Trial in Progress:

LoNAH Trial: A Phase III, Randomized Study of Low Dose Nivolumab Plus AVD or ABVD in Patients with Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma

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INTRODUCTION

The current standard of care for newly diagnosed advanced-stage Hodgkin lymphoma (HL) in lower- and middle-income countries continues to be doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), which has proven to be an affordable and easily administrable regimen, the risks of pulmonary toxicity not-withstanding.

Following data from the RATHL trial, a negative interim PET scan has allowed for the omission of bleomycin, with non-inferior results. However, about 15% of patients will have a positive interim PET scan, and escalation of therapy with BEACOPP is associated with increased costs, chemo-related toxicity and anincreased risk of secondary malignancies and infertility.

Recently, excellent results were shown from the interim analysis of the SWOG 1826 trial comparing brentuximab vedotin AVD (BV-AVD) to nivolumab AVD (N-AVD), with preliminary data suggesting superiority of N-AVD.
While this regimen may change the frontline treatment of advanced-stage HL in developed countries, the prohibitive costs of checkpoint inhibitors (CPIs) at approved doses/schedules make this approach out of reach for most of the world's population.

Since the Phase I study using PD-1 inhibition was focused on toxicity, the dose-response relationship was not established. The strategy of using low dose nivolumab is supported by a growing body of anecdotal real-world data on the efficacy of low dose nivolumab in the setting of relapsed/refractory HL.

AIM

1. To improve outcomes in advanced stage Hodgkin lymphoma in settings where ABVD is the standard of care.
2. To incorporate CPIs into frontline therapy of HL in a cost-effective manner

QUESTIONS

1. *Will addition of short-course low dose nivolumab into upfront therapy of advanced HL improve outcomes?*
2. *Will the addition of short-course low dose nivolumab improves outcomes in patients who have an interim PET positivity after 2x ABVD*
3. *Is a risk-adapted strategy cost effective in the treatment of newly diagnosed advanced cHL?*

TRIAL

CTRI/2024/03/063942 [Registered: 11/03/2024]) LoNAH (**Lo**w-dose **N**ivolumab in **A**dvanced **H**odgkin Lymphoma) is a randomized, phase III study in patients with newly diagnosed advanced-stage HL, comparing ABVD to a new regimen n-AVD (comprising of low dose nivolumab (flat dose of 40mg) + AVD) using a risk-adapted strategy.

Eligible patients must be 12 years or older and have stage IIBX or EN, III or IV HL. After stratification for bulk disease and IPS score, patients are centrally randomized in a 1:1 ratio to receive the initial phase of therapy with 2 cycles of either n-AVD or ABVD.
An interim PET scan will be done after the first 2 cycles (iPET2). If the iPET2 is negative, treatment is de-escalated on both arms, to a further 4 cycles of AVD alone. iPET2-positive patients will be marked as an event for the primary outcome and will receive center-specific protocols, with either BEACOPP or continuation with further cycles of N-AVD.

Event will be defined as any one of the following 'failure of therapy' events for the purpose of this trial
(1) iPET2 positive (DS >3)
(2) relapse/progression at any time-point
(3) death due to any cause.

The decision to include iPET2 positivity as an event for primary outcome represents an attempt to use a common-place occurrence that is currently considered "failure of ABVD" and is an indication to escalate therapy in real-world practice.

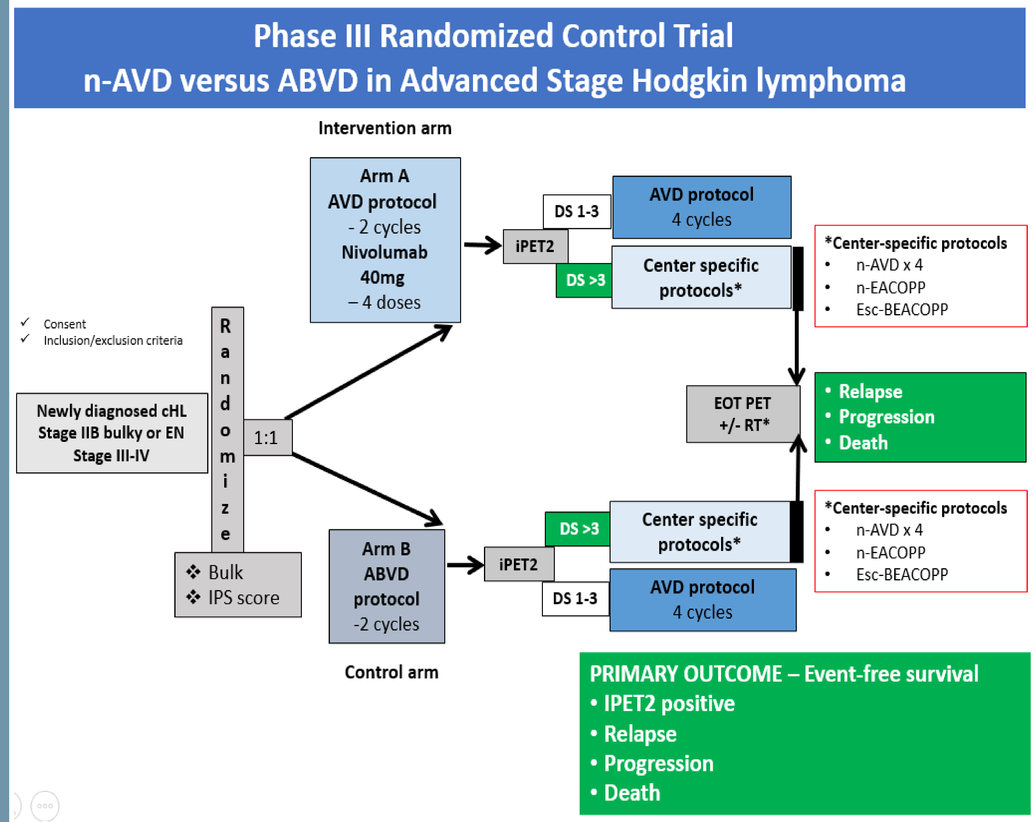
Patients with initial bulk disease will not receive RT if the iPET2 is negative. Patients are eligible to receive RT to residually metabolically active foci at the end of treatment (EOT) PET scan, at the discretion of the treating investigator.

The primary endpoint is to compare the EFS in patients randomized to n-AVD versus ABVD. Secondary endpoints include OS, PFS, EOT response rates in patients with iPET2 positive treated with either BEACOPP or continuation of n-AVD, safety/tolerability of N-AVD compared to ABVD, and a cost-benefit analysis of this approach.

280 eligible pts are expected to be accrued over 3 years, assuming a screening failure rate of 30% (the high screening failure rate is due to logistic difficulties in taking 6 months of therapy at a referral center when the standard of care ABVD is easily administered at smaller peripheral oncology facilities).

The LoNAH trial represents a collaborative effort enabled by the Haematology Cancer Consortium (https://www.hemecancer.org/), a platform for haematology centers in India to test hypotheses that will answer region-specific questions, in this case the use of CPIs in a cost-effective manner for advanced stage HL

TRIAL SCHEMA



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ANCILLARY STUDIES

Flow cytometry to measure duration of PD-1 receptor saturation
Pharmacokinetic study of low dose nivolumab
Cost-benefit analysis comparing ABVD with n-AVD

REFERENCES

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