Nirogacestat and Hypophosphatemia

To the Editor: Desmoid tumors are locally aggressive rare tumors that arise from fibrous tissue.[1] Nirogacestat is a small-molecule inhibitor targeting the γ-secretase enzyme complex, which is responsible for the proteolytic cleavage of multiple transmembrane proteins, including NOTCH (Neurogenic locus notch homolog protein receptor). Inhibition of NOTCH signaling leads to the disruption of cell growth, possibly slowing tumor growth.[1] A recent study by Gounder *et al.*[1] reported results of a phase 3 trial; patients receiving nirogacestat had a 71% lower risk of disease progression or death than those on a placebo. The study concluded that after 2 years, the chances of disease-free progression or death was 76% with nirogacestat compared to 44% with placebo.[1]

As nephrologists, it was interesting to note that nirogacestat was associated with a 42% incidence of hypophosphatemia, among other adverse events. However, the study does not provide insights into the possible mechanism of hypophosphatemia, and the etiology of the increased incidence of hypophosphatemia in the treatment group remains unclear. A summary of studies on γ-secretase inhibitor use in different cancers with the incidence of hypophosphatemia (%) is presented in Table 1.[1–5] On the basis of these results, we postulate that hypophosphatemia is likely a class effect.

It is uncertain whether this is causally linked to the augmented frequency of diarrhea observed in this cohort (hypophosphatemia mediated by downregulation of sodium phosphate transporter-2b). The potential of nirogacestat to induce renal phosphorus wasting mediated via sodium phosphate transporter-2a necessitates further investigation. Further investigations are required to examine potential concurrent electrolyte abnormalities, particularly involving serum calcium, in association with fractional excretion of phosphorus, as well as the levels of phosphaturic hormones such as parathyroid hormone and fibroblast growth factor-23. These studies will provide valuable insights into the intricate mechanisms that affect phosphate homeostasis in the context of nirogacestat treatment. Mechanistic studies will also aid in preventing strategies to mitigate a common side effect of this class of drugs.

Table 1. Summary of NOTCH inhibitor trials and associated risk of hypophosphatemia

Cancer	Pt no:/study type	Dose	Incidence of Hypophosphatemia
Desmoid tumor[1]	70, Phase 3 double-blind, placebo, RCT	Nirogacestat 150 mg BID	42% in Rx arm
Advanced sarcoma[2]	67, Investigator-initiated trial, phase 1b/2 RCT	RO4929097 (monoRx): 34 RO4929097 + Vismodegib: 33	MonoRx arm: 38% Combination arm: 3%
Desmoid tumor[3]	17, Open-label, single-arm, Phase 2	150 mg BID	76% Grade 2: 38% Grade 3: 62%
Metastatic breast[4]	15, Phase 1b dose-escalation trial	The dose escalated over 5 doses (20, 30, 45, 90, and 140 mg)	46.7% Grade 3 AE 13.4%
Solid organ cancer[5]	36, open-label phase 1 dose-escalation study	Once daily dosing 0.3, 0.6, 1.2, 1.5, 2.0 mg Twice weekly 2, 4, 8 mg	67% in once daily, 58% in weekly schedule

AE, adverse events; monoRx, monotherapy; RCT, randomized control trial; Rx, treatment.

1. Gounder M, Ratan R, Alcindor T, et al. Nirogacestat, a gamma-secretase inhibitor for desmoid tumors. *N Engl J Med*. 2023;388:898–912. https://doi.org/10.1056/NEJMoa2210140
2. Gounder MM, Rosenbaum E, Wu N, et al. A phase Ib/II randomized study of RO4929097, a gamma-secretase or notch inhibitor with or without vismodegib, a hedgehog inhibitor, in advanced sarcoma. *Clin Cancer Res*. 2022;28:1586–1594. https://doi.org/10.1158/1078-0432.CCR-21-3874
3. GHOS C, Kummar S, Steinberg SM, et al. Extended progression-free survival and long-term safety of nirogacestat in patients with desmoid tumors. *J Clin Oncol*. 2022;40(16_suppl):11545. https://doi.org/10.1200/JCO.2022.40.16_suppl.11545
4. Means-Powell JA, Mayer IA, Ismail-Khan R, et al. A Phase Ib Dose Escalation Trial of RO4929097 (a gamma-secretase inhibitor) in Combination with exemestane in Patients with ER + Metastatic Breast Cancer (MBC). *Clin Breast Cancer*. 2022;22:103–114. https://doi.org/10.1016/j.clbc.2021.10.013
5. Aung KL, El-Khoueiry AB, Gelmon K, et al. A multi-arm phase I dose escalating study of an oral NOTCH inhibitor BMS-986115 in patients with advanced solid tumours. *Investig New Drugs*. 2018;36:1026–1036. https://doi.org/10.1007/s10637-018-0597-6

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