Rucaparib has limited activity against the kinases PIM1, PIM2, and PIM3

Potential compounds have shown in vitro activity against the kinases PIM1, PIM2, and PIM3 in biochemical assays against PIM1, PIM2, and PIM3, and the IC50 values were 0.14, 0.83, and 2.04 µM, respectively. Rucaparib showed limited activity (IC50 > 40 µM) against PIM1, PIM2, and PIM3 in cellular recombinant expression. Increased PARP activity was observed with the PIM-3 inhibitor AZD12186.

Rucaparib has limited cellular activity against TNKS1/2

Rucaparib has weak activity against TNKS1/2 in enzymatic assays. TNKS/2 play an important role in Wnt pathway signaling. Rucaparib demonstrated limited activity in a NIH 3T3 cell reporter assay (IC50 > 50 µM) as compared to the positive control TNKS1/2 inhibitor GSK737-L (IC50 = 0.016 µM).

Rucaparib is a potential and selective PARP-1, PARP-2, and PARP-3 inhibitor

Rucaparib potency and selectivity WtPARP, PARP-1, PARP-2, and PARP-3 in enzymatic assays

Rucaparib mechanism of action

• Rucaparib treatment results in polyp-ADP-ribose (PAR) inhibition and increased DNA damage.
• Rucaparib treatment induces G2/M cell cycle arrest.

DNA Damage

1. Rucaparib treatment results in polyp-ADP-ribose (PAR) inhibition and increased DNA damage.
2. Rucaparib treatment induces G2/M cell cycle arrest.

Apoptosis

1. Increased apoptosis (apoptosis 37% levels) is observed after 5-10 days of rucaparib treatment.

Cell Death

1. Decreased cell viability is observed 5-12 days after rucaparib treatment.

Rucaparib has potently active xenograft and syngeneic BRCA2 mutant models

Rucaparib activity was evaluated in an established triple-negative breast cancer (TNBC) xenograft model (MDA-MB-436), TNBC patient-derived xenograft (PDX) model (MDA-MB-231), and ovarian cancer syngeneic model (BRCA1). PARP inhibition results in DNA damage, cell cycle arrest, apoptosis, and decreased cell viability.

CONCLUSIONS

• Rucaparib is a potent and selective PARP-1, PARP-2, and PARP-3 inhibitor with limited activity against other PARP enzymes including TNKS1/2.
• Rucaparib inhibited the proliferation of HRD cells and syngeneic BRCA2 mutant model.
• Rucaparib demonstrated potency in xenograft and syngeneic mutant BRCA2/TNBC and ovarian cancer models.
• Rucaparib treatment resulted in DNA damage, cell cycle arrest, apoptosis, and decreased cell viability.
• Rucaparib has good oral bioavailability and tumor distribution in mice.
• Rucaparib levels in the plasma and tumor increased with dose, and were inversely correlated with PK levels but directly correlated with greater tumor growth inhibition.

REFERENCES

1. Antoniou and Mischler. Oncotarget 2014;5:3020-3