|  |
| --- |
| cLINICAL UTILITY OF MOLECULAR TESTING IN  MATURE T- AND NK-cell lymphoma  DIAGNOSTIC utility  The presence of any assumed somatic variants is evidence of a clonal process within the specimen which may help support the diagnosis of a mature T-cell lymphoma.  Angioimmunoblastic T-cell lymphoma (AITL) and other lymphomas derived from T follicular helper (TFH) cells are characterised by recurrent mutations in *TET2* (50%-80%) and *DNMT3A* (20%-30%) along with *RHOA* Gly17Val (60%-70%) and *IDH2* Arg172 (25%) mutations1,2. *IDH2* Arg172 mutations are relatively specific for AITL, being rare in other PTCL subgroups3.  Detection of mutations in other genes are less specific but may support the diagnosis of other T-cell lymphoma subtypes including PTCL-NOS (*DNMT3A*, *TET2*), T/NK-LGL (*STAT3*, *STAT5B*), ATLL (*PLCG1*, *CARD11, STAT3, FYN*), subacute panniculitis-like T-cell lymphoma (*HAVCR2*) and EATL/MEITL (*STAT3*, *DDX3X*, *JAK1*, *SETD2*)1.  The detection of structural variants (not detected by this assay) may also be useful in subclassification of PTCL including *ALK*-*NPM1* t(2;5)(p23;q35) in ALK+ ALCL, rearrangements of *DUSP22*/*TP63* in ALK- ALCL, inv(14)(q11q32) in T-PLL and isochromosome 7q in hepatosplenic T-cell lymphoma, *CTLA4*-*CD28*/*ICOS*-*CD28* in ATLL/Sezary syndrome (amongst other subtypes) and *CD274*/*PDCDLG2* in EBV-associated T-cell lymphomas (*e.g.* extranodal NK/T-cell lymphoma)1.  Whilst the genomic profile of PTCL-NOS is relatively heterogeneous, two molecular subgroups have been identified by gene expression profiling (not detected by this assay), *PTCL-TBX21* and *PTCL-GATA3*4.  PROGNOSTIC utility  The correlation between specific molecular abnormalities and prognosis in mature T-cell lymphoma is not well established given the difficulty of subclassification and diversity of therapies utilised, however some of the more established prognostic markers include the favourable outcomes of ALK+ (*ALK*-*NPM1*) ALCL and *DUSP22* rearranged ALK- ALCL and the unfavourable outcomes of *TP63* rearranged ALK- ALCL as well as *TP53* abnormalities across the spectrum of T-cell lymphoma5-8.  BIOMARKERS OF RESPONSE TO THERAPY  The ALK-inhibitor class of agents target the ALK protein which is overexpressed in ALK+ ALCL9.  The checkpoint inhibitor therapeutic class are an emerging therapy for patients with genomic abnormalities involving *CD274*/*PDCDLG2*10,11.  REFERENCES  **1.** Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, editor. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. **2.** de Leval L. Approach to nodal-based T-cell lymphomas. *Pathology* 2020; **52**(1): 78-99. **3.** Wang C, et al. IDH2R172 mutations define a unique subgroup of patients with angioimmunoblastic T-cell lymphoma. *Blood* 2015; **126**(15): 1741-52. **4.** Heavican TB, et al. Genetic drivers of oncogenic pathways in molecular subgroups of peripheral T-cell lymphoma. *Blood* 2019; **133**(15): 1664-76. **5.** Ye Y, et al. Correlation of mutational landscape and survival outcome of peripheral T-cell lymphomas. *Exp Hematol Oncol* 2021; **10**(1): 9. **6.** Sakamoto Y, et al. Clinical significance of TP53 mutations in adult T-cell leukemia/lymphoma. *Br J Haematol* 2021. **7.** Lobello C, et al. STAT3 and TP53 mutations associate with poor prognosis in anaplastic large cell lymphoma. *Leukemia* 2020. **8.** Pedersen MB, et al. DUSP22 and TP63 rearrangements predict outcome of ALK-negative anaplastic large cell lymphoma: a Danish cohort study. *Blood* 2017; **130**(4): 554-7. **9.** Mosse YP, et al. Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study. *J Clin Oncol* 2017; **35**(28): 3215-21. **10.** Beygi S, et al. Pembrolizumab in mycosis fungoides with PD-L1 structural variants. *Blood Adv* 2021; **5**(3): 771-4. **11.** Lim JQ, et al. Whole-genome sequencing identifies responders to Pembrolizumab in relapse/refractory natural-killer/T cell lymphoma. *Leukemia* 2020; **34**(12): 3413-9. |