FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Oncologic Drugs Advisory Committee Meeting
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Questions to the Committee

NDA 21-661 **RSR13 (Efaproxiral Sodium)** (75 mg or 100 mg/kg)
Allos Therapeutics Inc.

Indication Adjunctive therapy to whole brain radiation for the treatment of brain metastasis originating from breast cancer

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Study RT-009 is a randomized, multi-center, open-label study designed to demonstrate the added benefit of RSR13 to whole brain radiation therapy (WBRT) in the treatment of brain metastasis. Patients on Treatment Arm A received an initial 100 or 75 mg/kg dose of RSR13 over 30 minutes via a central venous access device. Whole brain radiation therapy was given within 30 minutes after the completion of the RSR13 infusion. Patients on Treatment Arm B received WBRT without a placebo. WBRT was given as 3cGy per day for 10 days in both treatment arms. Supplemental oxygen was given to both treatment arms. The subjects were stratified prior to randomization into one of the four strata: RPA Class I, RPA Class II and NSCLC primary, RPA Class II and breast primary, and RPA Class II and 'Other' primary tumors. The primary efficacy endpoint was overall survival. The applicant is seeking the following indication based on efficacy results in a non-prespecified subgroup of 115 patients with primary breast cancer in study RT-009:

The following table summarizes the FDA's analysis of efficacy based on the updated survival data (January 2004 cut-off) from study RT-009:

	Overall WBRT (N=267)	**Overall RSR13 + WBRT (N=271)**	**NSCLC/ Breast 1^0 Subgroup WBRT (N=206)**	**NSCLC/ Breast 1^0 Subgroup RSR13 + WBRT (N=208)**	**Breast 1^0 Subgroup WBRT (N=55)**	**Breast 1^0 Subgroup RSR13 + WBRT (N=60)**
Median Survival in months (95% C.I.)	4.5 (3.7, 5.4)	5.3 (4.5, 6.2)	4.5 (3.8, 5.4)	5.9 (4.7, 7.0)	4.6 (3.8, 6.2)	8.8 (6.0, 11.3)
Hazard Ratio (95% C.I.)	0.87 (0.73, 1.04)		0.84 (0.68, 1.03)		0.63 (0.422, 0.946)	
P-value* (log-rank test)	0.13		0.084		0.02	

* Not adjusted for multiple analyses

The following table summarizes the FDA's analysis of the most common grade 3 and 4 adverse events from study RT-009:

RT-009: Grade 3 and 4 Adverse Events

	Control Total patients =264 N (%)	**RSR13 Total patients=268 N (%)**
Hypoxia	**6 (2)**	**30 (11)**
Dyspnea	**19 (7)**	**8 (3)**
Headache	**11 (4)**	**18 (7)**
Pneumonia	**7 (3)**	**14 (5)**
Hypotension	**1 (<1)**	**5 (2)**
Acute renal failure	**1 (<1)**	**6 (2)**
Cerebral edema	**1 (<1)**	**4 (1)**

There were some imbalances between the two treatment arms in the subgroup of patients with primary breast cancer. Most notably, these included baseline characteristics such as number of brain lesions. In addition, imbalances related to therapy during or subsequent to radiation included duration of oxygen administration and subsequent therapy. These imbalances favored the RSR13 + WBRT treatment arm. It is possible that these imbalances, in particular imbalance in tumor load, influenced the results in the breast subgroup.

Questions to the Committee

When the primary analysis in the overall study population is negative, subgroup analyses are considered to be exploratory, i.e. not capable of providing a conclusive finding. Although there could be exceptional cases, these analyses still pose multiplicity and potential bias problems.

1. The survival analysis in the overall population was negative. Do the observed survival results from this single study in the subgroup of patients with breast cancer metastatic to the brain represent substantial evidence of RSR13 efficacy in this subgroup?

2. If you have concluded that efficacy has been shown, is the safety of the RSR13 + WBRT combination acceptable for patients with brain metastasis from breast cancer?