decreased LVEF, administration can be resumed under the following conditions.

1) A re-evaluation of the LVEF performed within three weeks of the final administration shows an improvement to >49%
2) A re-evaluation of the LVEF performed within three weeks of the final administration shows an improvement to 45–49% and a decrease of ≤10% from its value before administration.

2.4.2.2 Docetaxel

2.4.2.2.1 Dose reduction

If one or more of the following conditions are present, the docetaxel dose can be decreased to 55 mg/m^2

and further reduced to a minimum of 45 mg/m^2. If the dose is decreased, the subsequent doses will also be decreased. If a further decrease below 45 mg/m^2 is necessary, the administration of docetaxel will be discontinued.

1) Febrile neutropenia (fever of 38·5°C and <1,000 neutrophils/m^3)
2) Grade 4 thrombocytopenia (<25,000/m^3)
3) Grade 3 or greater non-haematological adverse events other than nausea or vomiting
4) Grade 2 or greater neuropathy on the date of administration
5) The administration of docetaxel has been postponed for ≥8 days (≥29 days since the previous administration)
6) The physician responsible for the clinical trial judges that a decrease in the dose is necessary.

2.4.2.2.2 Discontinuation

Docetaxel will be discontinued under the following conditions:

1) The patient has not recovered from an AE from a previous treatment course six weeks after the treatment date and does not meet the standards for starting the next course of treatment.
2) Docetaxel is discontinued due to an AE, a further dose reduction is necessary even after two previous reductions, or an AE occurs in a patient aged ≥75 years, in accordance with the dose reduction standards described in 2.4.2.2.1.
3) Moderate AEs (Grade 2) due to hypersensitivity and the occurrence of more severe symptoms after treatment and the continuation of administration
4) Severe AEs (Grade 3) due to hypersensitivity
5) Symptomatic congestive heart failure (Grade 3 or 4 left ventricular failure)
6) Pleural effusion

2.4.2.2.3 Standards for resuming treatment

It will be verified that the participants satisfy the following standards at the time of administration. If they do not satisfy one or more of these standards, the administration of docetaxel will be postponed by one week at a time. The dose when treatment is resumed will be determined in accordance with the standards for changes in dosing (2.4.2.2.1). Postponement (temporary cessation) of docetaxel administration will be permitted for up to two weeks past the next scheduled administration date. If postponement in excess of this is required, docetaxel administration will be discontinued.

1) A minimum of three and maximum of six weeks have passed since the last treatment date in the previous course
2) Neutrophil count ≥1,500/mm^3
3) Platelet count ≥10,000/mm^3
4) Total bilirubin <1.5 mg/dL
5) AST/ALT levels lower than 1.5 times the ULN; maximum ALP levels lower than 2.5 times the ULN
6) Grade 2 or lower oedema and peripheral neuropathy

7) Grade 1 or lower non-haematological toxicity other than oedema, peripheral neuropathy, and alopecia
8) The physician responsible for the clinical trial judges that postponement of administration necessary

2.4.3 Combined therapy

Chemotherapy and hormone therapy agents that are assumed to affect the evaluation of the trial drug may not be used during the trial period.

There are no regulations regarding the use of preventative medication administered before the trial, preventative post-treatment medication, and other drugs to alleviate side effects (e.g. antiemetics, antibiotics, or granulocyte-colony stimulating factor).

Anti-receptor activator of nuclear factor kappa-B ligand (RANKL) monoclonal antibodies and bisphosphonates are not prohibited.

2.4.4 Endpoints

Primary endpoint: Overall response rate (ORR; percentage of cases with an overall CR or PR according to the RECIST, version 1.1)

Secondary endpoints: Clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and safety

2.5 Number of planned registrations and study period

Due to the rarity of this cancer type, a target for the number of patient registrations was not set.

Study period: 1 March 2012 to 31 March 2021, including the patients' follow-up period

3 Combined androgen blockade study

3.1 Objective

To evaluate the effectiveness and safety of anti-androgen therapy for androgen receptor (AR)-positive, unresectable, locally advanced and/or recurrent and/or metastatic salivary gland carcinoma

3.2 Patient selection

3.2.1 Inclusion criteria

1) Histologically confirmed salivary/lacrimal gland carcinoma
2) Confirmed AR expression in tissue from the primary tumour or metastases using immunohistochemistry
3) ECOG performance status 0–2
4) Age ≥20 years
5) Survival expectancy ≥3 months
6) At least two weeks must have passed since the end of prior treatment (if administered)
7) RECIST, version 1.1, measurable disease
8) Adequately maintained functions of the main organs and screening laboratory values meeting the following criteria: haemoglobin ≥9.0 g/dL, white blood cell count ≥3,000/mm^3 and ≤12,000/mm^3, neutrophil count ≥2,000/mm^3, platelet count ≥75,000/mm^3, serum total bilirubin level at or below the ULN, AST and ALT levels ≤1000 IU/L, serum creatinine level ≤1.5 × ULN
9) Written consent after a sufficient explanation of the study

3.2.2 Exclusion criteria

1) Known history of drug allergies that may interfere with the study treatment
2) Known history of an allergy to polysorbate 80
3) Severe complications that cannot be controlled
4) Active double cancers/multiple primary cancers
5) Previous bicalutamide, goserelin, or leuprorelin treatment
6) Fever, active, or suspected infection
7) Pleural effusion requiring treatment or pericardial fluid accumulation
8) Oedema of Grade 2 or higher
9) Interstitial pneumonia or pulmonary fibrosis
10) Known history or treatment of psychological diseases
11) Other conditions assessed as inappropriate for enrolment by the examining physician

3.3 Study design

Open-label, single-arm, single-centre, phase 2 trial

3.4 Treatment

3.4.1 Drug dosing

Bicalutamide tablet 80 mg (Casodex® tablet 80 mg; AstraZeneca, Cambridge, England) orally administered once daily

Leuprorelin acetate (Leuplin SR injection kit 11.2 ®; Takeda Pharmaceutical Company, Osaka, Japan) injected as a hormone-releasing hormone (LH-RH) analogue every 12 weeks or leuprorelin acetate (Leuplin Injection Kit 3.75®; Takeda Pharmaceutical Company, Osaka, Japan) subcutaneously injected every 4 weeks

Bicalutamide and leuprorelin acetate are continued until PD or unacceptable toxicity.

3.4.2 Dose modifications

The physician responsible for the clinical trial will permit continuous single treatment with one of the test drugs in patients with difficulties in 1) treatment continuation with bicalutamide tablets due to gynecomastia, breast tenderness, or hepatic dysfunction; or 2) treatment continuation with leuprorelin acetate or goserelin acetate depot because of a burning sensation.

3.4.3 Combined therapy

Chemotherapy and hormone therapy agents that are assumed to affect the evaluation of the trial drug may not be used during the trial period.

There are no regulations regarding the use of preventative medication administered before the trial, preventative post-treatment medication, and other drugs to alleviate side effects (e.g. antiemetics, antibiotics, or granulocyte-colony stimulating factor).

Anti-RANKL monoclonal antibodies and bisphosphonates are not prohibited.

3.5 Endpoints

Primary endpoint: Overall response rate (ORR; percentage of cases with an overall CR or PR according to the RECIST, version 1.1)

Secondary endpoints: CBR, PFS, OS, and safety

3.6 Number of planned registrations and study period

Due to the rarity of this cancer type, a target for the number of patient registrations was not set.

Study period: 1 March 2012 to 30 September 2016 for recruiting; 1 March 2012 to 31 March 2021, including the patients' follow-up period.

4 Contact information

4.1 Study representative

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