9p24 abnormalities in hematologic malignancies with a focus on diffuse large B-cell lymphoma

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To the Editor

Chromosome 9p24 contains four genes that are critical for immune evasion and propagating cell growth. Two of the genes, PD-L1 and PD-L2, interact with the PD-1 receptor on the surface of T cells to attenuate immune surveillance by decreasing T-cell activation and altering the tumor microenvironment [1]. Accordingly, the PDL axis has become an attractive drug target, and nivolumab, a PD1 receptor monoclonal antibody, was recently approved for treatment of classical Hodgkin’s lymphoma (cHL) [2]. Reed–Sternberg cells, characteristic of classical Hodgkin’s lymphoma, have 9p24 abnormalities that result in uniform expression of PD-L1 and PD-L2, which may explain the efficacy of PDL axis inhibitors for this malignancy [3]. Recent studies have explored the frequency and types of 9p24 structural variations in a number of B-cell malignancies, including cHL, diffuse large B-cell lymphoma (DLBCL), and primary mediastinal large B-cell lymphoma (PMBCL), utilizing FISH and next-generation sequencing and correlated them with increased PDL expression [2]. However, these studies have been in a small number of patients with B-cell malignancies.

Additionally, the 9p24 segment also contains the loci for JAK2 and KDM4C/JMJD2C, which have both been identified as potential drug targets. KDM4C/JMJD2C modifies histones and has been shown to regulate the expression of a few hundred genes, including some that enhance mitogenic signaling and cell cycle progression [2]. Furthermore, these genes seem to interact with each other to confer a survival advantage, particularly for PMBCL and cHL [2]. For example, preliminary studies suggest that simultaneous inhibition of both JAK2 and KDM4C/JMJD2C may be required to suppress signaling in PMBCL and cHL, indicating possible synergy between these druggable targets [1]. Furthermore, JAK2 amplification has been shown to increase PD-L1 and PD-L2 expression as well [2]. With limited but interesting data available on 9p24 structural variation in B-cell lymphomas, the goal of our analysis is to better understand the distribution of 9p24 abnormalities across a broader spectrum of leukemias and lymphomas.

We used the National Cancer Institute’s Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer to search for 9p24 breakpoint abnormalities across all subtypes of hematologic malignancies. The purpose of the query was to assess chromosome-level changes that may be associated with a gain-of-function phenotype, namely additions and rearrangements. Deletions, therefore, were not included in the analysis. The degree of potential gain of function for rearrangements and translocations was not ascertained on more than a chromosome level. Individual references were manually reviewed, and pathologic data were extracted as available from the primary literature. A more extensive analysis was performed on patients with diffuse large B-cell lymphoma, who made up the vast majority of patients in the study, and included coincident rearrangement of myc (8q24), BCL2 (18q21), and BCL6 (3q27) with 9p24. Our report includes all subtypes of malignancies with greater than 2% incidence of additions and/or rearrangements.

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Our findings provide support for the hypothesis that 9p24 abnormalities across a broad spectrum of hematologic malignancies should be further investigated with means such as FISH and array comparative genomic hybridization (aCGH). While fewer than 1% of patients across 53 subtypes of hematologic malignancy were found to have 9p24 additions or rearrangements and 21 of the 53 subtypes yielded no 9p24 abnormality, certain malignancies warrant further study as they had a higher than expected incidence. For example, in Table 1, among the more rare malignancies with 18 or fewer identified patients, B-cell-associated hemophagocytic syndrome, extranodal NK/T-cell lymphoma, and intravascular large B-cell lymphoma were all found to have over a 7% chance of having additions/rearrangements. Given the poor prognosis of these cancers, advocating for use of targeted, potentially less toxic agents may be warranted. The identification of the 9p24 amplicon in chronic eosinophilic leukemia may add to the existing use of targeted therapy in this malignancy, such as imatinib’s current use for the FIP1L1/PDGFR-alpha translocation. Our analysis suggests that certain subtypes of hematologic malignancies should be further investigated with targeted sequencing for potential gain-of-function chromosomal changes in 9p24 as it could identify novel drug targets for these malignancies.

### Compliance with ethical standards

**Conflict of interest** None.

**Human and animal rights** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** Informed consent was not needed due to lack of human participants in the study.

### References


