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POSTER ABSTRACTS

624.HODGKIN LYMPHOMAS AND T/NK CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Durable Remissions in Advanced Stage and Molecularly High Risk Untreated Classic Hodgkin Lymphoma with Pembrolizumab + AVD

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Introduction

We previously reported results of a frontline study of pembrolizumab + AVD (Lynch et al Blood 2023) in any stage classic Hodgkin lymphoma (CHL). Despite finding surprisingly high rates of positive interim and EOT PET/CT compared to historical data, this study revealed a 2-year PFS of 97%. Separately, recent data (Alig et al. ICML 2023) suggest that CHL is characterized by two dominant genetic subtypes (H1 vs. H2). H2 tumors harbor higher levels of genomic instability, are enriched for somatic mutations in *TP53*, *KMT2D*, and *BCL2*, and have increased risk of upfront treatment failure with conventional regimens. To better evaluate our findings in higher risk patients, we expanded the study to include 20 additional patients with advanced stage disease. Herein we present updated clinical data for our full 50-patient cohort, and report genotype associations including novel genetic subtypes of cHL.

Methods

We performed a single arm study (NCT03331341) combining concurrent pembrolizumab with AVD in untreated CHL of any stage. Pembrolizumab 200 mg IV was administered every 21 days concurrently with AVD chemotherapy. AVD was administered at the standard dosing and schedule. With the cohort expansion, total planned accrual was 50 patients. The objective of the expanded study was to evaluate longer term efficacy based on concerns with the utility of PET/CT. We defined success as a 1-year PFS in advanced stage patients of at least 85%. Samples were analyzed for ctDNA at baseline, post cycle 1 (if available), post cycle 2, and end of treatment. ctDNA levels were quantified as haploid genome equivalents/mL plasma using CAPP-Seq (Newman et al Nat Biotech 2016) and PhasED-Seq (Kurtz et al. Nat Biotech 2021). Using baseline CAPP-Seq genotypes from plasma ctDNA, patients were classified as H1 vs H2 cHL by a previously validated probabilistic Latent Dirichlet Allocation (LDA) algorithm (Alig et al, 2023, in review).

Results

50 patients, enrolled between Feb 1, 2019, and Apr 13, 2023, were evaluable for updated safety, response and/or exploratory analyses (one patient withdrew from study treatment prior to any response assessment). With a median follow up of 2.3 years, 2-year PFS and OS were 98% and 100%, respectively. Among advanced stage patients (n=38), 2-year PFS and OS were 97% and 100% respectively. PET2 was performed in 49 patients, with a CR rate of 73% in the early stage patients, and 58% in those with advanced stage. EOT PET was evaluable in 41 patients, with a CR rate of 91% in early stage, and 73% in those with advanced stage. To date, only one patient with a positive EOT PET has developed biopsy-proven recurrence. Four EOT PET+ patients are now > 3 years post treatment without relapse. Four additional EOT PET+ patients are less than 1 year post therapy, and one has resolved FDG uptake on repeat scan with the others undergoing surveillance. Eight (16%) patients experienced SAEs, including sepsis (one each G3 and G4), G3 Guillain Barre syndrome that resolved after permanent pembrolizumab discontinuation, and five (10%) G3 febrile neutropenia.

Non-invasive genotyping using ctDNA was available in 25 patients. Among 6 patients with H2 genotypes (24%), all had advanced stage, and this group included the only patient experiencing disease recurrence. The remaining patients including all early-stage patients were classified as H1 (76%). All patients will have completed treatment and safety evaluations by October 2023, and updated safety, efficacy, and exploratory data including ctDNA will be presented at the meeting.

Conclusion

With longer follow up, including patients who started therapy over 4 years ago, concurrent pembrolizumab + AVD represents a highly effective frontline therapy for CHL, including for advanced stage patients and those with high risk H2 genotypes. PET2 demonstrated limited clinical utility, and no late relapses have been seen to date.

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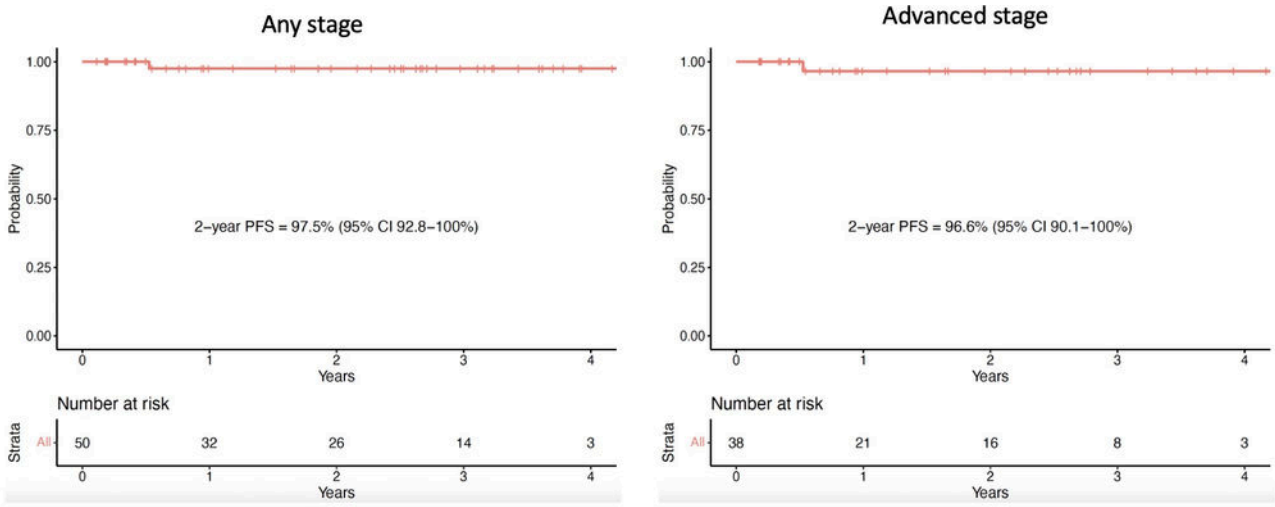

Figure 1

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