An Open-Label Trial of SMK Treatment of Advanced Metastatic Cancer

S. Hoffman[1], H. Bruckner[2], D. Stega[3,*], A. Demurjian[4], D. Gurell[5], R. Mull[1], M. Demurjian[1], G. Del Priore[6], J. Malanowska-Stega[1]

[1] *Luminant BioSciences, NJ, USA*
[2] *Bruckner Oncology, NY, USA*
[3] *University of Varmia and Masuria, Olsztyn, Poland*
[4] *Red Bank Catholic High School, NJ, USA*
[5] *University Diagnostic Medical Imaging, PC, NY, USA*
[6] *Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IND, USA*

* *Corresponding author: dstega@optonline.net*

SUMMARY

The purpose of this study was to determine the safety, tolerability, and efficacy of SMK in patients with advanced metastatic breast cancer. SMK (Lumeria) is a unique therapy that creates alteration in defenses to oxidative stress and increases free radical exposure to the cancer cell. This was an IRB-approved study for metastatic cancer. No additional chemotherapy was allowed. The first 30 (14 with breast cancer) patients meeting entry criteria were consented. SMK was given orally and subcutaneously (SC), 5 days/week for 6 weeks (1 cycle). Subjects were allowed to continue with additional cycles based on their preferences. Before they entered the study, 4/14 (29%) had declined routine treatment, 10/14 (71%) had used many available treatments, and all were considered incurable in the end stage of progressive disease. The median number of cycles was 3 (range: 1-10). At the end of the study, 13/14 (93%) were alive with a median survival over 15 months; 11/14 (79%) had a 1 to 3 point improvement in ECOG rating; 10/14 (71%) had a 1 to 5 point improvement in EORTC (scale 1-7) rating. There was no treatment-associated toxicity except for cutaneous hyperpigmentation. In conclusion, SMK is a promising life extension treatment for metastatic breast cancer with no significant toxicity.

 Code: **1917**

Keywords: Oxidative stress, free radical, cancer cell, tyrosine, rapamycin, phenytoin, melanin.

INTRODUCTION

Properties of the host micro-environment can significantly affect tumor morphology and growth dynamics, emphasizing the importance of understanding the tumor-host interaction. Cancer cells are anaerobic and have been designed or evolved to live in oxygen deprived conditions using hypoxia-inducible factor (HIF) protein [1].

HIF causes new blood vessels to grow around and into the tumor. The tumors continue to reproduce and replicate the anaerobic environment, thus, allowing for rapid reproduction of cancer cells. Current cancer drugs, for example, typically attempt to either limit the growth of tumors by cutting off the blood supply or attempt to limit the ability of the cancerous cell to replicate, but these therapies inevitably involve damaging healthy cells that surround the cancerous area, compromising the patient's immune system and ability to heal, and resulting in a therapy that is highly toxic to the patient.

SMK Therapy is a unique therapy designed to kill cancer cells with oxidative stress techniques of forcing cancer to be an electron donor and potentiating a reaction with reactive oxygen. Cancer cells are anaerobic in nature, requiring a complex reductase synthesis process to deal with oxygen. A hypothesized toxicity is that by introducing oxygen directly into the cancer cell, oxygen acts as the invading electron scavenger. Oxidative stress follows and the cancer cell dies. SMK is a combination of agents that alter the defenses of cancerous cells to oxidative stress. One class of such therapies increases free radical availability to cancerous cells.

To understand the rationale for this combination drug therapy, it is necessary to consider cancer differently, i.e., as a purposeful tool in maintenance of homeostasis that becomes rogue. For example, many cancers originate in areas of the body that may be exposed to viruses. Cancer may be manufactured as a system to eliminate viruses, designed to be a sacrificial cell, easily killed by abundant oxygen. Cancer cells are sent to engulf a cell infected with a virus as a boundary between that cell and other needed cells. Upon viral exposure the cancer cell is to be killed by the body, taking all remnant of «active» virus with it. The «disease» cancer may be from one or more of the following subsequent errors: 1) The virus changes the perishable cancer cell to become more robust; 2) The body fails to identify the completion of the cancer cell's mission and allows it to continue replication; 3) The body does not have the strength to apply the oxidative stress to kill the cancer cells.

