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A phase 2 randomized, double-blind, placebo-controlled study of tremelimumab for second and third line treatment in patients with unresectable pleural or peritoneal mesothelioma

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Introduction

Malignant mesothelioma (MM) is an uncommon cancer, caused principally by asbestos exposure. No treatments after first-line platinum-pemetrexed [1] have shown survival benefit [2], thus novel approaches are needed. Asbestos exposure induces immunosuppression and immune dysfunction in the mesothelium environment, mainly by hyperactivation of regulatory T lymphocytes and overproduction of cytokines that inhibit cytotoxic T lymphocytes and natural killer cells [3]. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4, CD152) modulates and eventually switches off T cell activation. Tremelimumab (treme) binds to the CTLA-4 antigen, preventing its negative regulatory signal to cytotoxic T cells. Results from a single arm phase 2 study of treme in 29 patients with MM who progressed on a platinum-based regimen showed promising 1- and 2- year survival rates and a safety profile consistent with previous treme studies [4]. This study has been expanded to enroll 29 patients currently treated with an optimized dosing schedule.

Study design

This is a phase 2, randomized, double-blind, placebo-controlled study. Patients with unresectable pleural or peritoneal MM who progressed following 1or 2 prior treatments, including a first-line platinum-pemetrexed regimen, will be randomized in a 2:1 ratio to receive either treme or placebo. Randomization will be stratified by EORTC status (low- vs high-risk), line of therapy (second vs third), and anatomical site (pleural vs peritoneal). Enrollment will include 180 subjects at approximately 150 centers in multiple countries. Recruiting began in May 2013.

Endpoints

Primary: overall survival. Secondary: durable disease-control rate (DCR); progression-free survival (PFS); patient-reported outcomes (pain, disease-related symptoms, and time to deterioration of disease-related symptoms); duration of response and overall response rate (ORR); treme safety profile, immunogenicity, and pharmacokinetics. Exploratory: DCR, PFS, duration of response and ORR based on immune related response criteria, health-related quality of life, disease-related symptoms, pain, and health status in patients with durable clinical activity. The association of biomarkers with treme and clinical outcomes will also be explored.

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