PET-adapted Anti-PD1 Based First Salvage Therapy For Hodgkin Lymphoma With Nivolumab +/- ICE (NICE)

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ABSTRACT

Introduction: Hodgkin Lymphoma is a cancer of the lymphatic system characterized by a neoplasm of lymphoid tissue containing malignant Hodgkin-Reed-Sternberg (HRS) cells. HL is estimated to be diagnosed in 8,800 individuals in 2021 and approximately 960 individuals will die. The 5-year survival rate for HL is 87%. If the cancer is found in its earliest stages, the 5-year survival rate is 91%. Despite the high survival rates approximately 30-40% of patients presenting with HL become refractory to initial therapy or relapse, leaving salvage chemotherapy + autologous hematopoietic cell transplantation as the only potential curative treatment. While this regiment is fairly effective, it is known that there is high toxicity associated with salvage-based chemotherapies. Recent studies have demonstrated that brentuximab vedotin (BV) is a highly efficacious salvage chemotherapy, however, due to promising results of the Echelon-1 trial, BV may become part of standard induction therapy. This would make BV potentially unviable as a salvage chemotherapy.

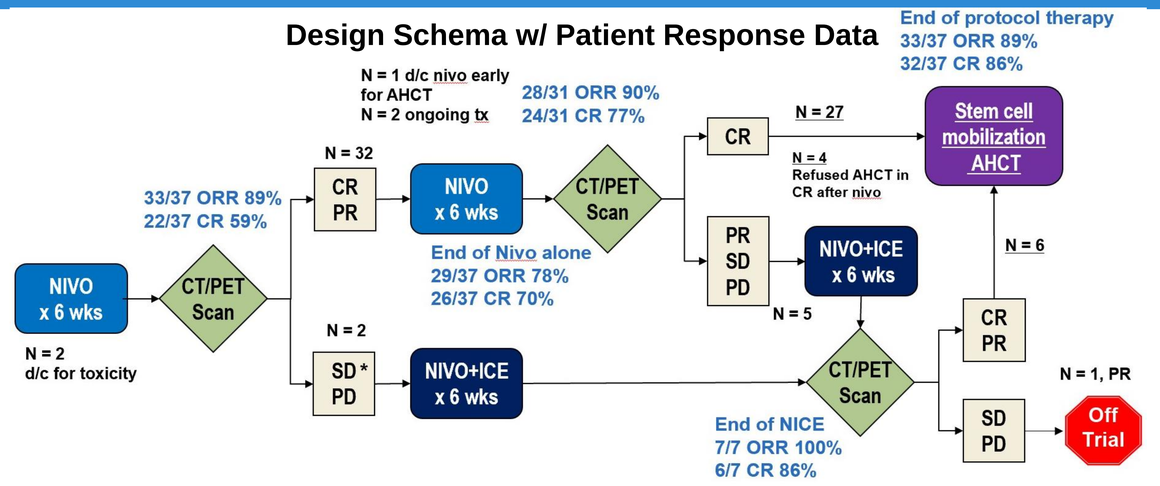
Nivolumab (Nivo) is a humanized monoclonal antibody that blocks the interaction between PD-1 and PD-L1. Specifically, Nivo binds to the human PD-1 receptor and inhibits the interaction between PD-1 and its ligands PD-L1 and PD-L2. In Hodgkin Lymphoma it is well known that the Reed-Sternberg cells exploit the PD-1 pathway in order to evade immune detection. Alterations in chromosome 9p24.1 found in classic Hodgkin increase the abundance of PD-1 ligands, PD-1 and PD-L2. Therefore, by targeting these pathways it is conceivable that Nivo will prove to be efficacious in treatment of Hodgkin Lymphoma. Currently, Nivolumab is approved for the treatment in a variety of solid tumor cancers in multiple countries such as the US, EU, and Japan.

Objective: The goal of this phase II clinical trial is to evaluate the response patients have to Nivo+ICE therapy in patients not in CR with Nivo alone.

Patient Criteria:

- Relapsed/refractory biopsy-proven CD30+ Hodgkin lymphoma
- Age > 18 years old and > 40kg
- Can only have received first line chemotherapy
  - mixed induction chemotherapy is allowed (ABVD/BEACOPP hybrid). Pediatric induction therapy also allowed.
- Prior consolidative radiation therapy is allowed.
- ECOG ≤ 2
- Adequate organ and marrow function

Design Schema w/ Patient Response Data



Baseline Patient Data

Characteristics	N (%)
Total	43 (100%)
Male gender	26 (60%)
Age (median, range) in years	35 (18 – 70)
Stage at Diagnosis	
I - II	18 (42%)
III - IV	25 (58%)
Frontline regimen	
A(B)VD	37 (86%)
BV+AVD	2 (5%)
BV->ABVD (sequential)	1 (2.3%)
ABVD/BV+AVD	1 (2.3%)
ABVE+PC	1 (2.3%)
BEACOPP escalated	1 (2.3%)
Stage at Baseline	
I - II	17 (40%)
III – IV	26 (60%)
B Symptoms at Baseline	16 (37%)
Extranodal Disease at Baseline	16 (37%)
Bulky Disease at Baseline (> 5cm)	18 (42%)
Prior radiation	5 (12%)
Primary refractory	19 (44%)
Relapsed	24 (56%)

Trail Design

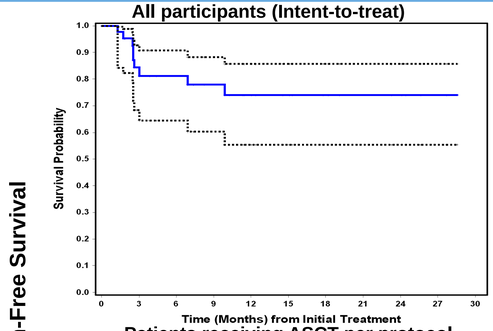
This phase II clinical trial implements a Simon Two-Stage Optimal Design to evaluate the anti-lymphoma activity of NIVO±ICE chemotherapy. A maximum of 43 participants are expected to be enrolled using a rate of 0.05 and power of 80% a type I error to create a sample size based on the desire to discriminate a promising CR rate of 70% from a disappointing CR rate of 50% (a rate below what current therapies can achieve).

