A randomized, double-blind Phase 3 study of vorasidenib versus placebo in patients with mutant IDH1/2 diffuse glioma (INDIGO): analysis of health-related quality of life, neurocognition and seizures

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KEY MESSAGES

- In the INDIGO study, patients had high HRQoL and neurocognitive scores in both arms at baseline
- Patient-reported HRQoL was preserved, as measured by the FACT-Br questionnaire, in both arms
- No meaningful changes in neurocognitive function were observed with vorasidenib or placebo
- The clinical benefit of treatment with vorasidenib in patients with mIDH1/2 adult-type diffuse glioma, which was well tolerated while showing improvements in PFS and TTNI, is further supported by the preservation of patient-reported HRQoL and neurocognition, and the maintenance of seizure control

FACT-Br, Functional Assessment of Cancer Therapy – Brain; HRQoL, health-related quality of life; mIDH1/2, mutations in isocitrate dehydrogenase 1 or 2; PFS, progression-free survival; TTNI, time to next intervention.

PATIENT SUMMARY

- The INDIGO study is the first clinical trial with positive results for a potential treatment in glioma that has abnormal IDH genes (a specific change in their DNA)[1]
- Patients had undergone surgery but had not received any other treatment, and were randomly given either vorasidenib or placebo (a lookalike drug that contains no medicine)[1]
- The average number of months without the cancer worsening was more than twice as long when patients took vorasidenib instead of placebo, and side effects were generally manageable[1]
- The results reported here show that patients had good quality of life at the beginning of the study, and this was preserved while taking vorasidenib, with no difference seen when compared with placebo
- Memory and thinking skills also tended to remain stable with vorasidenib
- The number of patients who needed to increase their anti-seizure medication was low and similar for patients who took vorasidenib or placebo
- These findings may help patients to understand what might be expected during vorasidenib treatment

IDH, isocitrate dehydrogenase.

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INTRODUCTION

- Mutations in isocitrate dehydrogenase 1 or 2 (mIDH1/2) occur in most adult-type diffuse gliomas[2,3]
- Current treatment options are not curative and can contribute to acute and long-term neurocognitive impairment or deterioration[4,5]
- Vorasidenib is an oral, brain penetrant, dual inhibitor of mIDH1/2[6]
- The randomized, placebo-controlled Phase 3 INDIGO study (NCT04164901) evaluated vorasidenib in patients with mIDH1/2 adult-type diffuse glioma previously treated with surgery only (**Supplementary Figure S1**)[1]
- Progression-free survival (PFS) was 27.7 months in the vorasidenib group, compared with 11.1 months in the placebo group (hazard ratio [HR], 0.39; 95% confidence interval [CI], 0.27–0.56; *P*=0.000000067)[1,7]
  - Time to next intervention (TTNI) was also significantly improved in the vorasidenib group (HR, 0.26; 95% CI, 0.15– 0.43; *P*=0.000000019)
  - Adverse events (AEs) in the vorasidenib group were mainly grade 1 or 2, and the most common grade ≥3 AE was an increased alanine aminotransferase level (9.6%)
- Patients with mIDH1/2 gliomas are prone to recurrent seizures, which are complex to manage[8]
- With a median age of ~40 years at diagnosis,[9] it is vital that cognitive function and health-related quality of life (HRQoL) are maintained, and symptomatic burden controlled in these young patients
- Here, we report HRQoL, neurocognitive function and seizure activity from the INDIGO study

METHODS

SECONDARY ENDPOINT

HRQoL: assessed by FACT-Br questionnaire

EXPLORATORY ENDPOINTS

Neurocognitive function: assessed by a validated battery of cognitive performance
- Verbal learning
- Working memory
- Attention
- Psychomotor function
- Executive function

Seizures: including frequency and severity; changes in anti-seizure medications

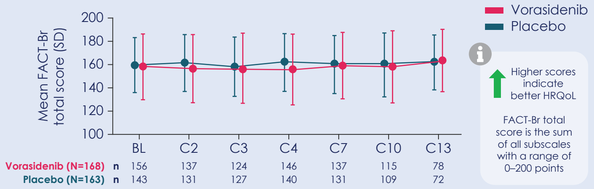
ASSESSMENT SCHEDULE

Questionnaire/test	Description/cognitive domain	Timepoints	
FACT-Br	BrCS, EWB, FWB, PWB, PGI-C/PGI-S/PGI-F/EQ-5D*	C1D1, C2D1, C3D1, C4D1, then every 3 months until EOT	PRO/PerfO
ISLT	Verbal learning	C1D1, then every 3 months until EOT	
DET	Psychomotor function		
IDN	Attention		
ONB	Working memory		
GMLT	Executive function		
Number and severity† of seizures were self-reported by patients during each cycle of treatment using a diary			Diary

*EWB, FWB, PWB, PGI-C, PGI-S, PGI-F and EQ-5D data are not presented here; †Severity of seizures data are not presented here.
BrCS, brain cancer subscale; C, cycle; D, day; DET, detection; EOT, end of treatment; EQ-5D, EuroQol 5-Dimension 5-Level questionnaire; EWB, emotional wellbeing; FACT-Br, Functional Assessment of Cancer Therapy – Brain; FWB, functional wellbeing; GMLT, groton maze learning; IDN, identification; ISLT, international shopping list; ONB, one back; PerfO, performance outcome; PGI, Patient Global Impression; PGI-C, PGI of Change; PGI-F, PGI of Frequency; PGI-S, PGI of Severity; PRO, patient-reported outcome; PWB, physical wellbeing.

