

### Mechanism of Action:

Multiple mechanisms have been identified that mediate acquired resistance to tyrosine kinase inhibitors in non-small cell lung cancer (NSCLC), including epidermal growth factor receptor (EGFR) secondary mutations and MET amplification. These resistance mechanisms can occur concurrently in the same tumor (Douillard *et al.*, 2010).

The data reported suggest that irrespective of the resistance mechanism, these cancer cells remain sensitive to Hsp90 inhibition. Hsp90 is a gene on chromosome 6p12 that encodes a constitutive Hsp90 chaperone with intrinsic ATPase activity which aids proper folding of specific target proteins, and therefore promotes the maturation, structural maintenance and proper regulation of client proteins involved in cell cycle control, signal transduction, protein degradation and other processes. retaspimycin potently induces apoptosis in these preclinical experiments (Goetz *et al.*, 2005).

In xenograft models of Gefitinib-resistant lung cancer, administration of retaspimycin resulted in significant anti-tumor activity. In addition, enhanced anti-tumor activity was reported in these models when retaspimycin was administered in combination with Iressa, even though the cells had acquired resistance to Iressa as a single agent (Chang *et al.*, 2008).

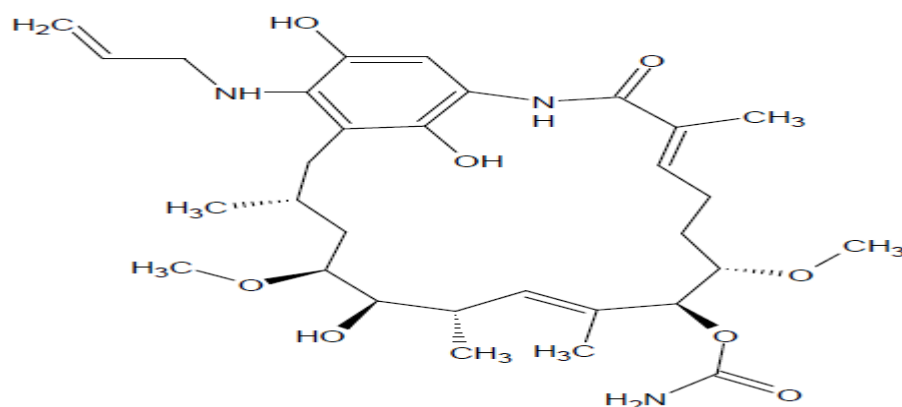


Figure 8: 18,21- Dihydro-17-demethoxy-18,21-dideoxy-17-(2 propenylamino) geldanamycin.