Differentiation of Niraparib and Olaparib Brain Penetration in Healthy Rhesus Macaque Monkeys

Abstract #3581

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Background

- There remains an unmet need to provide effective treatment for patients with primary and metastatic brain tumors[1]
  - Patients with brain metastases or primary brain tumors have a poor prognosis and low 5-year survival rates[1,2]
  - This is mainly due to a lack of drugs that can penetrate the blood–brain barrier (BBB)[3]
- Synthetic lethality is an attractive mechanism for treating brain tumors after radiotherapy; however, there are no poly(ADP-ribose) polymerase (PARP) inhibitors currently approved for central nervous system cancers[4]
- Recently Sanai et al showed that niraparib reached and maintained pharmacologically relevant concentrations in the brain and glioblastoma tumor tissue resulting in effective PARP inhibition in patients with newly diagnosed glioblastoma[5]
- Here we investigate the brain penetration of niraparib and olaparib in healthy monkeys to generate evidence of their ability to cross the BBB

Objective

- Evaluate the brain penetration and distribution of 2 PARP inhibitors (niraparib and olaparib) in a primate model of an intact BBB

Conclusions

- Niraparib showed markedly higher brain penetration than olaparib in healthy Rhesus macaque monkeys, demonstrating enhanced ability to cross an intact BBB compared with olaparib
  - Olaparib was not detected in any examined brain section
- Further studies are warranted to evaluate niraparib as a treatment for primary and metastatic brain tumors

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Presented at the American Association for Cancer Research (AACR) Annual Meeting, April 14–19, 2023; Orlando, FL, USA.

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Acknowledgments

This study was funded by GSK (Philadelphia, PA, USA). Writing and editorial support, funded by GSK and coordinated by Hasan Jamal, MSc, of GSK were provided by David M. Jensen, PhD, and Mary C. Wiggin of Ashfield MedComms, an Inizio company.

Conflicts of Interest

All authors are employees of GSK.

Methods

- Healthy male Rhesus macaque monkeys were dosed daily via oral gavage for 5 days with either niraparib (6 mg/kg) or olaparib (10 mg/kg)
- This study was conducted in accordance with the GSK policy on the Care, Welfare, and Treatment of Laboratory Animals and was reviewed by the Institutional Animal Care and Use Committee at GSK
- Predose blood was collected daily; terminal blood, cerebrospinal fluid (CSF), and brain tissue were collected at necropsy
- Coronal brain sections were analyzed by matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI IMS) to quantitatively assess the tissue distribution of the dosed compounds
- Blood, CSF, and bulk homogenates of brain tissue were analyzed by liquid chromatography-mass spectrometry (LC-MS) bioanalysis
- The unbound brain-to-plasma partition coefficient ($K_{p,uu,brain}$), which describes the unbound drug concentration in the brain compared with the blood based solely on the net influx and efflux crossing the BBB, is reported to increase clinical translation

Results

- A total of 4 Rhesus macaque monkeys were dosed with niraparib (n=2) or olaparib (n=2)
- The $K_{p,uu,brain}$ was approximately 15-fold higher for niraparib than olaparib (**Table 1**)
  - The mean $K_{p,uu,brain}$ was 0.30 in monkeys dosed with niraparib and 0.02 in monkeys dosed with olaparib
  - In bulk brain homogenates, LC-MS bioanalysis showed greater brain concentrations of niraparib (378 and 797 ng/g) than olaparib (12 and 11 ng/g)
  - Similar plasma and CSF concentrations were observed for niraparib and olaparib, suggesting that the greater brain concentrations of niraparib versus olaparib were due to the unique ability of niraparib to cross the BBB