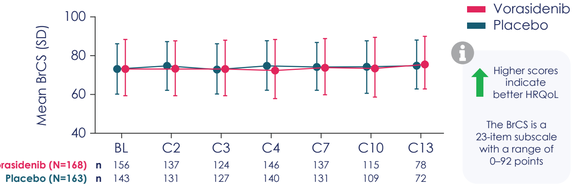
RESULTS AND INTERPRETATION

Treatment with vorasidenib did not affect HRQoL when assessed using the FACT-Br total score



Data cut-off: 6 September 2022.
BL, baseline; SD, standard deviation.

Treatment with vorasidenib did not affect brain cancer-specific HRQoL



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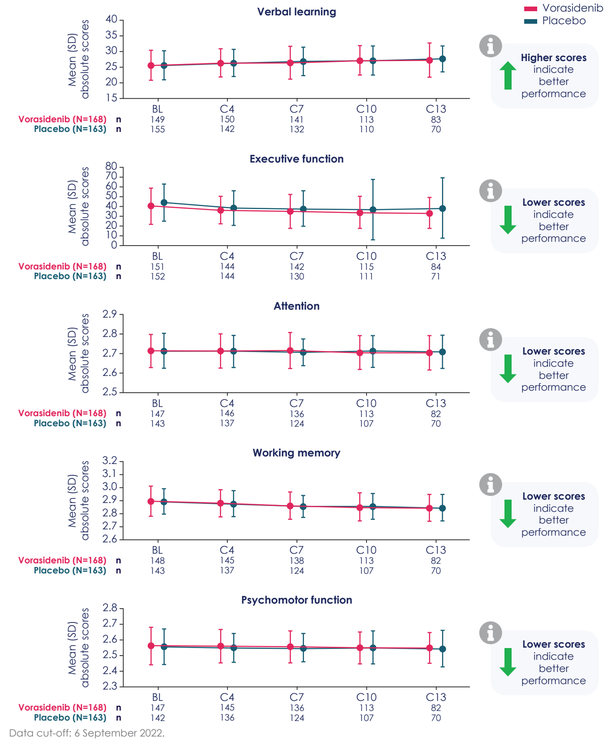
- FACT-Br completion rates were high (≥75%) in both arms at BL and all visits through the median treatment duration of 14.2 months (**Supplementary Figure S2**)
- In addition to FACT-Br total score and BrCS, there were consistent high scores for the FWB subscale in both the vorasidenib and placebo arms (**Supplementary Figure S3**)
- FACT-Br, BrCS and FWB subscale scores were maintained at every visit up to C13 in both the vorasidenib and placebo arms, with mean change from BL scores being small (**Supplementary Figure S4**)

Patients performed well in a series of objective neurocognitive tests and there was no evidence of neurological deterioration or decline in either arm



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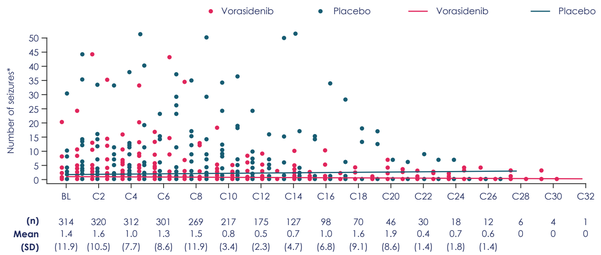
There was negligible difference in seizure frequency between the two arms

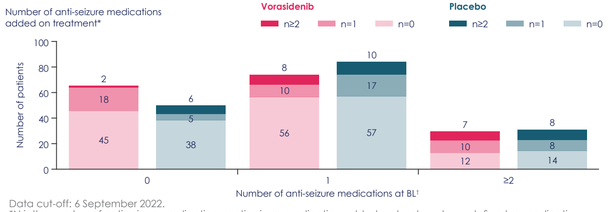
- At BL, 20 (12%) patients in each arm self-reported at least one seizure in the prior 30 days
- Patients reporting at least one seizure per cycle up to C13 ranged from:
  - Eight to 24 patients on vorasidenib
  - 10 to 24 patients on placebo



Data cut-off: 6 September 2022.
*Number of seizures was plotted against time based on a non-parametric locally estimated scatterplot smoothing regression. Seizure activity was assessed using a patient-reported diary recording the number of seizures during each treatment cycle.

The number of patients needing two or more additional anti-seizure medications was small in both groups

- Changes in anti-seizure medication use is indicative of seizure control, and adding two or more anti-seizure medications is clinically relevant for seizure management



Data cut-off: 6 September 2022.
*N is the number of anti-seizure medications; anti-seizure medication added on treatment was defined as medication initiated after the first dose of either vorasidenib or placebo, and before crossover; †Anti-seizure medication at BL was defined as medication initiated prior to the first dose of either vorasidenib or placebo, and ended on or after the first dose of either vorasidenib or placebo.

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