The tissue targeted prodrug, AQ4N, is activated to AQ4 in murine tissues and has anti-tumor efficacy in HCT116 colon and Panc1 pancreatic carcinoma xenograft models.

Susan E. Alters, Jeffrey L. Cleland, Alvin Wong and W.D. Henner

Novacea, Inc., South San Francisco, CA

Background

• AQ4N (banoxantrone) is a prodrug of a potent topoisomerase II inhibitor, AQ4.
• Systemic toxicity of AQ4N is minimized due to lack of systemic biodistribution to AQ4.
• AQ4N selectively accumulates in xenografts and murine intestines, pancreas and lymphoid tissues where it is bioreduced to AQ4.
• AQ4N has significant efficacy in several pre-clinical xenograft models including BXPC3 (pancreatic) and HT29 (colon carcinoma).
• AQ4N is being studied in human Phase I studies in the US and Europe.

Methodology

Biodistribution:

• 10^6 BXPC3 (human pancreatic cancer) cells were injected sc;
• Tumors grew to 200-300mm^3 prior to dosing;
• Single IV injection of AQ4N at 20 mg/kg;
• Mice were sacrificed at 24, 72, 168, 336 hours post AQ4N dose (3 mice/time point).
• AQ4N and AQ4 levels were determined by HPLC/MS-MS in human tumor and murine plasma and solid tissue.
• Limit of quantitation: 1) Plasma: 50ng/ml
  2) Tissue: 25ng/g.

Efficacy:

• Pan1 or HCT116 xenografts were implanted sc into nude mice (10/group).
• Treatment was initiated when tumors reached ~100mm^3.
• Treatment outcome determined as time to endpoint; endpoints were defined as 1200mm^3 for Panc1 and 2000mm^3 for HCT116.
• Significance in tumor growth delay (difference in time to endpoint in defined as 1200mm^3).

The highest levels of AQ4 are detected in the small and large intestine; elimination seen after 24 hours. AQ4N is converted to AQ4 within 24 hours following a single 20mg/kg dose. The highest levels of AQ4 are detected in the small and large intestine; elimination seen after 24 hours.

• Levels of AQ4 can be measured in the sc tumor at all sampling times from 24 to 336 hours following a single 20mg/kg dose of AQ4N. AQ4 concentrations are fairly stable for 7 days in the tumor.
• AQ4 is no longer detectable in plasma post 24 hours.
• AQ4N demonstrates significant efficacy in colon and pancreatic tumor xenograft models at dose levels below the MTD.
• In the Pan1 model, weekly doses of AQ4N at 120mg/kg result in a significant increase in time to endpoint of 56.5 days as compared to 28.8 for vehicle and 34.2 for gemcitabine.
• In the HCT116 colon model AQ4N given at 75mg/kg qod results in a significant increase in time to endpoint of 45.8 days as compared to 29.4 for vehicle and 34.2 for gemcitabine. Weekly doses of AQ4N at 90mg/kg also give a significant response.
• These data, taken together with our previous data showing a significant effect of AQ4N in BXPC3 pancreatic and HT29 colon carcinoma models, indicate the potential use of AQ4N as a single agent in these malignancies.

Summary

• AQ4N is being studied in human Phase I studies in the US and Europe.

Novel Therapies Improving Lives