A Phase Ib Study of Pre-Operative Pembrolizumab + Chemoradiation in Patients With Locally Advanced Esophageal Squamous Cell Carcinoma

Department of Thoracic Surgery

Ruijin Hospital Shanghai JiaoTong University School of Medicine

Registration Number: NCT03792347 (www.clinicaltrials.gov)

Date: April 08, 2019

Objectives

Neoadjuvant chemoradiotherapy followed by esophagectomy has been recommended the standard of care for locally advanced esophageal cancer, although, with limited outcomes. Pembrolizumab, an immune checkpoint inhibitor targeting PD-1, has been verified to be safe and effective for patients with advanced esophageal cancer.

This single center, single arm study will evaluate the safety and feasibility of preoperative pembrolizumab with concurrent chemoradiotherapy in patients with locally advanced esophageal squamous cell carcinoma. And this study will provide valuable information for further clinical trials of preoperative pembrolizumab and other immune checkpoint therapy in esophageal cancer treatment.

Research Strategy

We propose to conduct a prospective, single-center, single arm clinical trial.

Inclusion Criteria

A patient will be eligible for inclusion in this study only if all of the following criteria apply:

1. Histologically confirmed cT2-T4a, N0-N+, M0 resectable esophageal squamous cell carcinoma;
2. Eastern Cooperative Oncology Group (ECOG) performance status 0-1;
3. Patients approve and sign the informed consent.

Exclusion Criteria

1. Patients with active autoimmune disease or history of autoimmune disease;
2. Patients who have a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications;
3. Subjects with a history of symptomatic interstitial lung disease;
4. History of allergy to study drug components;
5. Women must not be pregnant or breast-feeding;
6. Men with female partners that are not willing to use contraception;

7. Patients who have received prior chemotherapy, radiotherapy, target therapy and immune therapy for this malignancy or for any other past malignancy;

8. Underlying medical conditions that, in the investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity or adverse events.

Case Load

Considering the exploratory nature of this study, a sample size of 20 participants was decided.

Treatment Plan

Participants will receive carboplatin (AUC=2) IV and paclitaxel (50mg/m^2) IV on day 1,8,15,22,29. Radiotherapy will start on day 1 of chemotherapy. A total of 41.4 Gy, 23 fractions of 1.8 Gy, 5 fractions a week will be provided. Participants will also receive pembrolizumab (2mg/kg) IV on days 1 and 22. Surgery will be performed within 4-6 weeks after completion of preoperative therapy described above.

Rules for Dose Modification

1. Serious adverse events that need dose modification for chemotherapy or radiotherapy in the investigator’s opinion;

2. When facing serious pembrolizumab related adverse events, suspension of pembrolizumab should be applied rather than dose modification.

Reasons for Early Cessation of Trial Therapy

1. Serious adverse events that do not improve after short term suspension of preoperative treatment, for example, leukopenia, lymphopenia and anemia;

2. Allergy to study drug components which occurred during preoperative treatment;

3. Intolerance to preoperative treatment or surgery due to non-treatment related reasons;

4. Unresectable disease observed before esophagectomy;

5. Patients who meet newly identified exclusion criteria.

Primary Outcome Measure

Safety (The rates of grade 3 and higher-grade treatment-related adverse events): Incidence of adverse events will be evaluated using CTCAE 4.0, grade 3 treatment-related adverse events and higher-grade adverse events will be reported.

Secondary Outcome Measures

1. Feasibility (The rates of patients who finished pembrolizumab with chemoradiotherapy and receive surgery within 4-6 weeks after preoperative therapies);
2. Pathologic complete response: Pathologic complete response was defined as pT0N0M0;
3. Radiographic response: To assess radiographic response to neoadjuvant pembrolizumab with concurrent chemoradiotherapy using RECIST 1.1.

Statistical Analysis

All statistical analyses were performed under STATA version 1.51 (StataCorp, College Station, TX). Continuous variables were presented as mean with standard deviation or median with range. Frequency with percentage was used for presenting categorical variables. Student's t test was conducted for comparing continuous variables. And chi-squared test or Fisher's exact test were performed for categorical variables.