# A phase 1, randomized, perioperative trial of vorasidenib and ivosidenib in IDH1-mutant diffuse glioma: Updated results

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# Background

- **Vorasidenib** (VOR, VORANIGO®): Oral, brain-penetrant dual inhibitor of mutant isocitrate dehydrogenases 1 and 2 (**mIDH1/2**).
  - Approved in the US (2024) for the treatment of patients ≥12 years old with grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation, following surgery including biopsy, subtotal resection, or gross total resection.[1]
  - VOR significantly improved progression free survival (PFS) and delayed the time to the next intervention (TTNI) in patients with grade 2 mIDH1/2 glioma in the phase 3 double-blind INDIGO study.[2]
- **Ivosidenib** (IVO, TIBSOVO®): First-in-class, oral, small-molecule inhibitor of **mIDH1**.
  - Approved for the treatment of subsets of mIDH1 acute myeloid leukemias, relapsed/refractory myelodysplastic syndrome, and previously treated, locally advanced/metastatic cholangiocarcinoma.[3,4]
  - IVO showed preliminary antitumor activity in patients with mIDH1 glioma in a phase 1 study.[4]

**1.** FDA Approves Vorasidenib for Grade 2 Astrocytoma or Oligodendroglioma With a Susceptible IDH1 or IDH2 Mutation. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-vorasidenib-grade-2-astrocytoma-or-oligodendroglioma-susceptible-idh1-or-idh2-mutation. Accessed September 9, 2024. **2.** Mellinghoff IK et al. *N Engl J Med.* 2023;389(7):589–601. **3.** TIBSOVO (ivosidenib) [Highlights of prescribing information]. Servier Pharmaceuticals LLC; 2022. **4.** Mellinghoff IK et al. *J Clin Oncol.* 2020;38(29):3398–34063.

