Olaptesed pegol (NOX-A12), a CXCL12 binding Spiegelmer®, was found to detach CXCL12 from the surface of bone marrow stromal cells (Hoellenriegel & Zborsalski et al., Blood 2014) and to long-term mobilize CXCR4 expressing, malignant cells from protective niches in the bone marrow or other secondary lymphoid tissues, thereby sensitizing them to standard therapy (Figure 1A) (Roccaro et al. 2014, Hinterseer et al. 2013). This therapeutic concept was corroborated in two Phase IIA trials in combination with bendamustine and rituximab in patients with Chronic Lymphocytic Leukemia (abstract #1956) and in combination with bortezomib and dexamethasone in patients with Multiple Myeloma (abstract #1111).

Instead of targeting the genetically unstable tumor cells, olaptesed selectively targets the tumor microenvironment, thereby increasing the efficacy of anti-cancer therapy.

In addition to malignant cells, CXCR4 expressing immune cells are effectively mobilized by olaptesed. In a phase I clinical trial with healthy volunteers a long-term mobilization of CXCR4-expressing cells was observed, such as CD34+ stem cells, B cells, T cells, neutrophils and monocytes (Figure 2).

The mechanism of action of olaptesed is partly overlapping with ibrutinib (BTK inhibitor) and idelalisib (PI3Kδ inhibitor). Ibrutinib and idelalisib induce a transient lymphocytosis, accompanied by a reduction of lymphoid organ size, suggesting that the mode of action of these drugs involves the mobilization of CLL cells from this microenvironment into the blood (Woyach et al. 2014, Brown et al. 2014). Mechanistically, BTK and PI3Kδ inhibition was observed to interfere with homing and adhesion of CLL cells, likely by the involvement of BTK and PI3Kδ in CXCL12/CXCR4 signaling in CLL cells (Figure 1B) (Ponader et al. 2012, Hoellenriegel et al. 2011). However, it has been shown that idelalisib antagonizes rituximab-mediated antibody-dependent cellular cytotoxicity (ADCC) (Kohrt et al. 2014). A recent study showed that besides the inhibition of ADCC, also antibody-dependent cellular phagocytosis (ADCP) is inhibited by idelalisib and that also idelalisib inhibits immune-cell functions (Da Roit et al. 2014).

Based on the mechanistic and pharmacodynamic similarities of olaptesed compared to ibrutinib or idelalisib, the aim was to analyze whether olaptesed influences the immune effector cell function mediated by rituximab or obinutuzumab as has been shown for the BTK or PI3Kδ inhibitors.

<table>
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<tr>
<th>Rituximab (µg/mL)</th>
<th>Obinutuzumab (µg/mL)</th>
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Results on the effect of olaptesed on the immune effector function mediated by rituximab or obinutuzumab

Olaptesed does not interfere with ADCC, whereas ibrutinib and idelalisib decrease ADCC activity of rituximab and obinutuzumab.

Olaptesed does not influence ADCP, whereas ibrutinib and idelalisib decrease ADCP activity of rituximab and obinutuzumab in neutrophils and monocytes.

CONCLUSION & OUTLOOK

- Olaptesed pegol showed no negative interference with the immune effector function of anti-CD20 mAbs (and potentially other mAbs as well), whereas ibrutinib and idelalisib inhibited ADCC and ADCP.
- Instead, neutrophils and monocytes are effectively mobilized with olaptesed which may increase ADCC and ADCP, important mechanisms of action for glycoengineered obinutuzumab (Galay et al. 2013).
- Furthermore, olaptesed may enhance the immune system contribution by mobilization of T cells which are described to be exhausted in the peripheral blood of hematological malignancies like CLL (Riches et al. 2013).
- Olaptesed represents an ideal combination partner for mAbs, as it not only mobilizes malignant cells from protective tissues that may not be accessible to mAbs, but also leads to effective mobilization of immune cells without impairing immune effector activity and adding toxicity.

References: