A Phase I/II Multi-Center Study of Nivolumab and Carboplatin/Paclitaxel with Radiation Therapy (RT) for Patients with Locally Advanced Esophageal Squamous Cell Carcinoma (NCT 03278626)

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**Background**

Esophageal Squamous Cell Carcinoma

2015: Esophageal Cancer Statistics

- U.S.: 16,688 cases, 15,698 deaths
- Worldwide: 458,890 cases, over 285,000 deaths
- 5-year overall survival (OS): 44.6%

**Two Major Histologies**

- Squamous cell carcinoma (SCC): 80% of esophageal cancers associated
- Adenocarcinoma: Incidence increased in Western societies

**Current standard of care**

- 2015: CROSS 2 (enrolment of patients for with ESCC) 3
- Median OS 14.6 months
- Combined chemoradiation therapy (CRT) vs. CRT + cetuximab
- No survival benefit

**Hypothesis**

As a single agent, nivolumab improves clinical and radiographic response rates in ESCC.

**Trial Schema**

1. Nivolumab 240 mg q 2 weeks x 2

2. Carboplatin + Paclitaxel x 2

3. Carboplatin + Paclitaxel + Radiation x 6

**Primary Objectives**

**Phase I**

- Assess the safety of induction nivolumab followed by chemoradiation with nivolumab and Carboplatin/Paclitaxel

- Estimate the CRR and pCR rate of induction nivolumab followed by chemoradiation with Carboplatin/Paclitaxel and nivolumab

- Assess the major toxicities encountered in this treatment

**Secondary Objectives**

- Assess whether clinical response to nivolumab on PET/CT can predict pCR, pFS, and OS
- Assess the association between the outcomes pCR, pFS, and OS and immune correlates

**Primary Endpoints**

- Unacceptable toxicity at 28 days after the last dose of chemotherapy
- Recurrence grade 3 or 4 hematologic toxicity (applies 1 prior dose reduction in chemotherapy)
- Any toxicity related to chemotherapy, radiography, or nivolumab that results in a 2-week delay in chemoradiation

**Secondary Endpoints**

- Clinical complete response (CCR) on PET/CT
- Pathologic complete response (pCR) on patients undergoing surgery
- Median progression-free survival (PFS) and median overall survival (OS)

**Hypotheses**

- Nivolumab as induction single-agent therapy followed by nivolumab combined with chemoradiation is safe and feasible.

- Nivolumab as induction single-agent therapy followed by chemoradiation with nivolumab will increase CCR and pCR rate beyond 55%.

- Assessment of induction nivolumab by PET/CT and/or correlational analyses of tumor tissue and peripheral blood may identify predictive immunologic and imaging biomarkers that correlate with outcomes.

**Study Center**

- Memorial Sloan Kettering Cancer Center (MSKCC)
- University of Southern California (USC): Norns Cancer Hospital and Los Angeles County (LAC) & USC Medical Center
- Oregon Health Sciences University Kight Cancer Institute

**Statistical Methodology**

- **If toxicity due to radiation, 1 dose reduction to 1.4 Gy total allowed on a study level.
- Dose reductions for toxicity: On an individual basis per the protocol.
- Complete clinical response: No tumor on repeat evaluation x complete resolution by PET/CT.
- If CCR, continue nivolumab x 6 doses. If no CCR, esophagostomy followed by nivolumab x 6 doses.

**Current open**

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**Treatment Schedule**

- Days 1-28: Nivolumab 240 mg q 2 weeks x 2
- Days 1-27: Upper endoscopy + core biopsy + PET/CT
- Days 29-66: Upper endoscopy + core biopsy + PET/CT
- Days 50-54: Surgery for cases x 6
- Days 5-14: Radiotherapy

**Endpoints**

- Efficacy: Disease control and clinical response

**Main Inclusion & Exclusion Criteria**

- **Inclusion criteria**
  - Histologically or cytologically confirmed, treatment-naive patients with locally advanced esophageal squamous cell carcinoma
  - ≥ 18 years old
  - ECOG 0-1
  - Mean Karnofsky performance status (KPS) ≥ 70
  - Adequate organ function
  - No prior treatment with immunotherapy or other systemic therapy

- **Exclusion criteria**
  - Active liver disease
  - Known neoplasm within 5 years of treatment
  - Known brain metastasis
  - Prior treatment with any immunotherapy
  - Significant intercurrent illness
  - Known primary immunodeficiency or solid organ transplantation

- **Primary objectives**
  - Assess the safety of induction nivolumab followed by chemoradiation with nivolumab and Carboplatin/Paclitaxel

- **Secondary objectives**
  - Assess whether clinical response to nivolumab on PET/CT can predict pCR, pFS, and OS

- **Assess the association between the outcomes pCR, pFS, and OS and immune correlates**

- **Hypothetical model**
  - Nivolumab as induction single-agent therapy followed by nivolumab combined with chemoradiation is safe and feasible.

- **Primary hypothesis**
  - Nivolumab as induction single-agent therapy followed by chemoradiation with nivolumab will increase CCR and pCR rate beyond 55%.

- **Assessment of induction nivolumab by PET/CT and/or correlational analyses of tumor tissue and peripheral blood may identify predictive immunologic and imaging biomarkers that correlate with outcomes.**

- **Secondary hypothesis**
  - Assessment of induction nivolumab by PET/CT and/or correlational analyses of tumor tissue and peripheral blood may identify predictive immunologic and imaging biomarkers that correlate with outcomes.

**References**

1. Ku et al. (2017)
2. Phase II: Nivolumab for advanced esophageal cancer
3. Trial conducted at NYU Langone Medical Center
4. Treatment responses and immune correlates
5. Immune Correlative Assays
6. Tumor microarray immune microenvironment analysis
7. Immune cell surface markers CD3, CD4, CD8, CXCR4, PD1D1, PD1D1, PD1D1, and IL-7R
8. Flow cytometry: T cell activation/inflammation panels

**Figures**

- Figure 1: Combining chemotherapy and PD-1 inhibition in a mouse esophageal model
- Figure 2: A Phase I/II Multi-Center Study of Nivolumab and Carboplatin/Paclitaxel with Radiation Therapy (RT) for Patients with Locally Advanced Esophageal Squamous Cell Carcinoma (NCT 03278626)