The exact failure of the system may someday be diagnostically determined in *vivo*, but a method to address all of this variation may be achieved in a non-toxic combination therapy as follows: The first step is to weaken a cancer cell. The protective mucin layer surrounding cancer cells has a complex structure with recurring amino acids. Following well-understood uptake of such imaging agents as 3-123I-Iodo-L-methyltyrosine (3-IMT), we incorporate a mix of entantiomers as our tyrosine isomer component. The ability to enter the cell is confirmed by imaging (a benefit of melanin connection, described later) and facilitated by l-transfer modulation also disclosed. The exact mechanisms of utility within the cancer cell are not well understood, but the effect is reduced or incomplete mucin protection, allowing access of free radical based oxygen.

The availability of free radicals to react with the cancer is accomplished by a multi-stepped process. The origin of the free radicals is the cytochrome p450 site of the liver, and is up regulated with the 3A4 inducer, phenytoin. The steering of these dielectrically encased and preserved free radicals is accomplished naturally, as evidenced by free radicals abundant in cancer clusters' periphery.

The next step is mutually advantageous to 2 parts of the process, and is achieved by use of C51H79NO13 rapamycin orally or bestatin, a leucine aminopeptidase inhibitor. This masking of leucine causes the liver to react as if a ketosis state is occurring, and recall leucine from systemic distribution. The leucine in part comes from the exterior surface of the cholesterol, releasing the still potentiated free radical contents. The absence of leucine has the dual function of greatly increasing l-transfer at the cancer cell.

At this point we have a mucin reduced cancer cell and directly contacted free radicals, requiring only a catalyst to compel a reaction. The melanin elevated in the body creates this electrical catalytic inducement. Melanin is elevated with oxsoralen (9-methoxy-7H-furo [3,2-g] [1] benzopyran-7-one methoxsalen) as oral melanin inducer or melanotan 2, (Ac-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]-NH_2) in the suspension. Both of these materials encourage melanin creation in vivo. Additionally, a combination of melanin, either naturally occurring or artificially created, can be structurally bound to the tyrosine isomer, bringing melanin directly to the reaction point, and potentially creating residual electrolysis fed oxygen creation within the cancer cell. This yields a potential longer term treatment benefit [2, 3, 4, 5].

MATERIAL AND METHODS

This was an IRB approved, open-label, pilot study. SMK was administered orally as 3 capsules and injected as an SC suspension, 5 days per week for a

period of 6 weeks (1 cycle). Each dose was comprised of the following: Capsule 1: melanin 50 µg, tyrosine derivative 75 mg, Capsule 2: dilantin 30 mg, tyrosine derivative 150 mg, Capsule 3: 3-Amino-2-hydroxy-4-phenylbutyryl]-L-leucine 50 µg, tyrosine 75 mg and suspension for subcutaneous (SC) injection: 3-Amino-2-hydroxy-4-phenylbutyryl]-L-leucine 5 µg, melontan 10 µg, dilantin 2 mg tyrosine derivative 5mg, in NaCl bacteriostatic water.

Inclusion Criteria

Patients were age ≥ 18 years; provided written informed consent; had evidence of histologically confirmed, metastatic cancer; and an ECOG performance status of 0-2. Measurable disease was required by RECIST criteria 1.1 [6] as follows: (a) at least one target lesion, that had not previously been radiated, measurable in at least one dimension of greater than 2 cm by conventional CT or MRI, or at least 10 mm by spiral CT; or (b) palpable disease which was biopsy-proven to be metastatic (eg, skin nodule or lymphadenopathy), and that was superficial and measurable by caliper. All patients had adequate renal and hepatic function.

Exclusion Criteria

Patients with known leptomeningeal metastases or symptomatic brain metastases were excluded. Chemotherapy, radiotherapy (other than palliative radiotherapy to non-target lesions), biological, or investigational agents within 2 weeks of baseline disease assessments were not allowed. Any clinically significant gastrointestinal abnormalities that might have impaired intake, transit, or absorption of SMK were excluded.

Assessments

Easter Cooperative Oncology Group (ECOG) performance status was assessed at Screening, Baseline, every 2 weeks, and at the End of Treatment Visit. Laboratory studies (i.e., hematology [including WBC and differential], blood chemistry, urinalysis, and coagulation studies) were done up to 72 hours prior to treatment and were performed at Baseline, every 2 weeks, and at the End of Treatment Visit. Pregnancy tests for women of child bearing potential were done at Baseline within 72 hours of start of dosing and at the End of Treatment Visit if mandated by institutional policy.