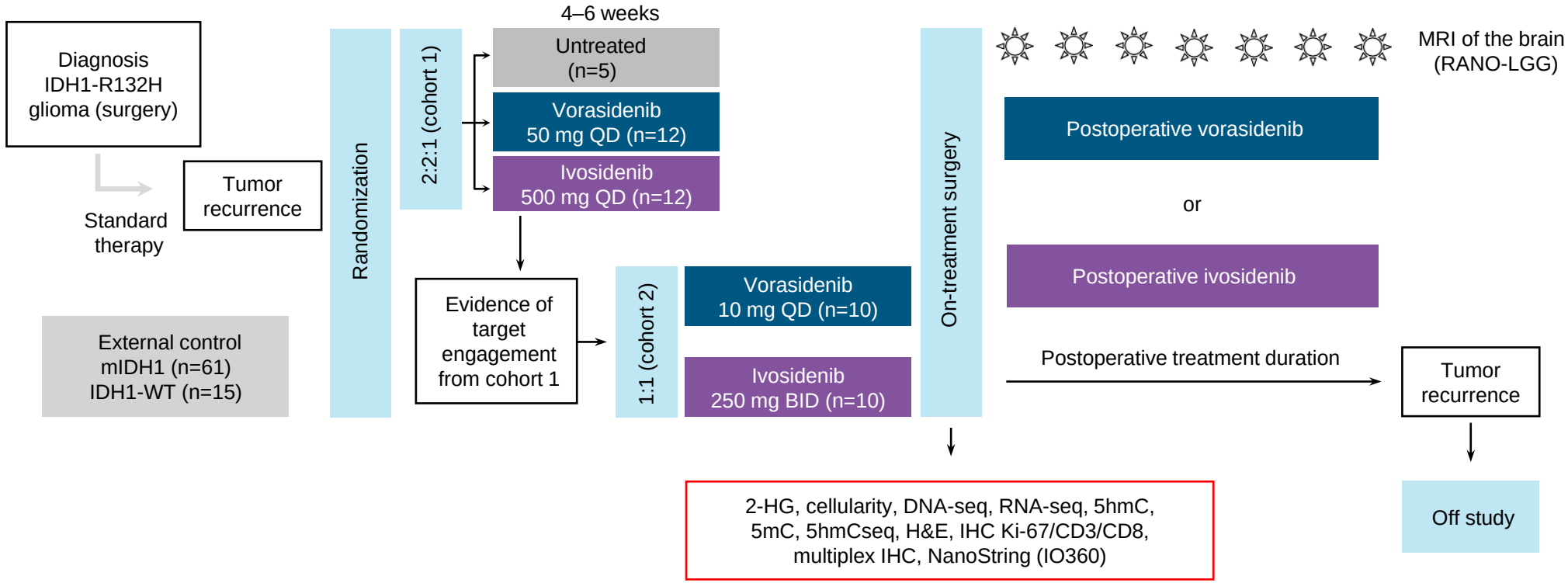
# Published results and objective

- Evaluation of VOR and IVO in a phase 1, randomized, open-label perioperative trial (NCT03343197) showed[1]:
  - Tumor 2-hydroxyglutarate (2-HG) concentrations were reduced by >90% in patients treated with VOR 50 mg once daily (QD) or IVO 500 mg QD.
  - Tumor:plasma ratios were considerably higher for VOR than IVO.
- 2-HG reduction was associated with:
  - Lower tumor cell proliferation.
  - Reversal of IDH1/2 mutation-associated gene expression programs.
  - Increased DNA 5-hydroxy-methylcytosine.
  - Increased tumor-infiltrating lymphocytes.
- A daily dose of VOR 50 mg showed the most consistent inhibition of the mutant enzyme and the greatest preliminary antitumor activity.
- Pharmacokinetics/pharmacodynamics (PK/PD) and objective response rate (ORR) data as of April 29, 2020 were previously published.[1]
- However, PFS data were not mature at the time of that publication.
- We report here an additional 3.5 years of follow-up data, including PFS.

**1.** Mellinghoff IK et al. *Nat Med.* 2023;29(3):615–622.
IDH = isocitrate dehydrogenases; IVO = ivosidenib; PFS = progression-free survival; VOR = vorasidenib

# Study design

- Participants with grade 2/3 non-enhancing mIDH1 R132H mutant gliomas were randomized to VOR (50 or 10 mg QD), IVO (500 mg QD or 250 mg twice daily [BID]), or no treatment (control) for 4 weeks prior to planned surgery with the option to continue treatment with VOR or IVO post-surgery.




All patients could opt to receive the study drug postoperatively. After surgery, patients in the untreated control group were re-randomized 1:1 to either VOR 50 mg QD or IVO 500 mg QD. Based on the PD and pharmacokinetic results of cohort 1, alternative dose regimens of VOR and/or IVO were to be tested in cohort 2.

Mellinghoff IK et al. *Nat Med.* 2023;29(3):615–622.

2-HG = 2-hydroxyglutarate; BID = twice daily; IVO = ivosidenib; LGG = low-grade glioma; mIDHI1 = mutant isocitrate dehydrogenase 1; MRI = magnetic resonance imaging; QD = once daily; RANO = Response Assessment in Neuro-Oncology; WT = wild type; VOR = vorasidenib

# Study endpoints

- **Primary**
  - 2-HG concentration in tumors resected following presurgical treatment with VOR or IVO, compared with untreated control tumors.
- **Secondary**
  - **Safety of VOR and IVO.**
  - PD of 2-HG in plasma.
  - PK in plasma and tumor.
  - **Preliminary clinical activity by RANO-LGG.**
- **Exploratory**
  - 2-HG in tumor pre- and post-treatment.
  - PK/PD relationship of VOR and IVO in tumor, plasma, and cerebrospinal fluid (CSF).

