SRA737 Monotherapy in CCNE1<sup>DD</sup>-High Grade Serous Ovarian Cancers

**Rationale**

- Approximately 30% of high grade serous ovarian cancers (HGSOC) harbor CCNE1 gene amplifications.<br>
- CCNE1 amplifications result in hyperactivation of CDK2, which is coupled to excessive replication fork collapse, genomic instability, and the potential resistance to PARPi therapy. <br>
- CCNE1 is known to induce replication stress (RS) and genome instability, leading to increased cellular radiosensitivity as Checkpoint kinase 1 (Chk1) is an essential effector of the cellular RS response to induced DNA damage. RS may be formed by single-strand breaks (SSBs) or double-strand breaks (DSBs), leading to cancer cell death if not repaired.

**Conclusions**

- Monotherapy, SRA737 led to a highly reduced ability of CCNE1<sup>DD</sup> to induce fork collapse, genomic instability, and the potential resistance to PARPi therapy. <br>
- CCNE1 amplification increases the risk of genomic instability resulting in subsequent cell death and tumor regression in CCNE1<sup>DD</sup>-ovarian cancer models.

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**SRA737 + PARPi in HRD deficient and Acquired PARPi-resistant High Grade Ovarian Cancers**

**Rationale**

- A distinct subgroup comprising approx 30% of HGSOC have distinct homologous recombination repair (hHRD) loss of function which confers a distinct sensitivity to poly (ADP-ribose) polymerase (PARPi) treatment, a mechanism that involves inactivating PARPi-resistant tumors. SRA737 is a potent Chk1 inhibitor, SRA737 in combination with PARPi may exploit this additional mechanism of PARPi sensitivity.

**Conclusions**

- The efficacy of SRA737 monotherapy is currently being investigated in HGSOC, A distinct subgroup comprising approximately 50% of HGSOC have defective homologous recombination repair (hHRD) loss of function which confers a distinct sensitivity to PARPi treatment.

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**Figure 1**

- Shows Chk1 is inhibited in HGSOC by SRA737 monotherapy and PARPi in combination.

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**Figure 2**

- Shows the efficacy of SRA737 monotherapy is currently being investigated in HGSOC, A distinct subgroup comprising approximately 50% of HGSOC have defective homologous recombination repair (hHRD) loss of function which confers a distinct sensitivity to PARPi treatment.

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**Figure 3**

- Shows the efficacy of SRA737 monotherapy is currently being investigated in HGSOC, A distinct subgroup comprising approximately 50% of HGSOC have defective homologous recombination repair (hHRD) loss of function which confers a distinct sensitivity to PARPi treatment.

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**Figure 4**

- Shows the efficacy of SRA737 monotherapy is currently being investigated in HGSOC, A distinct subgroup comprising approximately 50% of HGSOC have defective homologous recombination repair (hHRD) loss of function which confers a distinct sensitivity to PARPi treatment.

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**Figure 5**

- Shows the efficacy of SRA737 monotherapy is currently being investigated in HGSOC, A distinct subgroup comprising approximately 50% of HGSOC have defective homologous recombination repair (hHRD) loss of function which confers a distinct sensitivity to PARPi treatment.

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**Figure 6**

- Shows the efficacy of SRA737 monotherapy is currently being investigated in HGSOC, A distinct subgroup comprising approximately 50% of HGSOC have defective homologous recombination repair (hHRD) loss of function which confers a distinct sensitivity to PARPi treatment.

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**Figure 7**

- Shows the efficacy of SRA737 monotherapy is currently being investigated in HGSOC, A distinct subgroup comprising approximately 50% of HGSOC have defective homologous recombination repair (hHRD) loss of function which confers a distinct sensitivity to PARPi treatment.

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**Figure 8**

- Shows the efficacy of SRA737 monotherapy is currently being investigated in HGSOC, A distinct subgroup comprising approximately 50% of HGSOC have defective homologous recombination repair (hHRD) loss of function which confers a distinct sensitivity to PARPi treatment.