Safety and adverse event (AE) assessments included recording of tumor-related, treatment-related, and unrelated signs and symptoms. Targeted questioning for AEs was done between Days 10 to 14 of the cycle, and on Day 28 and at End of Treatment Visit. Patients were followed for AEs at the Post-Treatment Follow-up visit at least 28 (and no more than 35) days after the end of treat-

ment. Toxicity grading was by NCI Common Terminology Criteria for Adverse Events Version 3.0.1 (NCICTCAE 3.0.1.).

Patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), its lung cancer module (QLQ-LC13) [7], and the Dermatology Life Quality Index (DQLI) [8, 9] at Baseline, between Days 12 to 14, on Days 28 to 30, and at the End of Treatment Visit. Patients completed the questionnaire prior to being informed of their disease status.

At least 28 days, and no more than 35 days, after the last dose, patients underwent a physical exam including skin exam and recording of concomitant medications. Thereafter they were followed at least monthly for progression, treatment, and survival. For patients who came off treatment, follow-up data were collected either by follow-up visits with the investigator or designee, or telephone contact to the patient's outside physician on a monthly basis to assess tumor status. For all patients, the following information was collected on a monthly basis: date of start of new treatment, type of systemic therapy administered, duration of second line systemic therapy; and survival status.

RESULTS

Breast tumor characteristics included: 12/14 (86%) ER(+), 10/14 (71%) ER/PR(+), 1/14 (7%) ER/PR/HER(-), 2/14 (14%) ER/HER(+); with metastasis to: 15% each: bone, lung, bone/lymph; 8% each: lung, lymph, bone/brain/lung, bone/brain/spine, bone/liver, bone/brain, liver/bones/lymph. The average age was 55(40-70) years; all were female; 93% Caucasian and 7% Asian.

Prior to study participation, 4/14 (29%) declined routine treatment, 10/14 (71%) had used all available treatment, and all were considered incurable in the end stage of progressive disease. All patients completed at least 1 cycle (1/14 [7%]), 4/14 (29%) completed 2 cycles, 3/14 (21%) 3 cycles, 3/14 (21%) 6 cycles, and 3/14 (21%) 10 cycles, depending on patient preference.

Eleven of 14 (79%) had a 1-3 point improvements in ECOG rating and 10/14 (71%) had a 1-5 point improvements in EORTC (scale 1-7) rating. Four of 14 gained weight (1-5 lbs), 6/14 (43%) remained the same, and 4/14 (28.5%) lost weight (1-2 lbs.). Eight of 14 (57%) had a reduction in pain levels (1-9 points on a scale of 1-10); 6/14 (43%) entered the study with no pain and maintained the same level; 6/14 (43%) entered the study on pain medication and 5 of those 6 (83%) no longer needed pain medication at the end of Cycle 1.

Three of 14 (21%) after Cycle 1 and an additional 2/14 (14%) after Cycle 2 had no detectable disease with routine exam, and imaging by RECIST1.1 criteria showed complete remission (CR) and no uptake on a PET scan. Five of

14 (36%) had significant reductions in quantity and/or size of the tumor, 2/14 (14%) had a reduction in quantity and/or size of the tumor, and 4/14 (29%) had no progression of disease. Two of 14 (14%) remain disease free, 4/14 (29%) remain stable with no additional treatment, 8/14 (57%) remain stable with additional treatment through August 2013.

