**KIR3DL2 MUTATION MAY DEFINE A HIGH RATE OF RESPONSE OF AITL TO TIPIFARNIB**

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**INTRODUCTION**

Killer cell immunoglobulin-like receptors (KIRs) are transmembrane glycoproteins expressed in NK and T cells that play key regulatory functions, including the control of chemokine/cytokine release and angiogenesis. KIRs interact with MHC and transduce activating (KIR-DS) or inhibitory (KIR-DL) signals through their cytoplasmic domains.

**KIR-DL MUTATIONS IN AITL**

- KIR-DL receptors signal intracellularly through ITAM motifs and SIRP, whereas KIR-DL receptors signal through ITIM motifs and SHP. SHP dephosphorylates SIRP phosphoreceptors targets.
- Next Generation Sequencing (NGS) was conducted in pre-treatment biopsy samples from 17 AITL patients treated with tipifarnib in study KO-002. Increased KIR-DL gene variation was observed in patients who responded to tipifarnib treatment.
- The most notable tumor KIR-DL mutations found in patients who experienced objective responses with tipifarnib were located in:
  1. the ITIM2 domain of KIR3DL1 and KIR2DL3, and
  2. the vicinity of the CXCR2 phosphorylation sites of KIR3DL2 and KIR3DL2.
- Approximately half of the AITL tumor samples carried KIR3DL2 mutations.

**CXCL5 Downregulation in KIR3DL2 Variant AITL Tumors**

- Extensive mutation in ITIM2 domain including loss of Threonine-429 and a novel Threonine at position 426, was observed in KIR3DL1
- Mutation of the ITIM2 domain was only observed in 2 AITL patients responding to tipifarnib.
- KIR3DL2 (c.1065_1069del) located near the CX2 phosphorylation site was observed only in 3 AITL responders. It was also present in 1 unique case of CR in 21 PTCL NOS patients with NGS data (study KO-002) and 1 unique case of PR in 6 Hodgkin lymphoma patients with NGS data (study LS038B).

**KIR3DL2 Variation may Define Poor SOC Prognosis in AITL**

- AITL patients with KIR3DL2 gene variants appeared to experience better outcome with tipifarnib than with SOC treatment in their last prior line of therapy.
- A subset of AITL (~50%) carries mutations of KIR-DL genes and expresses high levels of CXCL12 and CXCL5, which can be associated with increased inflammatory properties of KIR-DL/SHP signaling, and in CXCL5 downregulation.

**GENETICS OF TIPIFARNIB’S ACTIVITY IN PTCL**

**CONCLUSIONS**

- CXCL12/CXCR4 and CXCL5/CXCR2 appear to drive respectively sensitivity and resistance to tipifarnib.
- Lymphomas of AITL histology and those (PTCL NOS, DLBCL) carrying CXCL2 reference (wild type) sequences express high levels of CXCL12 and are sensitive to tipifarnib therapy.
- AITL expresses also CXCL5; however, a subset of AITL (~50%) carries mutations of KIR-DL genes and express very low levels of this chemokine, suggesting that KIR-DL variants may increase the anti-inflammatory properties of KIR-DL/SHP signaling, including CXCL5 downregulation.
- KIR3DL2 C336R/Q386E were the most prevalent KIR-DL mutations in AITL and were associated with high activity of tipifarnib: 50% CR rate, 75% ORR, 100% clinical benefit rate.
- AITL patients carrying KIR3DL2 C336R/Q386E appeared to experience a better outcome with tipifarnib treatment than with prior SOC treatment.