Re: Jain HA. Nirogacestat in Desmoid Tumor Management: Painful to Painless?

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To the Editor:

I read with great interest the recent report by Jain et al[1] on nirogacestat in progressing desmoid tumors.[2] While the trial is methodologically sound and demonstrates significant efficacy of nirogacestat over placebo, I would like to highlight two critical issues that merit further discussion.

First, the choice of a placebo control arm raises concern, especially given that the same investigative group had earlier published a landmark randomized trial establishing the efficacy of sorafenib over placebo in desmoid tumors.[3] With the sorafenib study published in 2018 and patient accrual for the nirogacestat trial beginning in 2019, it is puzzling why sorafenib was not chosen as the comparator. If the goal were to establish the therapeutic value of nirogacestat in a post-sorafenib era, a head-to-head comparison with sorafenib would have been more appropriate. Selecting placebo as the comparator risks artificially inflating the perceived benefit of nirogacestat, potentially lowering the threshold for success, and sidestepping an opportunity to address the more pressing clinical question: Is nirogacestat superior or equivalent to sorafenib? This trial, while confirming efficacy, does not help the clinician choose between the two agents.

Second, while nirogacestat demonstrated a higher overall response rate (41 vs. 33%) and earlier responses compared with historical sorafenib data, the progression-free survival hazard ratio (HR) with sorafenib (HR: 0.13) appears more favorable than that of nirogacestat (HR: 0.29). Furthermore, the toxicity profile of nirogacestat, particularly ovarian dysfunction affecting 75% of premenopausal women, is nontrivial. In contrast, sorafenib's toxicities, although frequent, are more familiar to clinicians and generally manageable. Thus, based on existing data, sorafenib may still represent the more pragmatic first-line choice, especially in young women in whom the disease is more common.

In conclusion, while nirogacestat adds to the armamentarium for desmoid tumors, the choice of placebo as a comparator limits the trial's clinical utility in guiding therapeutic decision-making between existing and emerging options. As clinicians, what we need is not just more drugs or gaps in evidence, but clearer data to guide rational treatment sequencing.

Patient Consent

Patient's consent is not required.

Funding

None.

Conflict of Interest

None declared.

References

1 Jain HA, Bagri PK, Tripathy A, Chaudhary KG. Nirogacestat in desmoid tumor management: painful to painless? Indian J Med Paediatr Oncol 2025;46(03):47–348
2 Gounder M, Ratan R, Alcindor T, et al. Nirogacestat, a γ-secretase inhibitor for desmoid tumors. N Engl J Med 2023;388(10): 898–912
3 Gounder MM, Mahoney MR, Van Tine BA, et al. Sorafenib for advanced and refractory desmoid tumors. N Engl J Med 2018;379 (25):2417–2428

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