Nivolumab plus Gemcitabine - Cisplatin and Dexamethasone (GCD) in Relapsed/Refractory Hodgkin Lymphoma - Concept Sheet

Introduction

Around 30 percent of patients with classical Hodgkin lymphoma relapse or have progressive disease after first-line therapy. The standard of care for these patients is salvage chemotherapy followed by an autologous stem cell transplantation. Nivolumab has already been demonstrated to be effective in R/R Hodgkin Lymphoma. The addition of PD-1 inhibitors (Pembrolizumab and Nivolumab) have expanded the options for salvage therapy and has improved outcomes. However, the prohibitive cost of Nivolumab's standard dosing schedules precludes its use in resource-constrained settings. Phase one dose-finding studies done in Hodgkin Lymphoma did not study the adequacy or receptor occupancy status of lower doses of nivolumab. The FDA-approved dose of nivolumab (3 mg/kg) might be more than necessary for tumors with high PD-L1/L2 expression, such as Hodgkin lymphoma as T cell PD1 receptors are equally saturated at lower doses (from a dose of 0.3mg/kg onwards.

Objectives

1) To assess the efficacy of low-dose Nivolumab when added to standard salvage therapy of Gemcitabine, Cisplatin, and Dexamethasone for Relapsed/Refractory Hodgkin Lymphoma
2) To study the peak and trough PD-1 receptor occupancy status after infusion of low dose nivolumab

Description of Pilot Data

Our phase two data (CTRI/2022/04/042179 [Registered on: 26/04/2022] demonstrated that a low dose of 40 mg of Nivolumab is sufficient to completely saturate PD-1 receptors on the T cell surface even at trough levels, challenging the need for the higher doses that are currently used. 18-month progression-free survival for the whole cohort was 85.9% $\pm$ 9.3% (Median follow-up of 18.9mths).

Methodology

Trial Design – Phase II Randomized control Clinical Trial/2 arms/Single Centre/

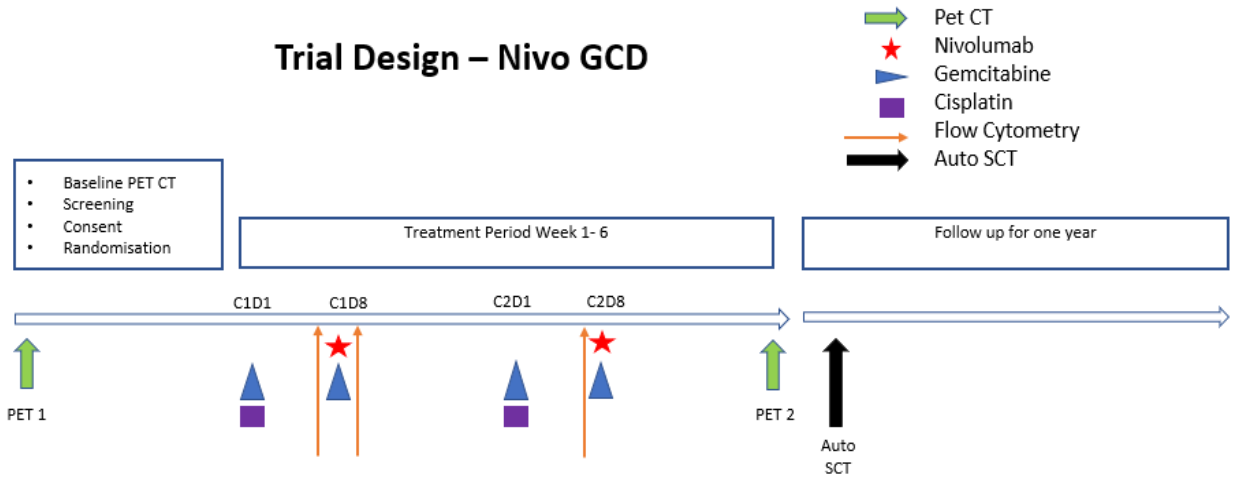
Hypothesis – Low dose Nivolumab will improve outcomes of Relapsed Refractory Hodgkin Lymphoma

Trial Summary

Patients with relapsed or refractory Hodgkin lymphoma will randomly be assigned to 2 arms to receive 2 doses of Nivolumab concomitantly with GCD chemotherapy. The first arm will receive Nivolumab at a dose of 20 mg and the second arm will receive Nivolumab at a dose of 10 mg. Blood will be collected at defined time points for all patients for flow cytometry for measurement of receptor occupancy. The time points are as follows

- Prior to the first infusion of nivolumab
- One hour after the first infusion of nivolumab
- Prior to the second infusion of nivolumab

Treatment response will be assessed by FDG PET Scan after 2 cycles of Nivo GCD using the International Working Group criteria and LYRIC criteria



Outcomes

Primary outcome

- Overall Response rates post-therapy (end-of-therapy PET) - Composite of both complete response and partial response in both the arms

Secondary Outcome

- Progression free survival at 1 year
- Complete response at end of therapy
- Partial response at end of therapy
- Adverse event profile after the use of low dose nivolumab
- Cost-effectiveness of the addition of low dose nivolumab compared to standard therapy
- Peak and trough PD-1 receptor occupancy status after infusion of low dose nivolumab
- Correlation between receptor occupancy status and primary outcome/ other secondary outcomes

Anticipated outcomes

Through this clinical trial, we hope to gather data on the effectiveness of low dose nivolumab as an add-on to conventional chemotherapy and reduce unnecessary and costly drug dosing.

Timelines

- One year for recruitment
- Follow up of one year after recruitment of last patient
- Total study duration - two years