B. NPM1, p.Trp288CysfsTer12

Variant annotation: The identified termination mutation, NPM1, p.Trp288CysfsTer12 , occurs in the nucleolar localization signals (NoLS) within the C-terminal domain and in the exon 11 of the NPM1 gene. Cytoplasmic NPM1 interacts and stabilize the PML in cytoplasm and this PML modulate the autophagic activity by AKT signal, which is beneficial for leukemia survival. Thus, the NPM1, p.Trp288CysfsTer12 mutation is a loss of wild type nucleolar function of NPM1.(6)

Gene Summary: NPM1 is generally reported as a protein that promotes cellular growth and survival upon apoptotic stimuli and it appears to regulate these functions in a cell-type specific manner. Furthermore, in hematopoietic cells, NPM expression decreases during differentiation and NPM overexpression limits maturation rate both in vitro and in-vivo.(7)

Variant Incidence: NPM1 is altered in 0.99% of all cancers with acute myeloid leukemia, acute myeloid leukemia with mutated NPM1, lung adenocarcinoma, colon adenocarcinoma, and endometrial endometrioid adenocarcinoma having the greatest prevalence of alterations. NPM1 is one of the most frequently (25-30%) mutated tumor suppressor genes in adult CN-AML.(8)

CLINICAL RELEVANCE FOR BCR-ABL1 GENE FUSION AND NPM1:

De novo AML with BCR—ABL is aggressive disease, unusual and rare. Its predicted to have overlapping features chronic myeloid leukemia in blastic phase (CML-BP), however there is no definitive criteria to differentiate CML-BP with AML with BCR-ABL. De novo AML with BCR-ABL may get benefited from Tyrosine kinase inhibitors. Diagnostic challenges and controversy remain as to whether de novo AML with BCR-ABL1 is a distinct entity and represents truly new leukemia or a transformed CML presenting in blast crisis.(9)

Breakpoint cluster region - Abelson (BCR-ABL1) chimeric protein and mutated Nucleophosmin (NPM1) are often present in leukemias as distinct entities, however, their co-existence is rare. Presence of both these aberrations inhibit differentiation and apoptosis. According to the model proposed by Gilliland and Griffin, the paradigm of leukemogenesis features: 1)) class I mutations conferring a proliferative advantage to the clone 2) class II mutation as leukemia-initiating event, causing inhibition of differentiation and apoptosis. The association of BCR-ABL1 and mutated NPM1 in the same clone is unusual but not contradictory to either of the models. If NPM1 is the founder, class II mutation, and BCR-ABL1 acts a class I mutation, conferring a proliferative advantage to the affected cells. Relevance of the same in seen in otherwise normal bone marrow where molecular aberration was found in tumor subclones and even in oligoclones.(10) A clinical case study of a 43 years male was published in 2020, where the patient was initial diagnosed in April 2013 supposedly with a CML onset in BP and treated with 3 days Idarubicin plus seven days of high dose Aracytin (IA 3+7) resulting