Table 1. Drug Concentrations

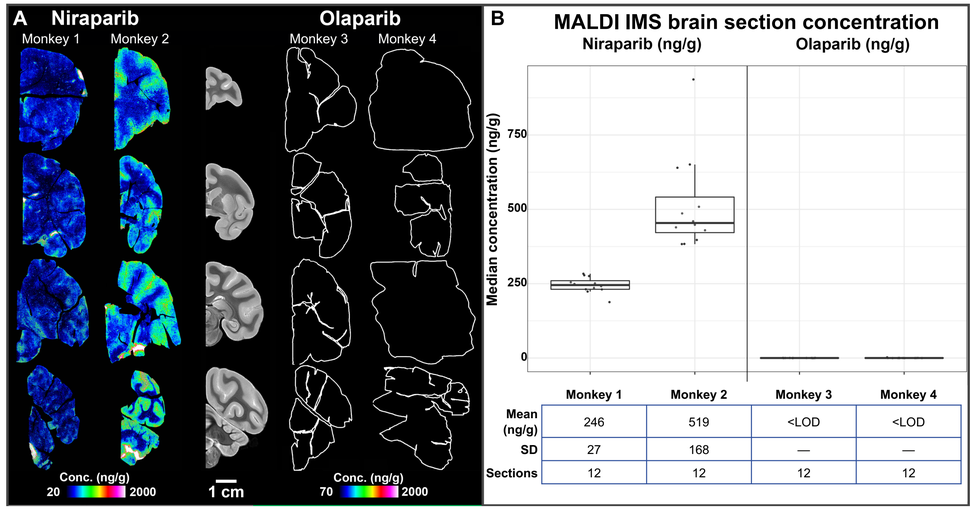
Drug and animal	Terminal plasma, ng/mL	Terminal CSF, ng/mL	Bulk brain homogenate, ng/g	$K_{p,uu,brain}$	Mean $K_{p,uu,brain}$
Niraparib					
Monkey 1	84	9	378	0.45	0.300
Monkey 2	436	25	797	0.16	
Olaparib					
Monkey 3	322	13	12	0.02	0.023
Monkey 4	254	6	11	0.03	

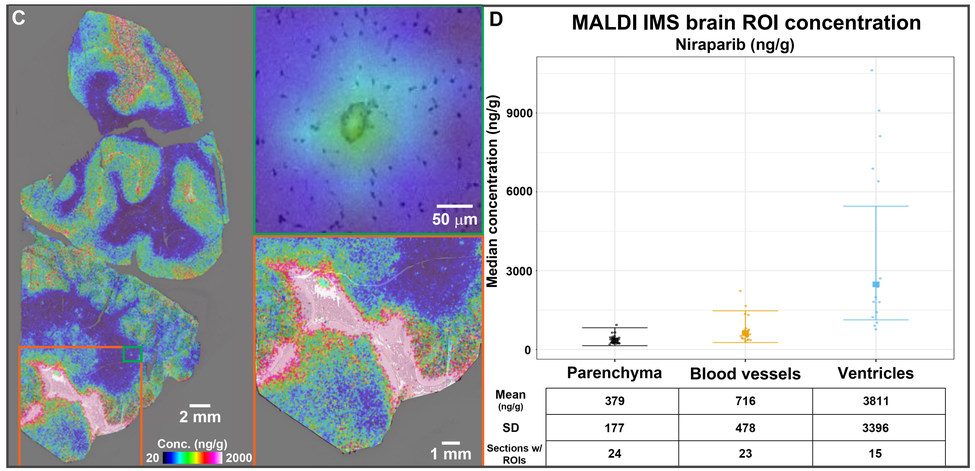
Values are total concentrations. $K_{p,uu,brain}$ calculated using bulk brain homogenate and terminal plasma-free concentrations.
CSF, cerebrospinal fluid; $K_{p,uu,brain}$, unbound brain-to-plasma partition coefficient; LC-MS, liquid chromatography-mass spectrometry.

- Drug penetration and distribution in the brain was assessed by overlaying MALDI IMS analysis of coronal brain sections with hematoxylin and eosin stained sections (**Figure 1**)
  - Niraparib distribution was nominally higher in the ventricles than in the blood vessels and brain parenchyma; olaparib was not detected in any examined brain section

Results *(cont'd)*

Figure 1. Brain Penetration and Distribution by MALDI IMS and H&E Staining





The estimated LOD is 12 ng/g for niraparib and 16 ng/g for olaparib. **(A)** MALDI IMS of representative brain tissue sections collected at 4 different anatomical planes from monkeys administered either niraparib or olaparib. **(B)** Above: Tissue section median concentration box plots for niraparib and olaparib for each monkey. Below: table of the mean of the median concentration for each section for each respective animal, SD, and tissue section count. **(C)** Representative brain tissue section from a monkey administered niraparib displayed as overlay of ion image for niraparib with H&E-stained section and a magnified view of a blood vessel and ventricle region. **(D)** Above: estimated marginal means of the concentration of niraparib in each of the ROIs (square points) with 95% CIs of these estimated marginal means (error bars). Below: table of the average, SD, and count of the number of sections from niraparib-dosed monkeys that included each respective region. For sections that contained multiple ROIs for a histological feature, the values were combined and the median concentration was reported.

H&E, hematoxylin and eosin; LOD, limit of detection; MALDI IMS, matrix-assisted laser desorption/ionization imaging mass spectrometry; ROI, region of interest; SD, standard deviation.