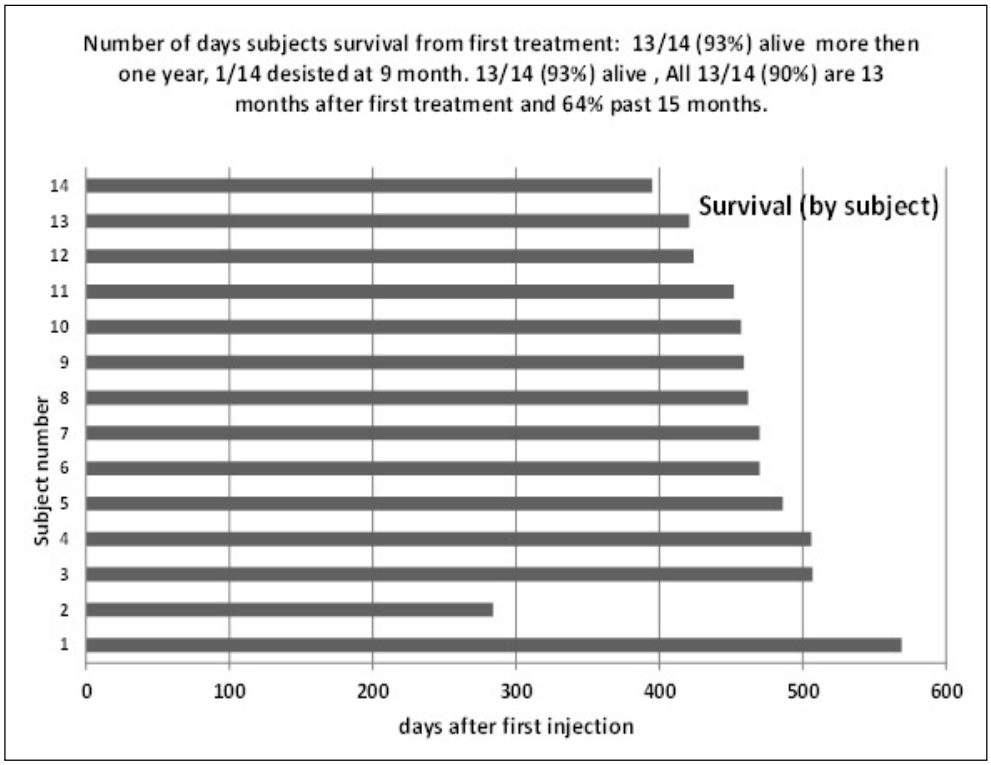

Fig. 1. Subject Survival in Days from First Treatment.

Survival times are shown in Fig 1. Thirteen of 14 (93%) are alive with median survival over 15 months: 9/14 (64%) 15 months, 3/14 (21%) 16-17 months, and 1/14 (7%) 18 months. From the first day of treatment until August 2013, 1/14 (7%) died after 9 months. All subjects developed hyperpigmentation and tolerated the SMK compounds well. No other AEs have been reported related to the product. In all patients, tumor markers improved and liver function remained stable.

CONCLUSIONS

SMK is a promising treatment for metastatic breast cancer. It is a unique therapy with no significant toxicity except for cutaneous hyperpigmentation. It was well tolerated among 30 subjects with a variety of cancers, including 14 patients with breast cancer, and all patients either maintained the same ECOG rating (13.3%) or had improvements of 1 to 3 points; most patients also experienced improvements on the EORTC health rating and quality of life ratings. In part, these benefits are likely related to tumor response as documented by imaging. Equally important, the median survival as of August 2013 in the study sample is now over one year. Moreover, several of the individual patient case reports include dramatic radiographic responses such as, «No functional evidence of active neoplastic.»

ACKNOWLEGMENTS

Nancy Wise Oglesby of Wise Medical Writing, LLC provided writing assistance.

REFERENCES

1. Yang J, Staples O, Thomas LW, et al. Human CHCHD4 mitochondrial proteins regulate cellular oxygen consumption rate and metabolism and provide a critical role in hypoxia signaling and tumor progression. *J Clin Invest.* 2012. 122(2); 600-611.

2. Hashimoto H, Toide K, Kitamura R, et al. Gene structure of CYP3A4, an adult-specific form of cytochrome P450 in human livers, and its transcriptional control. *Eur. J. Biochem*. 1993; 218(2):585-95.

3. Inoue K, Inazawa J, Nakagawa H, et al. Assignment of the human cytochrome P-450 nifedipine oxidase gene (CYP3A4) to chromosome 7 at band q22.1 by fluorescence in situ hybridization. *Jpn J Hum Genet*. 1992; 37 (2):133-138.

4. CYP3A4 cytochrome P450, family 3, subfamily A, polypeptide 4 [Homo sapiens (human)]. Gene ID: 1576, updated on 15-Sep-2013. http://www.ncbi.nlm.nih.gov/gene/1576 (accessed on 20 Sep 2013).

5. Shinkyo R, Guengerich FP. Inhibition of human cytochrome P450 3A4 by cholesterol. *J Biol Chem*. 2011; 286(21):18426-18433.

6. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45(2):228-247.

7. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. *Eur J Cancer*. 1994; 30A(5): 635-642.

8. Finlay AY, Khan, GK. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994; 19(3):210-216.
9. Lewis V, Finlay AY. 10 years experience of the Dermatology Life Quality Index (DLQI). *J Investig Dermatol Symp Proc*. 2004; 9(2):169-180.