Mellinghoff IK et al. *Nat Med.* 2023;29(3):615–622.
2-HG = 2-hydroxyglutarate; IVO = ivosidenib; LGG = low-grade glioma; PK/PD = pharmacokinetic/pharmacodynamic; RANO = Response Assessment for Neuro-Oncology; VOR = vorasidenib

# Results: Baseline characteristics

| | VOR Total (N=24)[a] | IVO Total (N=25)[b] |
|---|---|---|
| **Median (range) age, years** | 49 (31-75) | 37 (19-66) |
| **Male/female, n (%)** | 16 (66.7)/8 (33.3) | 17 (68.0)/8 (32.0) |
| **KPS score at baseline, n (%)** | | |
| 100% | 8 (33.3) | 11 (44.0) |
| 90% | 13 (54.2) | 12 (48.0) |
| 80% | 3 (12.5) | 1 (4.0) |
| Missing | - | 1 (4.0) |
| **WHO tumor grade at screening n (%)** | | |
| Grade 2 | 22 (91.7) | 21 (84.0) |
| Grade 3 | 2 (8.3) | 4 (16.0) |
| **Histological subtype, n (%)** | | |
| Oligodendroglioma | 13 (54.2) | 12 (48.0) |
| Astrocytoma | 11 (45.8) | 11 (44.0) |
| Anaplastic oligodendroglioma | - | 1 (4.0) |
| Anaplastic oligoastrocytoma | - | 1 (4.0) |
| **1p19q status (if known), n (%)** | | |
| Co-deleted | 12 (50.0) | 13 (52.0) |
| Intact[c] | 10 (41.7) | 9 (36.0) |
| Not determined | 2 (8.3) | 3 (12.0) |
| **Previous surgery, n (%)** | 24 (100) | 25 (100) |
| **Previous radiation therapy, n (%)** | 7 (29.2) | 7 (28.0) |
| **Previous systemic therapy, n (%)** | 10 (41.7) | 14 (56.0) |

[a]Includes two patients who were assigned to the control arm before surgery.
[b]Includes three patients who were assigned to the control arm before surgery.
[c]Includes patients with no 1p19q co-deletion, 1p deletion only or 19q deletion only.
Mellinghoff IK et al. *Nat Med.* 2023;29(3):615–622.
IVO = ivosidenib; KPS = Karnofsky performance status; VOR = vorasidenib; WHO = World Health Organization

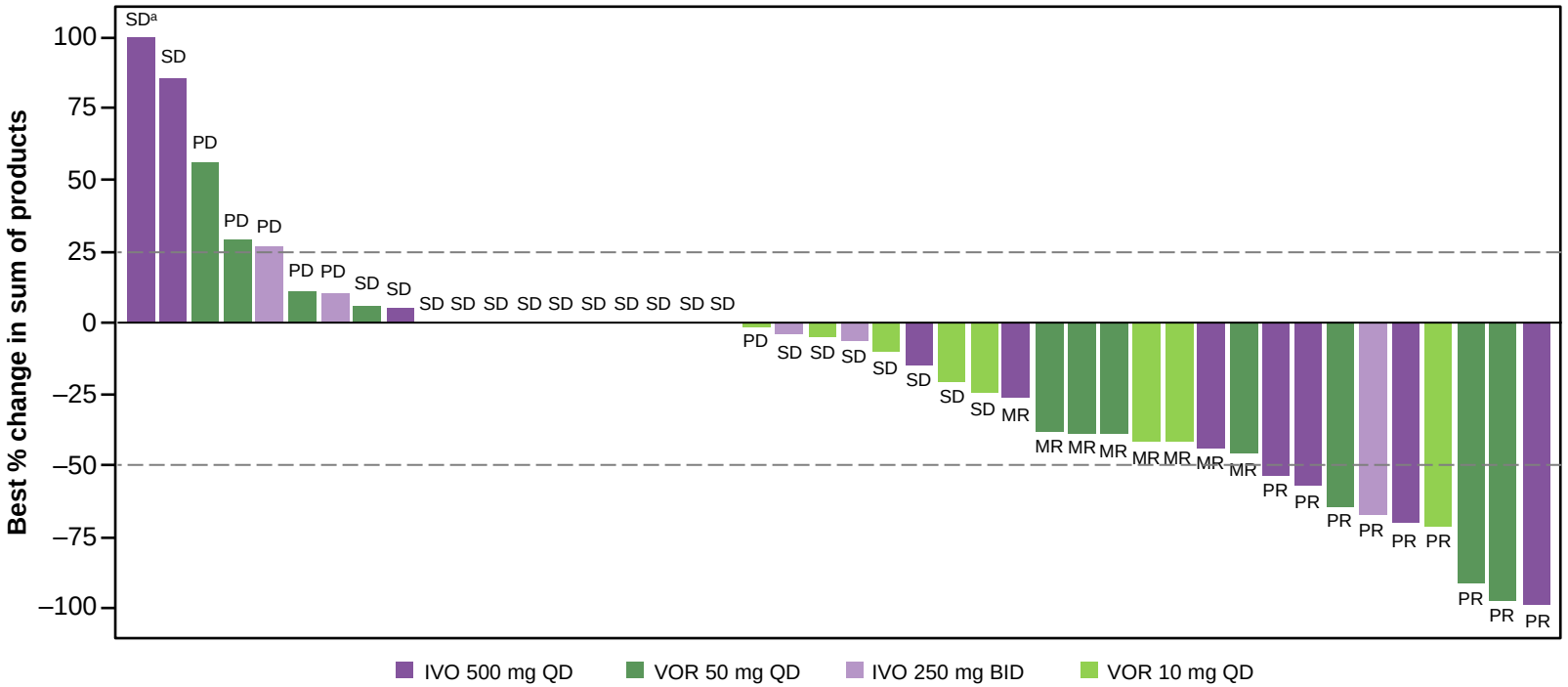
# Results: Patient disposition

- Study was initiated in March 2018 with enrollment completed in April 2019.
- **49** patients were randomized before surgery, and all proceeded to surgery without unplanned delays.
  - A total of 46 participants (24 oligodendroglioma, 20 astrocytoma, 1 anaplastic oligodendroglioma, 1 anaplastic oligoastrocytoma) received treatment with either VOR (N=24) or IVO (N=22) after surgery.
- As of **September 23, 2023**, the number of patients remaining on treatment with VOR was more than twice of those remaining on IVO**.**

| Safety analysis set[a] Status, n (%) | VOR Total (N=24) | IVO Total (N=25) |
|---|---|---|
| **On-treatment** | 11 (45.8) | 5 (20.0) |
| **Discontinued** | 13 (54.2) | 20 (80.0) |
| Disease progression | 10 (41.7) | 14 (56.0) |
| Adverse event | 1 (4.2) | 2 (8.0) |
| Did not continue post-surgery | 0 | 3 (12.0) |
| Investigator decision | 2 (8.3) | 1 (4.0) |

Data as of September 23, 2023.
[a]All subjects who were randomized and received at least one dose of study drug.
This table includes 5 subjects assigned to untreated in the pre-surgery period who were re-randomized to IVO (3 subjects) or VOR (2 subjects) post-surgery.
IVO = ivosidenib; VOR = vorasidenib

# Results: Best percent change from baseline and tumor response by RANO-LGG (as determined by the investigator)

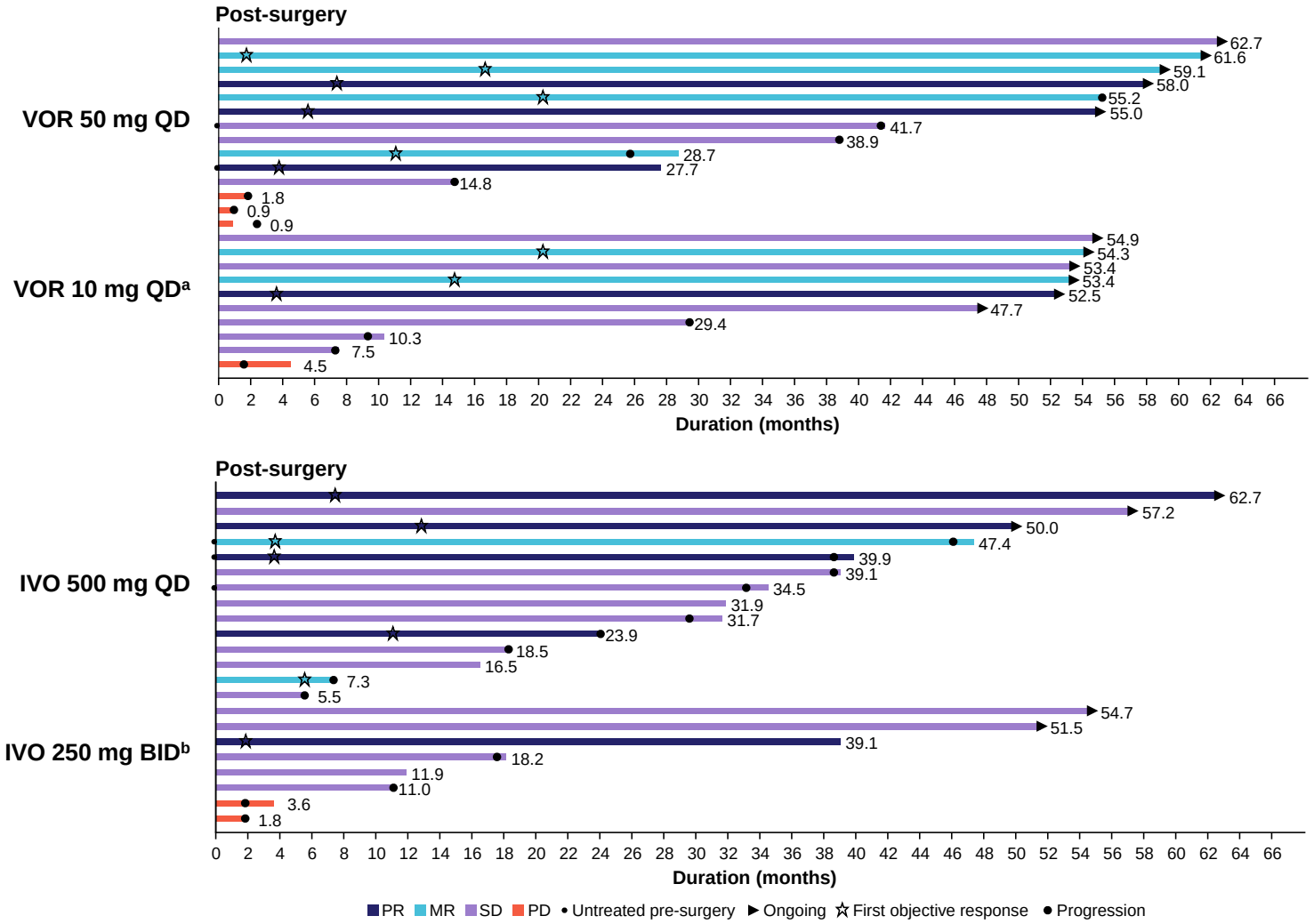



| Efficacy analysis set[b] RANO response | VOR Total (N=22) | IVO Total (N=22) |
|---|---|---|
| Partial response (PR), n (%) | 4 (18.2) | 5 (22.7) |
| Minor response (MR), n (%) | 6 (27.3) | 2 (9.1) |
| Stable disease (SD), n (%) | 8 (36.4) | 13 (59.1) |
| Progressive disease (PD), n (%) | 4 (18.2) | 2 (9.1) |
| Objective response rate (ORR), n (%) | 10 (45.5) | 7 (31.8) |
| Time to response in months, median (range) | 9.2 (2, 20) | 5.6 (2, 13) |
| Duration of response in months, median (range) | NE (14.7, NE) | 42.4 (1.8, NE) |

- 14 (64%) patients who received VOR, and 10 (45.4%) patients who received IVO had tumor reduction.

Data as of September 23, 2023.
[a]Percent change > 100%. [b]Efficacy analysis set: All subjects who were randomized and received at least one dose of study treatment post-surgery and for whom the baseline scan and at least one post baseline scan are available and evaluable for disease response. In IVO 500 mg QD group two patients with > 75% increase in target lesion size experienced SD as best overall response.
BID = twice daily; IVO = ivosidenib; MR = minor response: a decrease between 25% and 50% of non-enhancing abnormalities from baseline; PD = progressive disease: ≥25% increase of non-enhancing abnormalities from baseline; PR = partial response: ≥50% decrease of non-enhancing abnormalities from baseline; SD = stable disease: stable area of non-enhancing disease; VOR = vorasidenib

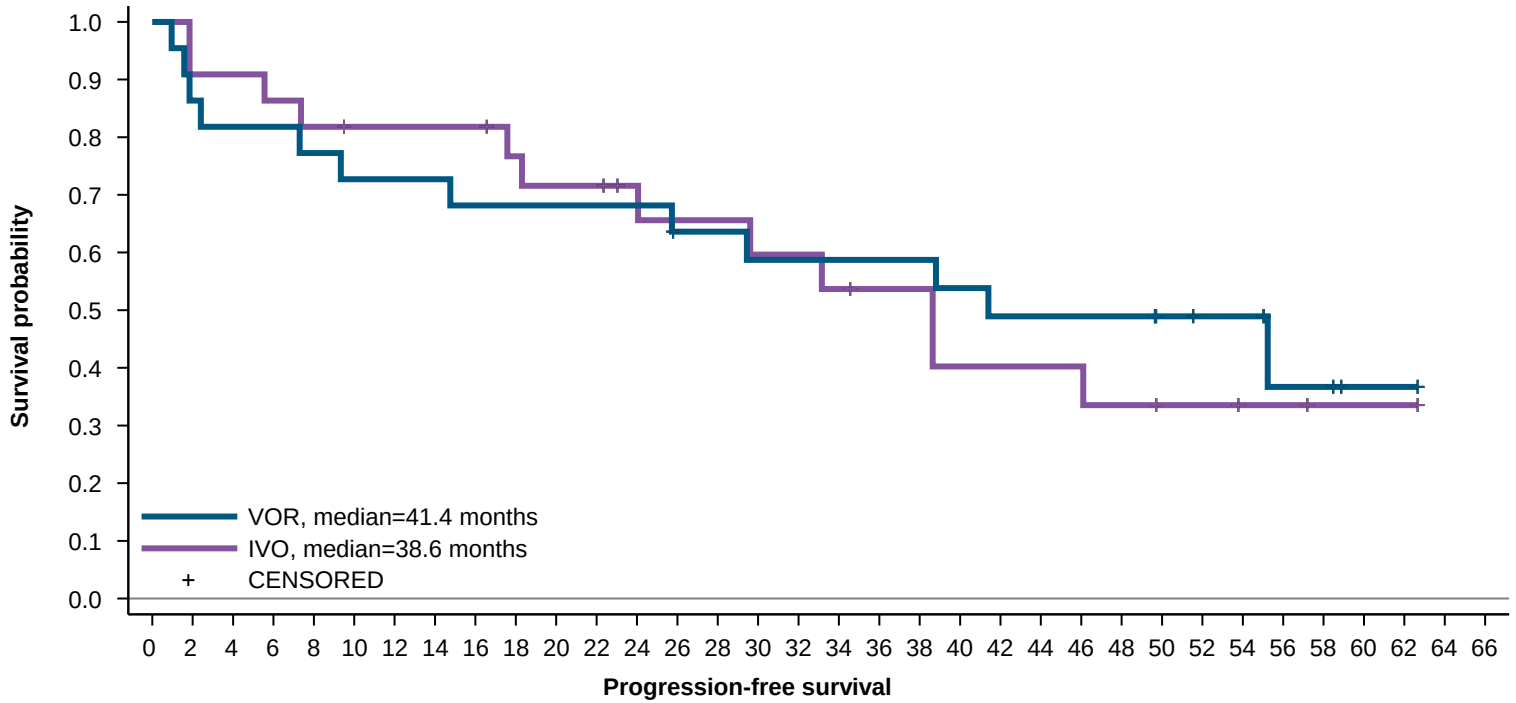
# Results: Treatment duration and best tumor response




