SUPPLEMENTAL MATERIAL

Table of Contents

Supplement Table S1. Analysis of time to CNS progression reported by BICR per specific study-modified RANO-BM criteria 2

Supplement Table S2. Adverse events 3

Supplement Figure S1. CNS tumor reduction in two patients treated with sotorasib. 5

Supplement Table S1. *Analysis of time to CNS progression reported by BICR per specific study-modified RANO-BM criteria*

	Sotorasib (N = 40)	**Docetaxel (N = 29)**
Time to CNS progression (months)[a]		
25th percentile (95% CI)	5.09 (2.86–9.63)	3.35 (1.41–6.01)
Median (95% CI)	11.60 (5.59–NE)	6.01 (3.35–NE)
75th percentile (95% CI)	NE (11.60–NE)	9.79 (6.01–NE)
Min, Max (+ for censored)	0.0+, 20.1+	0.0+, 15.5+
CNS progression-free rate,[b] % (95% CI)		
3 months	88.80 (72.75–95.66)	85.71 (61.39–95.25)
6 months	62.52 (41.62–77.75)	58.02 (30.42–77.96)
12 months	44.76 (23.14–64.31)	23.21 (3.99–51.56)
18 months	35.81 (14.42–58.00)	NE (NE–NE)
24 months	NE (NE–NE)	NE (NE–NE)
Follow-up time (months)[c]		
Median (95% CI)	8.64 (4.21–15.24)	4.04 (2.43–13.17)

[a]Medians and percentiles are estimated using the Kaplan-Meier method. 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation. [b]CNS progression-free rates are estimated using the method by Kalbfleisch and Prentice with log-log transformation. [c]Medians and percentiles of follow-up time are estimated using the reverse Kaplan-Meier method. 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation. BICR = blinded independent central review; CI = confidence interval; CNS = central nervous system; max = maximum; min = minimum; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases.

Supplement Table S2. *Adverse events*

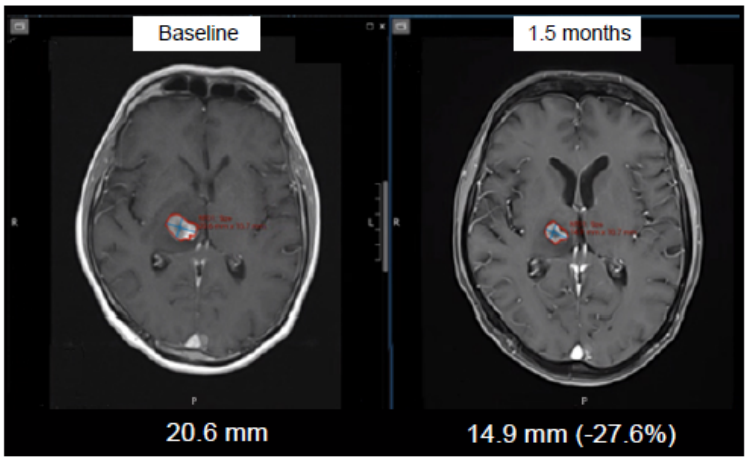
	Sotorasib (n = 40)		Docetaxel (n = 29)	
n (%)	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Treatment-emergent adverse events	39 (97.5)	30 (75.0)	27 (93.1)	10 (34.5)
Serious adverse events	26 (65.0)	–	9 (31.0)	–
Leading to discontinuation	2 (5.0)	–	1 (3.4)	–
Leading to dose reduction	5 (12.5)	–	8 (27.6)	–
Leading to dose interruption	21 (52.5)	–	7 (24.1)	–
Fatal adverse events	7 (17.5)	–	2 (6.9)	–
Treatment-related adverse events	31 (77.5)	12 (30.0)	26 (89.7)	8 (27.6)
Serious adverse events	5 (12.5)	–	4 (13.8)	–
Leading to discontinuation	1 (2.5)	–	0 (0.0)	–
Leading to dose reduction	5 (12.5)	–	8 (27.6)	–
Leading to dose interruption	13 (32.5)	–	3 (10.3)	–
Fatal adverse events	0 (0.0)		1 (3.4)[a]	
Treatment-related treatment-emergent adverse events by preferred term[b]				
Diarrhea	14 (35.0)	4 (10.0)	5 (17.2)	0 (0.0)
Nausea	12 (30.0)	2 (5.0)	5 (17.2)	0 (0.0)
Hypokalemia	4 (10.0)	1 (2.5)	1 (3.4)	1 (3.4)
Blood alkaline phosphatase increased	4 (10.0)	2 (5.0)	1 (3.4)	0 (0.0)
Alanine aminotransferase increased	4 (10.0)	3 (7.5)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	4 (10.0)	1 (2.5)	0 (0.0)	0 (0.0)
Anemia	3 (7.5)	1 (2.5)	8 (27.6)	1 (3.4)

