RBTT-01

A phase 2 trial with ABI-009 (*nab*-sirolimus) as single-agent and combinations in recurrent high-grade glioma (rHGG) and in newly diagnosed glioblastoma (ndGBM)

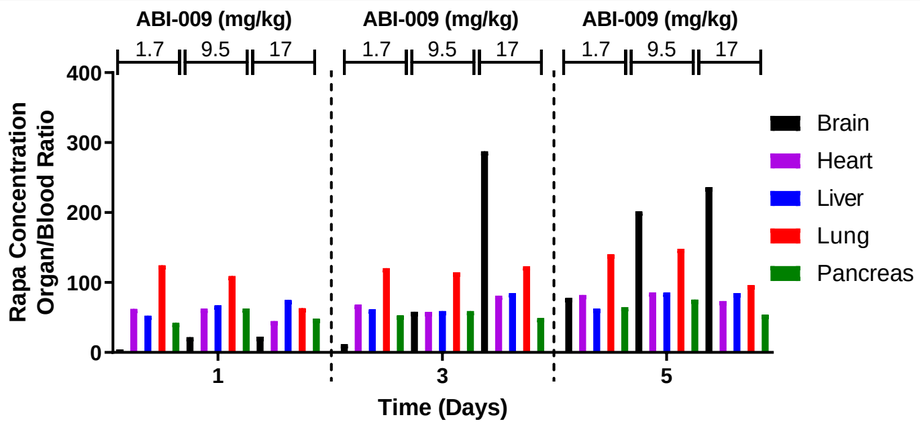
Santosh Kesari, MD, PhD,[1] Tiffany Juarez, PhD,[1] Jose Carrillo, MD,[2] David Park, MD,[3] Judy Truong, PA-C,[1] Minhdan Nguyen, PA-C,[1] Annie Heng, RN,[1] Jaya Gill, RN,[1] Hanh Nguyen,[1] Natsuko Nomura,[1] Berta Grigorian,[4] Shihe Hou, PhD,[4] Anita Schmid, PhD,[4] Neil Desai, PhD [4]

1. John Wayne Cancer Institute at Providence Saint John's Health Center, and Pacific Neuroscience Institute, Santa Monica, CA; 2. Hoag Memorial Hospital Presbyterian, Newport Beach, CA; 3. St. Joseph Heritage Healthcare, Fullerton, CA; 4. Aadi Bioscience, Pacific Palisades, CA

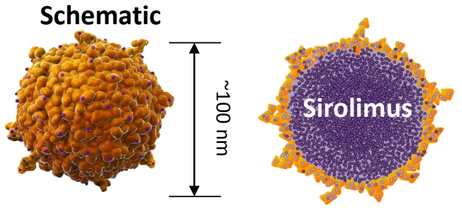
BACKGROUND

- The mTOR pathway is frequently activated in patients with GBM and is associated with reduced survival, making this pathway a promising target. However, mTOR inhibitors, including everolimus and temsirolimus, have poor brain penetration, limiting their potential use for GBM. *nab*-Sirolimus (ABI-009) is a novel albumin-bound mTOR inhibitor that has a distinct PK profile and biodistribution, including CNS penetration.[1]

Figure 1. Tissue vs blood sirolimus concentration ratios at days 1, 3, and 5 after administration

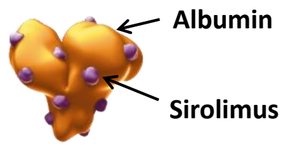


nab-Sirolimus Nanoparticle Schematic



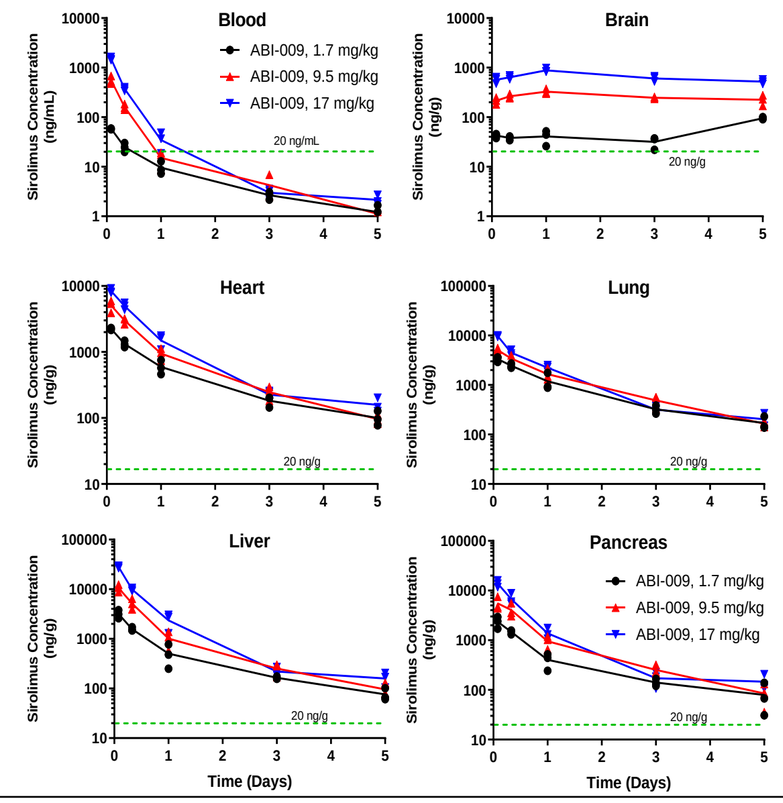
Cross Section

Albumin-bound Sirolimus



- Brain levels of sirolimus from ABI-009 were maintained steady over the 5-day period tested suggesting a retention and accumulation in brain tissue. This was in contrast to the several tissues tested which showed a drop in sirolimus over time.

