**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.

**SY-1365 induces tumor growth inhibition, including regressions, in ovarian carcinoma PDX models derived from patients with high tumor dependencies driven by CDK7.**

- Responses observed in PDXs derived from patients treated with multiple prior therapies including platinum therapy.
- Responses observed irrespective of BRCA status and/or RB1 expression.

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

- Successful outcome through the cell cycle requires orderly activation of transcriptional and CDK7 expression pathways.
- RB-deleted (e.g., RB1 loss, CDKN2A loss, CDK7 amplification) tumors are completely dependent on the cell cycle and have developed adaptations that enable successful progression through the cell cycle despite damaged DNA and genes (e.g., expression of mitochondrial apoptosis, activation of DNA damage response and repair pathways).
- SY-1365 is predicted to inhibit these transcriptional and CDK7 dependent adaptations at multiple points, thereby unveiling resolution of mitochondrial apoptosis.

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

- 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 RB1 expression.
- 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 exploration 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.

**SY-1365 induces cytotoxic responses in human tumor cell lines.**

- All tumor cell lines (n=422) + Ovarian Cancer (n=26).

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

- Low expression of BCL2L1 and BCL2 are associated with SY-1365 responses in ovarian carcinoma PDX models.

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

- Successful outcome through the cell cycle requires orderly activation of transcriptional and CDK7 expression pathways.
- RB-deleted (e.g., RB1 loss, CDKN2A loss, CDK7 amplification) tumors are completely dependent on the cell cycle and have developed adaptations that enable successful progression through the cell cycle despite damaged DNA and genes (e.g., expression of mitochondrial apoptosis, activation of DNA damage response and repair pathways).
- SY-1365 is predicted to inhibit these transcriptional and CDK7 dependent adaptations at multiple points, thereby unveiling resolution of mitochondrial apoptosis.

**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 RB1 expression.
- 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 exploration 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.