

RESEARCH SUMMARY

Nirogacestat, a γ -Secretase Inhibitor for Desmoid Tumors

Gounder M et al. DOI: 10.1056/NEJMoa2210140

CLINICAL PROBLEM

Desmoid tumors — rare, nonmetastatic, mesenchymal tumors — are locally aggressive and invasive, conferring substantial morbidity. No therapies are currently approved for their treatment. Nirogacestat, a selective γ -secretase inhibitor, has shown promising antitumor activity in early trials involving patients with desmoid tumors, but additional data are needed.

CLINICAL TRIAL

Design: A phase 3, international, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of nirogacestat in adults with progressing desmoid tumors.

Intervention: 142 patients ≥ 18 years of age with either progressing tumors that had not been treated or refractory or recurrent tumors after ≥ 1 previous line of therapy were assigned to receive oral nirogacestat (150 mg) or placebo twice daily. The primary end point was progression-free survival.

RESULTS

Efficacy: During a median follow-up of 15.9 months, the risk of disease progression or death was 71% lower with nirogacestat than with placebo.

Safety: The most frequent adverse events with nirogacestat were diarrhea, nausea, fatigue, and hypophosphatemia. Ovarian dysfunction was common in women of childbearing age receiving nirogacestat but resolved in all the women who discontinued nirogacestat and in the majority who continued to receive it.

LIMITATIONS AND REMAINING QUESTIONS

- The appropriate duration of nirogacestat treatment is unknown.
- Further evaluation of ovarian dysfunction with nirogacestat is ongoing in the open-label extension phase of the trial.
- The efficacy of nirogacestat in children with desmoid tumors is unknown and under investigation.

Links: [Full Article](#) | [NEJM Quick Take](#)

Desmoid Tumors



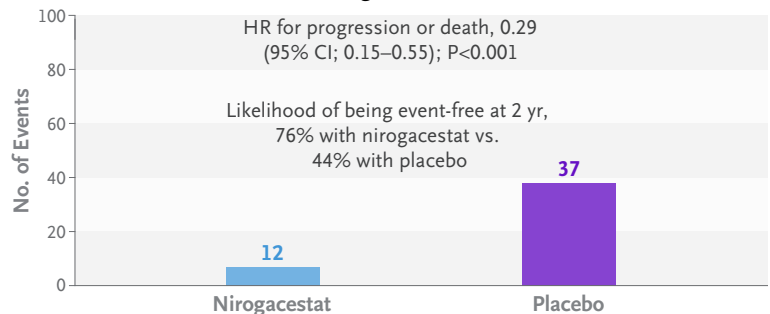
Nirogacestat
(N=70)



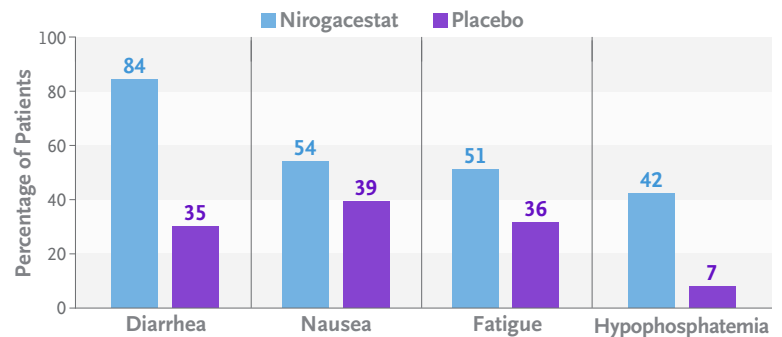
Placebo
(N=72)



Disease Progression or Death



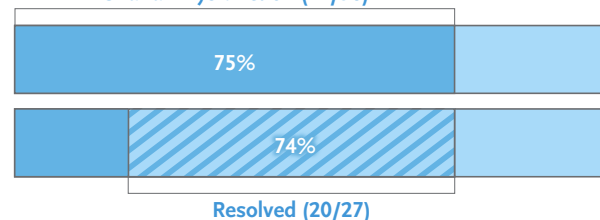
Adverse Events



Ovarian Dysfunction

Nirogacestat recipients of childbearing age (N=36)

Ovarian Dysfunction (27/36)



CONCLUSIONS

In adults with progressing desmoid tumors, oral nirogacestat resulted in longer progression-free survival than placebo. Adverse events were frequent but mostly low grade.