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POSTER ABSTRACTS

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Comparison of the CXCR5-Antibody Drug Conjugate (ADC; VIP924) to a CD19-ADC and a CD79b-ADC in a Humanized Rec-1 Mantle Cell Lymphoma (MCL) Mouse Model

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Introduction
The chemokine receptor CXCR5 is highly expressed in MCL, which is a rare subtype of non-Hodgkin lymphoma. VIP924 is a first-in-class CXCR5-targeting ADC composed of a legumain-cleavable linker and a kinesin spindle protein inhibitor (KSPi) payload. We compared VIP924 with a CD19- and a CD79b- targeting ADC in a humanized mouse model of MCL.
Methods
Expression of CXCR5 and the B-cell targets CD19 and CD79b were analyzed on tumor samples from patients with MCL using immunohistochemistry. Slides were examined by a pathologist and scored for expression. NSG-SGM3 mice were transplanted with human hematopoietic stem cells from 4 different donors and after engraftment transplanted subcutaneously with REC-1 MCL cells into their flanks. When subcutaneous tumors reached a size of 100 mm ^{3}, mice were randomized into 5 groups and treated with 10 mg/kg of an isotype control ADC, 3 mg/kg polatuzumab vedotin, 0.66 mg/kg loncastuximab teserine, 3 mg/kg VIP924, or 10 mg/kg VIP924 every 5 days for 4 doses. Immunophenotyping of peripheral blood was performed by flow cytometry before starting treatment (Day 0) and on Day 5 and Day 18 during the treatment. At the end of the experiment, immunophenotyping was also done on tumors, spleen, and bone marrow. Complete blood count was analyzed based on single cell evaluation (Drew Scientific HemaVet 950FS Auto Blood Analyzer).
Results
By immunohistochemistry CXCR5 and CD19 showed comparable high expression on patient samples, whereas CD79b expression was moderate. Treatment of humanized mice bearing REC-1 tumors with VIP924 at 10 mg/kg reduced tumor growth effectively ($p<0.0001$ vs. isotype control on Day 10), while treatment with polatuzumab vedotin and loncastuximab teserine showed no effects on tumor growth. This outcome was also reflected in the median survival rates for the different groups with 17 days for isotype control and polatuzumab vedotin, 14 days for loncastuximab teserine and not reached for the 10-mg/kg VIP924 group. However, polatuzumab vedotin treatment significantly reduced hCD45+ cells in peripheral blood and spleen, while loncastuximab teserine treatment showed a clear trend for reduction. VIP924 treatment in both arms had no effect on peripheral or splenic hCD45+ cells. All tested ADCs reduced the CD19+ and more mature CD19+/CXCR5+ B-cells in peripheral blood and spleen, with polatuzumab vedotin and loncastuximab teserine showing significant ($p<0.0001$ vs. isotype control on Day 18) effects on CD19+ cell reductions, while VIP924 treatment showed a milder reduction in CD19+ cells ($p= 0.0051$ for 3 mg/kg and $p= 0.0407$ for 10 mg/kg VIP924). Loncastuximab teserine treatment increased the amount of myeloid derived suppressor cells in the peripheral blood significantly ($p= 0.0467$). In contrast, VIP924 led to a significant ($p< 0.0001$) increase in peripheral regulatory T-cells compared with isotype control. Complete blood counts from treated mice showed a reduction of white blood cells (WBC), absolute lymphocyte count, and absolute monocyte count in loncastuximab teserine-treated animals. Loncastuximab teserine treatment also reduced red blood cell count and hemoglobin values. In VIP924-treated animals, no effects on WBC, red blood cell count, or hemoglobin values were observed. All treatments showed no detrimental effects on body weights of the mice.
Conclusion
CXCR5 is a highly attractive target in B-cell malignancies such as diffuse large B-cell lymphoma and MCL due to high CXCR5 surface expression. VIP924, a CXCR5-targeting ADC, showed high potency and superiority to other B-cell-targeted ADCs in a humanized mouse model of MCL. In this MCL model in humanized mice, VIP924 at 10 mg/kg treatment showed a significant reduction in tumor growth and improvement in survival, while polatuzumab vedotin and loncastuximab teserine had no effect

on tumor growth or survival. Interestingly, VIP924 was the only ADC to cause a significant increase in peripheral T regulatory cells, which may enhance tumor growth inhibition. Loncastuximab teserine had a deleterious effect on several hematologic parameters, which was not observed with VIP924 or polatuzumab vedotin. The efficacy and tolerability observed in this study with VIP924 suggests further testing in human clinical trials is warranted.

Disclosures Schomber: *Vincerx Pharma:* Current Employment, Current equity holder in publicly-traded company. **Stelte-Ludwig:** *Vincerx Pharma:* Current Employment, Current equity holder in publicly-traded company. **Rebstock:** *Vincerx Pharma:* Current Employment, Current equity holder in publicly-traded company. **Johnson:** *Vincerx Pharma:* Current Employment, Current equity holder in publicly-traded company. **Izumi:** *Vincerx Pharma:* Current Employment, Current equity holder in publicly-traded company. **Hamdy:** *Vincerx Pharma:* Current Employment, Current equity holder in publicly-traded company.

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