ABSTRACT

Background: SM88 is a novel combination of five therapies (aminopterin, melatonin, melanotan, phenylalanine, and tyrosine isomers) that when administered together, has demonstrated anti-cancer activity with little to no toxicity in a preliminary study of 30 patients (J Clin Oncol 2013; suppl. abstr e22095) and Hoffman et al. GynOncol 130(1), 443). We now present preclinical animal data related to toxicity of the proprietary tyrosine agent and possible mechanism of action.

Material and Methods: Preclinical animal model with 7 day escalating dose and 28 day repeat dosing toxicology studies in Sprague Dawley rats and beagle dogs using the tyrosine agent of SM88. Test and control/vehicle items were administered daily or three times per week over a 4-week period, at doses of 3, 15, 75, and 150 mg/kg/day. All changes were considered within an acceptable range for biologic variation. Other – There were no changes in hematology, clinical chemistry, coagulation, urinalysis, or ECG. Test and control/test animals were maintained in accordance with the principles outlined in the current “Guide to the Care and Use of Experimental Animals” as published by the Canadian Council on Animal Care and the “Guide for the Care and Use of Laboratory Animals”, an NIH publication.

RESULTS

There were no deaths, clinical signs, change in body weights and food consumption (except as previously noted), no effects on ECGs, ocular findings, changes in hematology, coagulation, clinical chemistry, no toxicity in any organ weights and no macroscopic and microscopic findings that could be attributed to the administration of the tyrosine agent and possible mechanism of action. Future clinical dosing will be determined and is being used as part of an ongoing dose escalation that the toxicokinetic parameters, no changes in other organ weights and no macroscopic and microscopic findings could be attributed to the administration of the tyrosine agent. Test and control/test animals were maintained in accordance with the principles outlined in the current “Guide to the Care and Use of Experimental Animals” as published by the Canadian Council on Animal Care and the “Guide for the Care and Use of Laboratory Animals”, an NIH publication.

CONCLUSIONS

SM88 tyrosine isomers are not toxic in this preclinical animal study. The dose levels administered are consistent with other SM88 preclinical and clinical data from independent investigators. Human clinical experience using an extrapolated dose consistent with this animal data is also non-toxic. Human clinical trials are now in Phase I (Tyme Cancer Systems, Inc.; clinicaltrials.gov: NCT02748386). All animals used on this study were cared for in accordance with the principles outlined in the current “Guide to the Care and Use of Experimental Animals” as published by the Canadian Council on Animal Care and the “Guide for the Care and Use of Laboratory Animals”, an NIH publication.

FUTURE DIRECTIONS

The non-toxic results of SM88 isomers may be due to the high selectivity of amino acids (aa) for cancer cells based on the Warburg Effect. This selectivity allows for relatively low doses in clinical use and has been confirmed by others using aa based tumor imaging. Downstream mechanism may include altered mucin production, a known effect of aa in amino acids (aa) for cancer cells. Combined with other SM88 components, SM88 is a non-toxic, broadly applicable novel cancer treatment.

References

1. Hoffman et al. GynOncol 130(1), e43].

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INTRODUCTION

SM88 tyrosine isomers are a patented non-toxic anti-neoplastic, active through many well established mechanisms described in preclinical bench and animal models. We now present preclinically for the first time, our preclinical animal toxicity data.

MATERIALS AND METHODS

Test animals received racemate of tyrosine isomers, by oral administration. Testing was done after 4 weeks and to allow assessment of reversibility of any changes occurring over 28-day repeat dosing. Blood samples were collected on Days 1 and 27 at 8 time points relative to treatment in order to determine the toxicokinetic profile. All test rats regardless of sex, demonstrated consistent organ volume decrease in the pancreas (decreased cell volume, and reduced concentration of zymogenic vesicles), ovaries and uterus. These changes were completely reversible upon the discontinuation of the SM88 agent. 28 consecutive days resulted in a reduction in mean body weight gain in the 300 mg/kg/day males, which correlated to a lower food consumption and a dose-related increase in mean body weight gain in the females of all dose groups. Dogs had no such observations. There were no deaths, no clinical signs, no effects on ECGs, no ocular findings, no changes in hematologic, coagulation, clinical chemistry and urinalysis parameters, no changes in other organ weights and no macroscopic and microscopic findings that could be attributed to the administration of the isomers at doses up to 300 mg/kg. Consequently, the No Observed Effect Level (NOEL) for the tyrosine agent when administered three times per week for 4 weeks was determined to be 150 (dog)/300 (rat) mg/kg.

RESULTS

There were no clinical signs that could be attributed to the administration of the isomers at doses up to 150 mg/kg/day. All changes were considered within an acceptable range for biologic variation. There were no deaths, clinical signs, change in body weights and food consumption (except as previously noted), no effects on ECGs, ocular findings, changes in hematology, coagulation, clinical chemistry, no toxicity in any organ weights and no macroscopic and microscopic findings that could be attributed to the administration of the tyrosine agent. Mortality - There were no unscheduled deaths in the study. Clinical Signs - There were no clinical signs that could be attributed to the administration of the isomers at doses up to 150 mg/kg/day. All changes were considered within an acceptable range for biologic variation. Food Consumption - There were no changes in food consumption that could be attributed to the administration of the isomers of tyrosine at doses up to 150 mg/kg/day. All changes were considered within an acceptable range for biologic variation.

CONCLUSIONS

SM88 tyrosine isomers were not toxic in this preclinical animal study. The dose levels administered are consistent with other SM88 preclinical and clinical data from independent investigators. Human clinical experience using an extrapolated dose consistent with this animal data is also non-toxic. Human clinical trials are now in Phase I (Tyme Cancer Systems, Inc.; clinicaltrials.gov: NCT02748386). All animals used on this study were cared for in accordance with the principles outlined in the current “Guide to the Care and Use of Experimental Animals” as published by the Canadian Council on Animal Care and the “Guide for the Care and Use of Laboratory Animals”, an NIH publication.

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The non-toxic results of SM88 isomers may be due to the high selectivity of amino acids (aa) for cancer cells based on the Warburg Effect. This selectivity allows for relatively low doses in clinical use and has been confirmed by others using aa based tumor imaging. Downstream mechanism may include altered mucin production, a known effect of aa in amino acids (aa) for cancer cells. Combined with other SM88 components, SM88 is a non-toxic, broadly applicable novel cancer treatment. 

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