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SY-1365, a potent and selective CDK7 inhibitor, exhibits anti-tumor activity in preclinical models of hematologic malignancies and demonstrates interactions with the BCLXL/BCL2 mitochondrial apoptosis signaling pathway in leukemia

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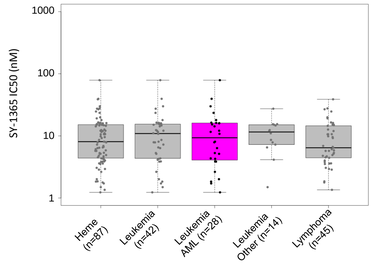
Introduction

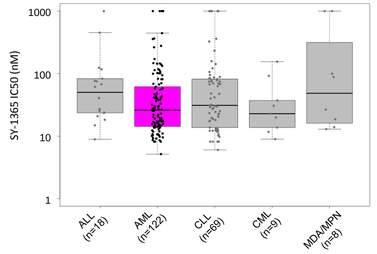
- CDK7 is an important regulator of transcription through regulation of RNA Pol II and CDK9, and cell cycle progression through regulation of cell-cycle kinases CDK1, CDK2, CDK4 and CDK6
- CDK7 has been implicated in the pathogenesis of multiple malignancies, including hematologic malignancies
- SY-1365, a covalent and selective inhibitor of CDK7, has been developed to exploit tumor dependencies driven by CDK7 and is in clinical development in patients with advanced solid tumors
- SY-1365 potently inhibits leukemia cell lines, lymphoma cell lines, and primary cultures derived from leukemia patients in vitro
- SY-1365 in vitro sensitivity is associated with regulation of mitochondrial apoptosis antagonists, and is synergistic with the BCL2 inhibitor venetoclax
- In AML xenografts, intermittent dosing of SY-1365 has potent anti-leukemic activity as a single agent, and enhances response to venetoclax in combination

SY-1365 potently inhibits proliferation of hematologic malignancy models in vitro

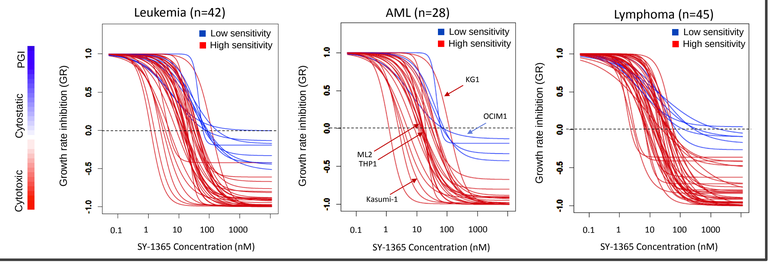
Leukemia and lymphoma cell lines (n=87)



Leukemia patient primary cultures (n=226)

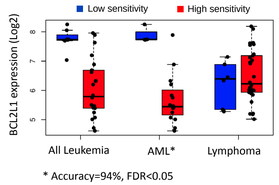


SY-1365 induces cytotoxic responses in leukemia and lymphoma cell lines

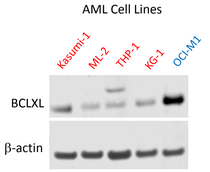


The combination of SY-1365-induced MCL1 downregulation and low baseline *BCL2L1*/BCLXL expression is associated with SY-1365 cytotoxicity in AML cell lines

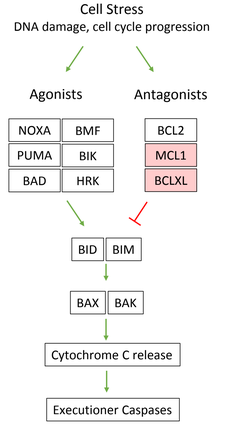
Low *BCL2L1*/BCLXL expression is associated with SY-1365 sensitivity in AML