n (%)	Sotorasib (n = 40)		Docetaxel (n = 29)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Decreased appetite	3 (7.5)	0 (0.0)	6 (20.7)	0 (0.0)
Fatigue	3 (7.5)	0 (0.0)	4 (13.8)	2 (6.9)
Asthenia	3 (7.5)	1 (2.5)	4 (13.8)	1 (3.4)
Vomiting	3 (7.5)	0 (0.0)	4 (13.8)	0 (0.0)
Constipation	3 (7.5)	0 (0.0)	3 (10.3)	0 (0.0)
Alopecia	2 (5.0)	0 (0.0)	7 (24.1)	0 (0.0)
Neutropenia	1 (2.5)	0 (0.0)	4 (13.8)	3 (10.3)
Mucosal inflammation	0 (0.0)	0 (0.0)	4 (13.8)	1 (3.4)

Adverse events were graded using the Common Terminology Criteria for Adverse Events v5.0, which incorporates certain elements of the Medical Dictionary for Regulatory Activities terminology. The CNS safety analysis set included all patients in the CNS full analysis set who received at least one dose of the investigational product. [a]Due to ileus. [b]Occurring in ≥ 10% of patients (either arm). CNS = central nervous system.

Supplement Figure S1. CNS tumor reduction in two patients treated with sotorasib.

Patient Case 1: Intracranial Efficacy After Randomization to Sotorasib



	Baseline	1.5 months
Brain frontal lobe right		
Size	LA: 20.6 mm Present	LA: 14.9 mm (-27.7% ΔP) Present

All progress values are relative to their previous value (ΔP)

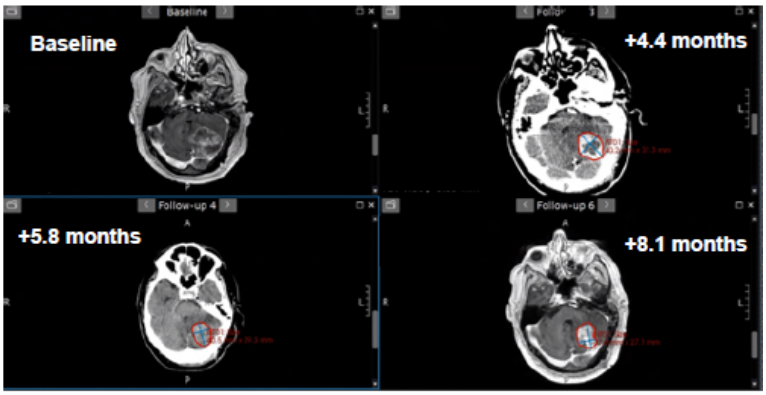
Date of first dose sotorasib: January 2021
Location: Right thalamus
Date of CNS involvement: October 2020
Prior gamma knife, October 2020, with best intracranial response of stable disease
Randomized: Sotorasib
Date of first dose sotorasib: January 2021
Non-brain PD

Patient Case 2: Intracranial Efficacy After Crossover From Docetaxel

	Baseline	+ 1.8 months	+ 3.5 months	+ 4.4 months	+ 5.8 months	+ 7.2 months	+ 8.1 months
Brain cerebellum hemisphere left							
Size	49 mm	43.5 mm (-11.2%)	43.8 mm	40.2 mm (-17.9%)	40.5 mm	35.7 mm	37.6 mm (-23.2%)

Point of crossover from docetaxel to sotorasib

Location: Left cerebellar hemisphere
Date of CNS involvement: December 2018
Prior stereotactic radiation, December 2018, with best intracranial response of stable disease
Randomized: Docetaxel
Date of first dose of docetaxel: January 2021
Crossover to sotorasib: April 2021
Non-brain PD



Patient 1, randomized to sotorasib, had a measurable brain lesion in the right thalamus and non-brain progressive disease. Patient was treated with gamma knife at the time of CNS involvement diagnosis, with best response of stable disease. Prior systemic treatments included carboplatin, pemetrexed, and pembrolizumab. Time from gamma knife to start of sotorasib was about 3 months. Patient 2, randomized to docetaxel and then crossed over to sotorasib, had a measurable brain lesion in the left cerebellar hemisphere and non-brain progressive disease. Patient was treated with stereotactic radiation at time of CNS involvement diagnosis, with best response of stable disease. Prior systemic treatments included carboplatin, pemetrexed, and atezolizumab. Time from stereotactic radiation to start of docetaxel was about 38 months; time from stereotactic radiation to start of sotorasib was about 41 months. CNS = central nervous system; PD = progressive disease.