Figure 2. Blood and tissue sirolimus concentration-time profiles



The goal of this prospective open-label phase 2 study is to evaluate the efficacy and safety of *nab*-sirolimus monotherapy and combination therapies in rHGG and ndGBM

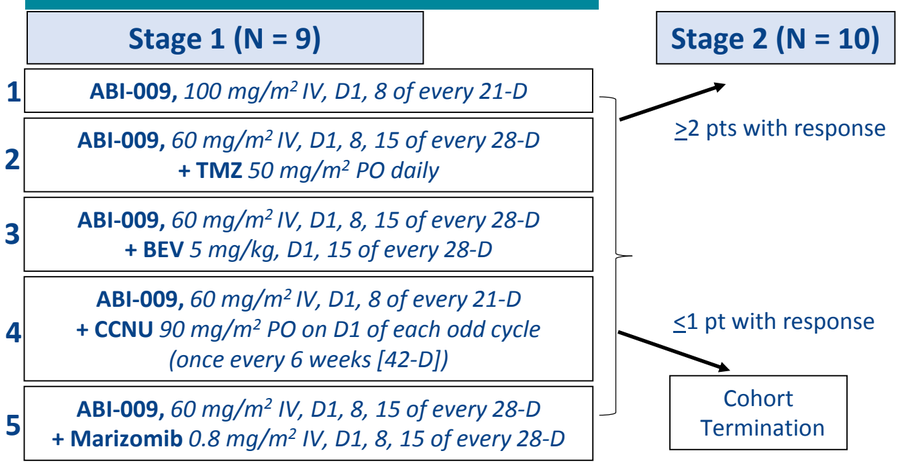
METHODS

- Eligible patients are ≥18 years old, KPS score ≥70, and have histologically confirmed rHGG or ndGBM.
- Arm A has 5 cohorts in patients with rHGG, naïve to mTOR inhibitors, and Arm B enrolls patients with ndGBM, see study schema.
- Up to 19 patients per cohort will be enrolled: initial 9 patients with a stopping rule that only if there are ≥2 responses will the study cohort proceed to further enrollment of the next 10 patients (Simon's 2-stage design).
- Treatment will continue until disease progression or unacceptable toxicity.
- The primary endpoint for all cohorts is overall response rate per RANO criteria; secondary endpoints are median PFS and OS, 6-month and 12-month PFS, 12-month OS, and adverse events. Exploratory endpoints are blood levels of sirolimus and biomarkers, and tumor molecular profiling.

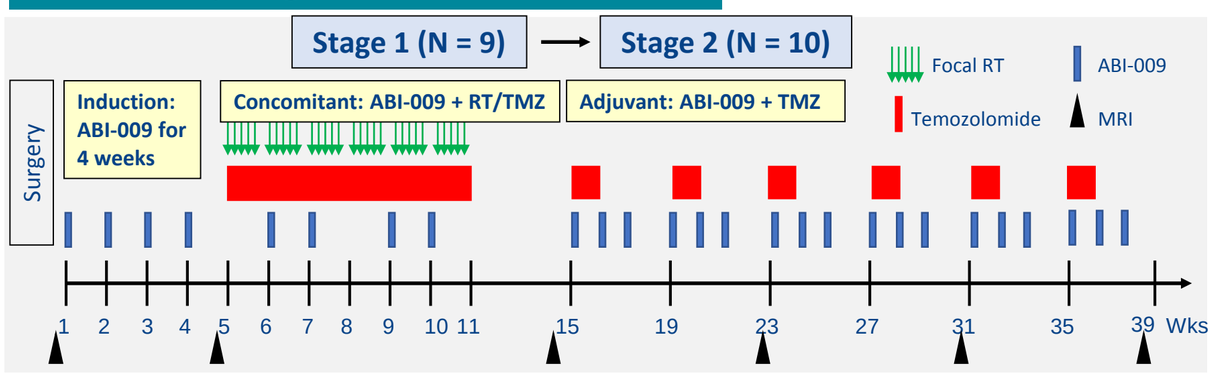
Dose Levels	ABI-009 Single agent
1	**100**
-1	75
-2	60

Dose Levels	ABI-009, mg/m² + Combination
1	**60**
-1	45
-2	30
-3	20

Arm A: Recurrent Glioblastoma



Arm B: Newly Diagnosed Glioblastoma



- This study is actively enrolling patients. The anticipated enrollment period is 24 months. NCT03463265

REFERENCES

1. Hou et al., AACR 2019, #3896

Santosh Kesari, MD, PhD: KesariS@jwci.org

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