We identified potent and selective CDK8 inhibitors, including BI-1347 and BI-9811, that we previously reported as valuable probe compounds (Hofmann M.H., et al., AACR Annual Meeting 2017). CDK8 inhibition promoted activation of NK cells but had no direct cytotoxic activity on the majority of cancer cell lines tested. Single agent treatment with the CDK8 inhibitor BI-1347 increased the survival of mice bearing melanoma and breast cancer allografts.

We evaluated whether increased efficiency could be observed upon activation of both the innate and the adaptive immune system by combining the CDK8 inhibitor with Fc engineered antibodies or SMAC mimetics. SMAC mimetic treatment enhanced NK cell cytotoxicity and increased NK cell number in the murine EMT6 breast cancer model.

CDK8 inhibitors: Enhanced NK cell cytotoxicity

Figure 1.

Methods

Selection of our CDK8 inhibitors was based on the Kinase profiling from ICR and CD biomarker modulation of STAT1/UGK following treatment of N82-M2 cells. Modulation of phospho-S1252/1265 in primary human NK cells from healthy donors by CDK8 inhibitor with Fc engineered antibodies or SMAC mimetics was assessed. SMAC mimetic treatment enhanced T-cell activity and increased NK cell number in the murine EMT6 breast cancer model.

Results

In vivo biomarker modulation and efficacy in monotherapy

Figure 4. A) In vivo biomarker modulation in ovarian cancer xenografts treated with BI-1347 (4-5 mg/kg qd) and BI-9811, qd. B) Treatment with the SMAC mimetic BI-3382 enhanced the number of CD4, CD8 T-cells and NK cells.

CDK8 inhibitors enhance ADCC of Fc engineered antibodies

Figure 5. A) Depletion of primary leukemia cells from chronic lymphocytic leukemia patients in monotherapy with CDK8 inhibitors, which was increased in combination with Tol替米特. B) Enhanced ADCC by CDK8 inhibitor treated NK cells. Effector NK cells (m2 healthy donors) were treated with CDK8 inhibitor over night before using for ADCC with radiolabeled HL-60 target cells treated with CD33 mAb (BI 836858) or isotype control.

Conclusions

We propose new strategies for development and positioning of CDK8 inhibitors in solid tumors by:

- Using CDK8 inhibitors as mediators of NK cell activity, rather than tumor directed therapy in solid cancers;
- Applying intermittent scheduling in order to avoid NK cell hypo-responsiveness and to minimize safety concerns.

We would like to thank all technical scientists that supported this work.

Acknowledgements

References