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SY-1365, a selective CDK7 inhibitor, exhibits potent anti-tumor activity against ovarian cancer models in vitro and in vivo

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Summary

Background

- The outlook for patients with treatment resistant ovarian cancer is poor and novel therapies are needed
- Recent preclinical studies have identified CDK7 as a potentially important new therapeutic target in solid tumors, including ovarian cancer
- CDK7 is a transcriptional kinase that acts as a master regulator of transcription and cell cycle progression
- SY-1365, a covalent and selective inhibitor of CDK7, has been developed to exploit tumor dependencies driven by CDK7

Results

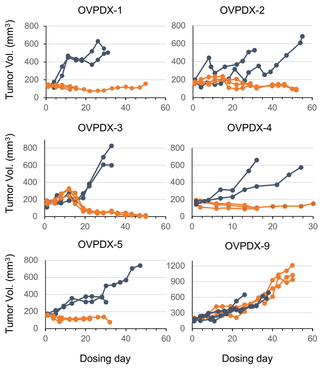
- SY-1365 induces cytotoxicity and MCL1 downregulation in ovarian cancer cell lines in vitro
- SY-1365 induces tumor growth inhibition, including complete regressions, in ovarian cancer PDX models
- SY-1365 responses in preclinical models are associated with alterations in mitochondrial apoptosis and RB signaling pathways

Conclusions

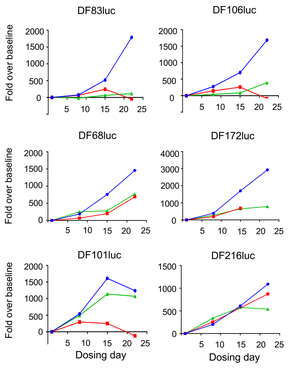
- These results support further exploration of SY-1365 activity and biomarkers of response in patients with ovarian cancer
- SY-1365 is currently being assessed in a phase 1 trial in adult patients with advanced solid tumors, including expansion cohorts in patients with high-grade serous ovarian cancer (HGSOC) as a single agent and in combination with carboplatin (NCT03134638)

SY-1365 induces tumor growth inhibition, including regressions, in ovarian carcinoma PDX models derived from previously treated patients

- Responses observed in PDXs derived from patients treated with multiple prior therapies including platinum therapy
- Responses observed irrespective of BRCA status and/or olaparib sensitivity



Growth of ovarian PDX models (Crown Bioscience) with twice weekly (BIW) dosing of SY-1365 at either 30 mg/kg or 40 mg/kg. Orange curves represent tumor growth in individually treated mice (n=3). Blue curves represent historical tumor growth. All 5 responsive models and 1 representative non-responsive model are shown.



Growth of luciferase-expressing ovarian PDX models. Results normalized to luminescence measured at baseline. Red curves represent growth in individual mice treated with 30 mg/kg SY-1365 BIW; green curves, 40 mg/kg once weekly (QW); blue curves, vehicle twice weekly. All 5 responsive models and 1 non-responsive model are shown.

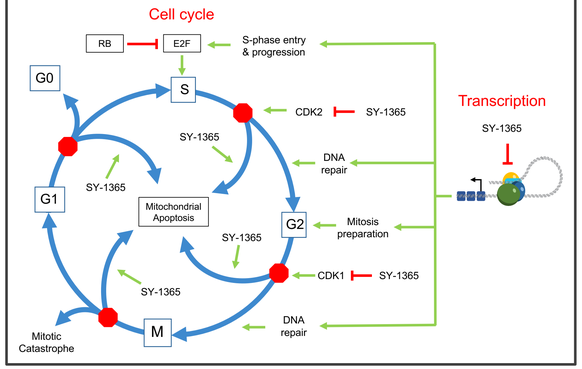
PDX Model[a]	SY-1365 Response	RB Pathway Alterations[b]	HRD Pathway Alterations[c]	# of Prior Therapies[d]	Olaparib Sensitivity
OVPDX-1	≥100% TGI	Low RB1	ATM mut	4	unknown
OVPDX-2	≥100% TGI	Low RB1	BRCA1 mut, ATM mut	4	unknown
OVPDX-3	≥100% TGI	Low CDKN2A	none	3	unknown
OVPDX-4	≥100% TGI	none	none	unknown	unknown
OVPDX-5	≥100% TGI	pending	pending	5	unknown
OVPDX-6	No TGI	none	none	4	unknown
OVPDX-7	No TGI	none	none	2	unknown
OVPDX-8	No TGI	none	BRCA2 mut	unknown	unknown
OVPDX-9	No TGI	none	ATR mut	4	unknown

PDX Model[a]	SY-1365 Response	RB Pathway Alterations[e]	HRD Pathway Alterations	# of Prior Therapies[d]	Olaparib Sensitivity[f]
DF83luc	≥100% TGI	CDKN2A loss	none	5	Sensitive
DF106luc	≥100% TGI	CDKN2A loss	none	2	Partially sensitive
DF172luc	Partial TGI	High CCNE1	RAD51C mut	3	Resistant
DF68luc	Partial TGI	High CCNE1	BRCA1 mut	8	Resistant
DF101luc	TGI[g]	none	BRCA1 mut	3	Resistant
DF86luc	No TGI	none	BRCA1 mut	unknown	Partially sensitive
DF149luc	No TGI	none	none	2	Resistant
DF216luc	No TGI	none	none	3	Resistant