- **Stage 1**: 15 entered, if ≤ 8 CR then study will be terminated. If at least 9 subjects achieve a CR, the trial will continue to the second stage.
- **Stage 2**: 28 additional subjects entered. If 27+ achieve a CR, the combination will be considered worthy of further study. If ≤ 26 subjects achieve a CR, then no further investigation of the regimen is warranted.

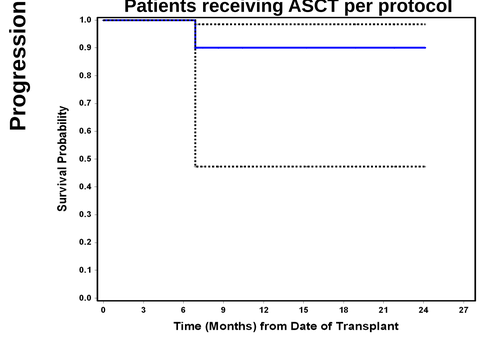
Treatment Disposition

	N (%)
Total	43 (100%)
Treatment Regimen	
NIVO only	35 (81%)
NIVO + ICE	8 (19%)
Completed treatment	32 (82%)
Discontinued prior to end of treatment[a]	5 (13%)
Autologous SCT directly after protocol therapy[b]	27 (69%)
Received alternative salvage therapy prior to ASCT	1 (3%)
ASCT anytime after protocol therapy	25 (89%)

All participants (Intent-to-treat)

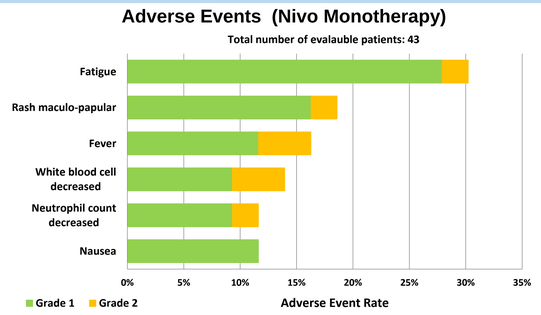


Patients receiving ASCT per protocol

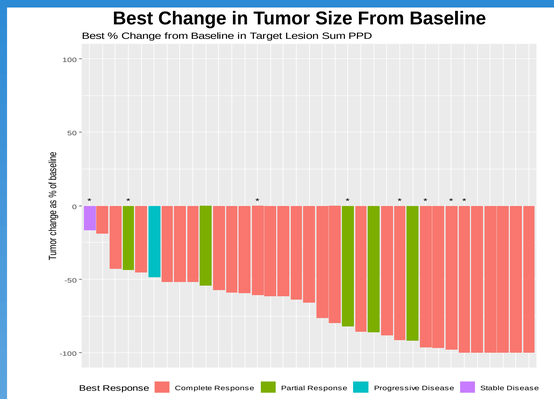


Progression-Free Survival

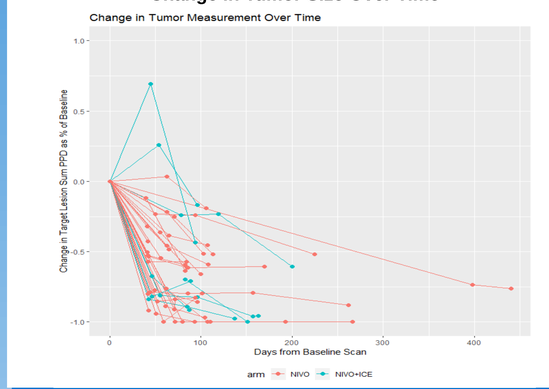
Adverse Events (Nivo Monotherapy)



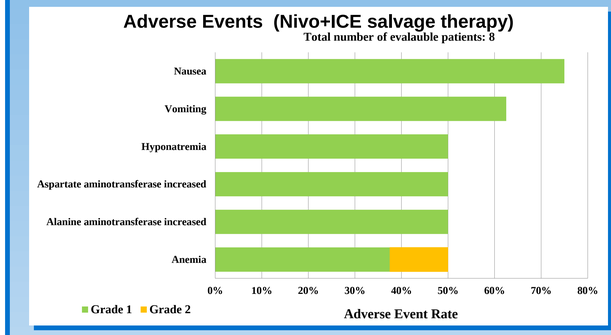
Best Change in Tumor Size From Baseline



Change in Tumor Size Over Time



Adverse Events (Nivo+ICE salvage therapy)



CONCLUSION

- Nivo +/- ICE resulted in a high CR rate in patients with refractory/relapsed HL and bridged most patients to transplant without traditional chemotherapy
- CR rate of Nivo monotherapy was unexpectedly high as first salvage therapy
- Nivo+ICE is fairly tolerable and efficacious in patients that did not exhibit CR when treated using Nivo alone
- PD-1 blockade with Nivo can be an effective bridge to autologous hematopoietic stem cell (ASCT) transplantation independent of BV

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