**INTRODUCTION**

- B-cell maturation antigen (BCMA) is expressed on the cell membrane of normal plasma cells and multiple myeloma (MM) cells.
- BCMA is the target of several approved products and investigational agents for the treatment of MM.
- Low BCMA receptor density may be associated with lower response rates, worse durability of response, or resistance to BCMA-targeted agents.
- The enzyme gamma secretase (GS) cleaves BCMA from the cell surface, which results in reduced levels of membrane-bound BCMA (mbBCMA) and generation of soluble BCMA (sBCMA).
- GS inhibitors (GSIs) have been shown to increase levels of mbBCMA and, in both preclinical and clinical studies, they have potentiated the therapeutic activity of several BCMA-targeted therapies when used in combination.
- Although the effect of GS inhibition on mbBCMA has been reproducibly characterized preclinically, additional studies are necessary to adequately characterize the effect on BCMA dynamics in humans.
- Nirogacestat is an investigational, small-molecule GSi in clinical development as a monotherapy for de novo tumors and ovarian granulosa cell tumors and is being evaluated in combination with several BCMA-directed therapies in ongoing or planned clinical trials [Figure 1].

**CONCLUSIONS**

- Nirogacestat treatment resulted in rapid and robust increases in mbBCMA levels on plasma cells isolated from BM and WB.
- Continuous inhibition of GS is necessary to sustain elevated levels of mbBCMA on plasma cells.
- BID dosing of nirogacestat is recommended to sustain inhibition of GS on plasma cells and increase mbBCMA receptor density.
- A 100-mg, twice-daily dose of nirogacestat is being tested in clinical trial subjects with MM who are receiving BCMA-directed therapy.
- Evaluating mbBCMA dynamics in plasma cells isolated from either BM or WB is feasible.
- mbBCMA remains elevated throughout the nirogacestat dosing interval when nirogacestat was administered at 100 mg twice daily (Figure 7).
- Dose-related reductions in mbBCMA were observed following treatment with nirogacestat, although the baseline levels were low in this healthy population and the effect was modest (data not shown).

**RESULTS**

- Serum concentrations of nirogacestat increased rapidly, with a T_{max} of approximately 1 hour, and declined quickly over the first 12 hours (Figure 4).
- Fold increases in mbBCMA on plasma cells isolated from WB after administration of a single 50-, 150-, or 300-mg dose of nirogacestat were analyzed and compared across timepoints.