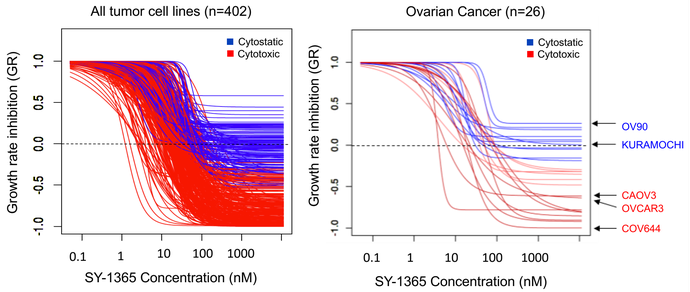
[a] All models derived from patients diagnosed with HGSOC except DF172luc (mixed serous and endometrioid) and DF216luc (adenocarcinoma); [b] RB1 and CDKN2A RNA expression assessed by Nanostring; [c] Mutations in BRCA1/2, ATM, ATR, and RAD51 assessed by exome sequencing; [d] Number of different therapies the patient received prior to establishment of the PDX model; [e] CCNE1 RNA expression assessed by QRT-PCR, CDKN2A loss assessed by DNA sequencing; [f] Assessed in prior PDX efficacy studies; [g] Possible responder, regression observed at 30 mg/kg BIW, no TGI at 40 mg/kg QW.

Model of the interplay between SY-1365, transcription, cell cycle progression, and mitochondrial apoptosis

- Successful transition through the cell cycle requires orderly activation of transcriptional- and CDK-dependent mechanisms
- RB-deficient (e.g. RB1 loss, CDKN2A loss, CCNE1 amplification) tumor cells are perpetually committed to the cell cycle and have developed adaptations that enable successful progression through the cell cycle despite damaged DNA and genomes (e.g. suppression of mitochondrial apoptosis, activation of DNA damage response and repair pathways)
- SY-1365 is predicted to inhibit these transcriptional- and CDK-dependent adaptations at multiple points, thereby promoting induction of mitochondrial apoptosis



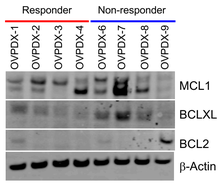
SY-1365 induces cytotoxic responses in human tumor cell lines



SY-1365 activity was evaluated in a panel of 402 cell lines from solid tumor and hematologic malignancies (Chempartner). Growth rate inhibition (GR) curves were generated by comparing cell number at baseline to cell number 72h after treatment with SY-1365 at various concentrations (10-point serial dilution). GR<0 indicates cytotoxicity (cell death exceeds cell proliferation). GRmax (depth of response) and GR50 (concentration of SY-1365 required to induce 50% of the maximal effect) were used to classify cell lines into cytotoxic lines (low GRmax, low GR50; red) and cytostatic lines (high GRmax, high GR50; blue).

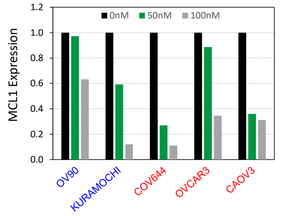
SY-1365 responses are associated with alterations in mitochondrial apoptosis and RB signaling pathways

Low expression of BCLXL and BCL2 are associated with SY-1365 responses in ovarian PDX models



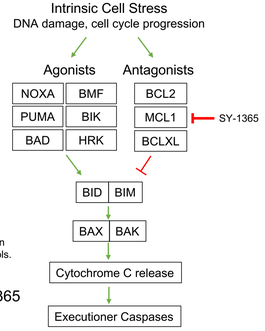
Note: Tissue not available for OVPDX-5

SY-1365 induces MCL1 protein downregulation in ovarian cancer cell lines

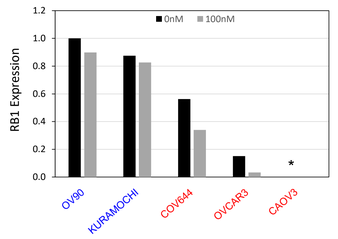


Cells treated for 24h with SY-1365; MCL1 protein measured by Western blot. Data normalized relative to β-actin and no treatment (0 nM) controls.

Mitochondrial Apoptosis Pathway



Low RB1 protein expression is associated with SY-1365 cytotoxicity in ovarian cancer cell lines



Cells treated for 24h with SY-1365; RB1 protein measured by Western blot. Data normalized relative to β-actin and no treatment (0 nM) controls for the highest RB1-expressing ovarian cancer line OV90. * No RB1 protein expression detected in CAOV3.

- Low expression of BCL2L1 (BCLXL gene) is the most predictive marker of SY-1365 sensitivity across all 402 cancer cell lines (Accuracy = 70%; FDR=0.006)
- Trend maintained in ovarian cancer lines (Accuracy =73%; FDR=0.1)

Conclusions

- SY-1365 is a first-in-class selective CDK7 inhibitor with therapeutic potential across a range of difficult-to-treat solid tumors and blood cancers
- SY-1365 induces cytotoxicity and MCL1 protein downregulation in ovarian cancer cell lines in vitro
- SY-1365 induces tumor growth inhibition, including complete regressions, in a majority of PDX models derived from heavily pretreated ovarian cancer patients
  - Responses observed irrespective of BRCA status and/or olaparib sensitivity
- SY-1365 responses in preclinical models are associated with alterations in mitochondrial apoptosis and RB signaling pathways
- These results highlight the potential for SY-1365 in the treatment of ovarian cancer. Further explorations of SY-1365 activity and predictive markers of response in solid tumors including ovarian cancer are ongoing
- SY-1365 is currently being assessed in a phase 1 trial in adult patients with advanced solid tumors, including expansion cohorts in patients with high-grade serous ovarian cancer (HGSOC) as a single agent and in combination with carboplatin (NCT03134638)

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