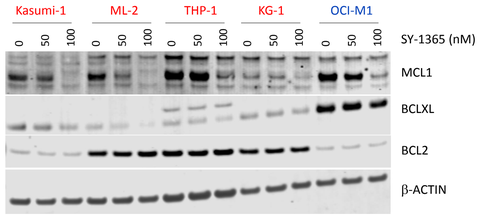
* Accuracy=94%, FDR<0.05



Mitochondrial Apoptosis Pathway



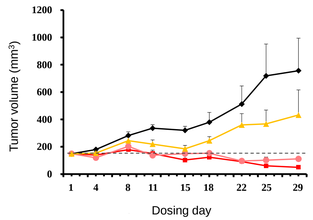
SY-1365 induces MCL1 downregulation in AML cell lines



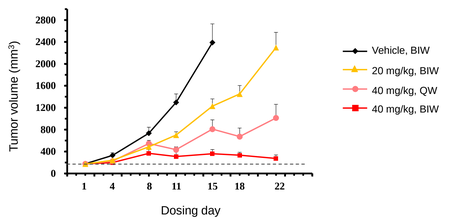
24 hours post SY-1365 treatment

SY-1365 induces tumor growth inhibition including regressions in AML xenograft models using intermittent dosing

Kasumi-1



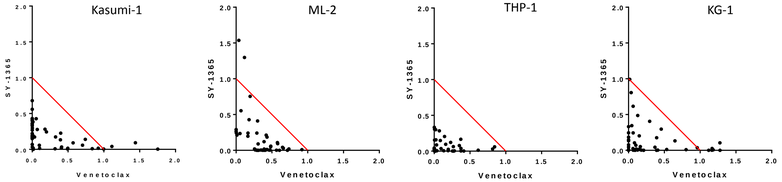
ML-2



SY-1365 was administered i.v. twice weekly (BIW) on the dosing days shown, or once weekly (QW) on dosing days 1, 8, 15, 22.

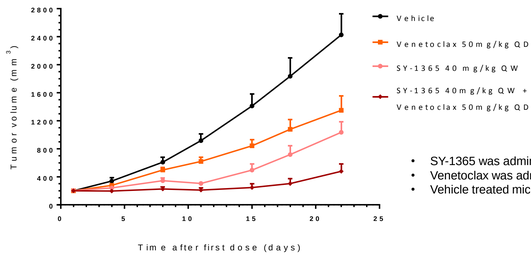
SY-1365 enhances activity of the BCL2 inhibitor venetoclax in AML models

SY-1365 synergizes with venetoclax in AML cell lines in vitro



Isobolograms from SY-1365 and venetoclax in vitro combination studies. The red line represents expected data from an additive interaction. Data points below and left of the red line represent synergistic interactions; data points above and right of the red line represent antagonistic interactions). No isobologram is available for OCI-M1 since additivity, synergy, or antagonism were not observed in this high BCLXL-expressing line.

SY-1365 enhances response to venetoclax in KG-1 AML xenografts



- SY-1365 was administered once weekly (QW) i.v.
- Venetoclax was administered once daily (QD) by oral gavage
- Vehicle treated mice received vehicle of both regimens

Conclusions

- SY-1365 potently inhibits proliferation of hematologic malignancy cell lines and leukemia-patient-derived primary cultures in vitro
- SY-1365 induces cytotoxic responses in hematologic cell lines in vitro and tumor growth inhibition, including regressions, in AML xenografts in vivo
- Sensitivity to SY-1365 in AML cell lines is associated with low baseline expression of *BCL2L1*/BCLXL, and SY-1365-induced down-regulation of MCL1
- SY-1365 synergizes with the BCL2 inhibitor venetoclax in AML cell lines in vitro, and enhances responses to venetoclax in KG-1 AML xenografts in vivo
- SY-1365 is currently being assessed in a phase 1 trial in adult patients with advanced solid tumors (NCT03134638)
- These results support the potential for SY-1365 in treatment of AML and future clinical evaluation in hematologic malignancies

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