

## Journal Watch

### **A Spicamycin Derivative (KRN5500) Provides Neuropathic Pain Relief in Patients With Advanced Cancer: A Placebo-Controlled, Proof-of-Concept Trial.**

Presented by Jarret Morrow (MD, PGY-2 FM), on February 7, 2013

Reference: Weinstein SM, Abernethy AP, Spruill SE, Pike IM, True Kelly A, Jett LG. *J Pain Symptom Manage.* 2012 Apr;43(4):679-93. doi: 10.1016/j.jpainsymman.2011.05.003. Epub 2011 Oct 7.

#### Abstract

**Context.** Neuropathic pain in patients with cancer can be difficult to treat effectively.

**Objectives.** The purpose of the study was to determine safety and efficacy of KRN5500, a novel, spicamycin-derived, nonopioid analgesic agent, in patients with advanced cancer and neuropathic pain of any etiology.

**Methods.** The study was a Phase 2a, multicenter, double-blind, placebo-controlled, dose escalation clinical trial. Patients with refractory neuropathic pain and advanced cancer were randomly assigned 2:1 to receive a maximum of eight single escalating doses of KRN5500 or placebo, ranging from 0.6 to 2.2 mg/m<sup>2</sup>. The primary objective was safety and tolerability. The secondary objective was efficacy, measured by change in average pain intensity on a 0e10 numeric rating scale administered one week after the patient's final dose.

**Results.** Nineteen patients received treatment (KRN5500 n 1 /4 12; placebo n 1 /4 7). The most frequently reported adverse events were gastrointestinal symptoms, which were more frequent and severe with KRN5500 than placebo; two (17%) KRN5500 patients discontinued the study because of nausea and vomiting. At study endpoint, KRN5500 exhibited a significant median decrease in pain intensity from baseline of 24% compared with 0% for placebo (P 1 /4 0.03). The median for largest weekly reduction in target pain intensity was 29.5% for KRN5500 and 0% for placebo patients (P 1 /4 0.02).

**Conclusion.** This proof-of-concept study for KRN5500 in patients with advanced cancer and any type of neuropathic pain found gastrointestinal adverse events to be the predominant safety concern. The results also provided the first indication of clinical and statistical efficacy in reducing pain intensity.

#### **Strengths of study**

The study itself was a Phase 2a multicenter, double-blind, randomized, placebo-controlled albeit dose escalation trial. Patients selected for the study were those with advanced cancer and treatment-resistant neuropathy.

#### **Weaknesses of study**

The study had a very small sample size. In fact, the authors conceded that the study was not powered to measure prospective efficacy outcomes. As well, efficacy was the secondary not primary objective of the trial. No discussion of allocation concealment was included. Subjects in the intervention and placebo groups differed at baseline in terms of both severity of neuropathic pain (higher in KRN5500) as well as etiology of neuropathic pain. Patients in both groups were allowed to continue adjuvant pain medication, which was not recorded or discussed. The study was funded by industry (Dara Therapeutics).

#### **Relevance to palliative care**

The patients enrolled in this study had advanced cancer and refractory neuropathic pain (failing to achieve symptom relieve from at least 2 commonly used medications for neuropathic pain). The investigational agent, KRN5500, is not clinically available but may be in the future depending on the results of subsequent clinical trials. With the lack of records or controls for adjuvant medication usage, greater severity of baseline pain severity in the intervention group and longer duration of treatment in this group as well, one could argue that the deck was stacked in favor of KRN5500 in terms of efficacy. Of note, clinician rated measures found some evidence for efficacy while patient ratings did not.