| Metric | VOR Total (N=24) | IVO Total (N=25) |
|---|---|---|
| Treatment duration[c] (median [range]), months | 44.67 (0.9, 62.7) | 23.92 (0.0, 62.7) |

Data as of September 23, 2023.
[a]Efficacy analysis set: 9 out of 10 subjects receiving VOR 10 mg QD in pre-surgery period escalated to 50 mg QD of VOR in post surgery phase.
[b]Efficacy analysis set: 2 out of 10 subjects receiving IVO 250 mg BID in pre-surgery period received 500 mg QD of IVO in post surgery phase.
[c]Safety analysis set: all subjects who were randomized and received at least one dose of study drug.
BID = twice daily; IVO = ivosidenib; MR = minor response; NE = not evaluable; PD = progressive disease; PFS = progression-free survival; PR = partial response; QD = once daily; SD = stable disease; VOR = vorasidenib

# Progression-free survival (PFS)




| Metric | VOR total (N=22) | IVO total (N=22) |
|---|---|---|
| PFS[a] (median [95% CI], months) | 41.4 (9.3, NE) | 38.6 (18.3, NE) |

| Metric | VOR total (N=9) | IVO total (N=9) |
|---|---|---|
| PFS (median [95% CI], months) in subjects with prior surgery only | 55.2 (2.4, NE) | 38.6 (24.0, NE) |

Data as of September 23, 2023.
[a]Efficacy analysis set: all subjects who were randomized and received at least one dose of study treatment post-surgery and for whom the baseline scan and at least one post baseline scan are available and evaluable for disease response.
CI = confidence interval; IVO = ivosidenib; NE = not evaluable; PFS = progression-free survival

# Results: Safety summary

- No new safety signals were detected.
- The safety profile was consistent with previously published studies.
- No TEAEs led to on-treatment death.

| Safety analysis set[a]<br>Subjects with event, n (%) | VOR<br>Total (N=24) | IVO<br>Total (N=25) |
|---|---|---|
| Any TEAEs | 24 (100.0) | 25 (100.0) |
| Treatment-related TEAEs | 16 (66.7) | 18 (72.0) |
| Serious TEAEs | 10 (41.7) | 8 (32.0) |
| Treatment-related serious TEAEs | 1 (4.2) | 0 |
| Grade ≥3 TEAEs | 15 (62.5) | 8 (32.0) |
| Treatment-related Grade ≥3 TEAEs | 3 (12.5) | 1 (4.0) |
| AESI | 3 (12.5) | 0 |
| TEAE leading to treatment discontinuation | 1 (4.2) | 2 (8.0) |
| TEAE leading to dose reduction | 1 (4.2) | 1 (4.0) |
| TEAE leading to dose interruption | 9 (37.5) | 5 (20.0) |

Data as of September 23, 2023.
[a]All subjects who were randomized and received at least one dose of study drug.
AESI = adverse event of special interest; IVO = ivosidenib; TEAE = treatment-emergent adverse event; VOR = vorasidenib

# Conclusions

- With additional ~3.5 years of follow-up from previously published results,[1] VOR and IVO continue to show clinical benefit immediately after surgery in patients with predominantly non-enhancing glioma
  - VOR resulted in durable disease control including objective responses, consistent with phase III INDIGO study results[2]
- Safety profiles remain favorable with no new risk identified for either drug

**1.** Mellinghoff IK et al. *Nat Med.* 2023;29(3):615–622**. 2.** Mellinghoff IK, et al. *N Engl J Med.* 2023;389(7):589-601.
IVO = ivosidenib; VOR = vorasidenib

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