AN OPEN LABEL TRIAL OF SMK TREATMENT IN ADVANCED METASTATIC CANCER

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ABSTRACT

Abstract No:
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Objective:
To determine the safety, tolerability and efficacy of SMK on subjects with advanced metastatic breast cancer.

Background:
SMK is a novel therapy that creates alteration in defenses to oxidative stress and increases free radical availability to the cancer cell. SMK is designed to penetrate the living cancer cells and introduce multiple mechanisms to kill the cell. The liberation of electrons in the cancer cells promotes oxidative stress while simultaneously the mitigation of the cancer cell created defense allows catalyzed external free radicals to react. SMK is a combination of low dose agents that the generally recognizes as safe for typical use other than in cancer treatment.

Methods:
This was an IRB approved, open-label pilot study. SMK was administered orally and subcutaneously, five days per week for a period of six weeks (1 cycle). More than 200 were screened. Criteria included all metastatic cancers; 30 subjects meeting criteria were consented; 14 with breast cancer are reported now.

Results:
Average age 55(40-70); all female; 93% Caucasian.
4/14 declined routine treatment prior to enrolling in the study, 10/14 had used all available treatment and were considered incurable.
11/14 (79%) had 1-3 point improvement in ECOG rating. 10/14 (71%) had 1-5 point improvement in EORTC (scale 1-7) rating. 4/14 gained weight (1-5 lbs.). 6/14 (43%) remained the same. 4/14 (28.5%) lost weight (1-2 lbs.). 8/14 (57%) had reduction in pain levels (1-9 pt. on scale of 1-10). 6/14 (43%) entered with no pain and maintained the same level. 6/14 (43%) entered study on pain medication. 5/6 (83%) no longer needed pain medication at the end of cycle 1. 3/14 (21%) are disease free with normal physical exam, review of systems and imaging, 5/14 (36%) have significant reduction in quantity and/or size of the largest tumor, 2/14 (14%) have reduction in quantity and/or size of the largest tumor, 4/14 (29%) no progression of disease,
14/14 (100%) are alive with median survival 28 weeks: {4/14 (33-37 weeks) (29%), 5/14 (27-29 weeks) (36%), 5/14 (12-19 weeks) (36%0)}. 3/14(21%) went home, 11/14(89%) continue with the treatment. All subjects develop hyperpigmentation. Overall, all subjects have tolerated the SMK compounds well, no adverse events have been reported related to the product, responses have been documented to the treatment 100%.

Conclusions:
SMK is a very promising treatment for all types of metastatic breast cancer.

BACKGROUND

In cancer progression, studies have shown cancer cells result in reverse embryogenesis dedifferentiation. Many steps have been identified as powerful regulators of epithelial-to-mesenchymal transition (EMT). Recent findings have connected cancer adhesion, invasion and progression to stem cell maintenance and point at a connection between EMT and stem cell formation(1). A part of tumor progression can be viewed as a continuum of progressive dedifferentiation (EMT) with a cell at the endpoint that has stem cell-like properties(1).

Treatment with systemic chemotherapy for advanced disease yields modest benefits. Despite the introduction of new agents, platinum-based doublets have plateaued in progression free-survivals of 4-6 months and median overall survival (OS) of 7.4 to 9.9 months(3). The addition of the angiogenesis inhibitor bevicizumab improves the expected outcome for the minority or patients who are not excluded from treatment with this agent (ie, squamous histology, central nervous system (CNS) metastases, hemoptysis or significant concurrent cardiovascular issues). However the additional benefit remains limited with the combination of chemotherapy-bevacizumab: median PFS of 6.2 months and median survival 12.5 months. The combination of other targeted agents such as epidermal growth factor receptor (EGFR), tyrosine kinase inhibitors (TKI) with chemotherapy have not shown consistent benefit compared to chemotherapy alone.

SMK is a novel therapy that creates alteration in defenses to oxidative stress and increases free radical exposure to the cancer cell. SMK is designed to penetrate the living cancer cells and introduce multiple mechanisms to kill the cell. The liberation of electrons in the cancer cells promotes oxidative stress which allows catalyzed external free radicals to react with vital cellular targets. SMK is a proprietary patent pending combination of 4 agents.

MATERIALS AND METHODS

This IRB approved study for metastatic cancer. No additional chemotherapy allowed in previous 2 weeks. First 30 subjects meeting criteria were consented, 14 subjects with metastatic or recurrent breast cancer. SMK was given orally and SQ, 5 days/wk, for 6 weeks (1cycle).

INCLUSION CRITERIA
1. Signed voluntary written informed consent document;
2. Age ≥18 years, male or female;
3. Evidence of histologically confirmed, metastatic cancer;
4. ECOG 0-2 performance status;
5. Measurable disease by RECIST criteria:
   a. At least one target lesion, that has not previously been radiated, measurable in at least one dimension of greater than 1 cm by conventional CT or MRI, or at least 10 mm by spiral CT, must be present;
   b. Palpable disease which is biopsy proven to be metastatic (eg., skin nodule or lymphadenopathy), superficial, and measurable by caliper is allowed, though confirmation of measurement by CT or ultrasound is encouraged;
   c. Acceptable radiologic procedures for disease assessment include contrast enhanced conventional or spiral CT, or MRI; contrast enhanced scans are required in the absence of contrast-allergy and patient intolerance of MRI. The following are not allowed as sole documentation of target lesions: ultrasound alone, nuclear scans (including bone or PET scans), plain CXR or bone radiographs, and tumor markers.
6. Adequate Renal Function, including:
   a. Estimated creatinine clearance ≥60 mL/min;
   b. Serum creatinine <1.5 x ULN (upper limit of normal);
   c. No known history of renal papillary necrosis or pyelonephritis.
7. Adequate Liver Function, including:
   a. Bilirubin ≤1.5 x ULN;
   b. AST (SGOT) ≤2.5 x ULN (≤5.0 x ULN if hepatic metastases);
   c. ALT (SGPT) ≤2.5 x ULN (≤5.0 x ULN if hepatic metastases).
8. Female patients or their partners must be surgically sterile or be postmenopausal, or must agree to use effective contraception while receiving trial treatment and for at least 3 months thereafter.
9. All female patients with reproductive potential must have a negative pregnancy test (serum/urine) within 72 hours prior to starting treatment;
10. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

EXCLUSION CRITERIA
1. Patients with known leptomeningeal metastases, or symptomatic brain metastases. (Screening CNS imaging in asymptomatic patients is not a required trial procedure). Patients with previously diagnosed brain metastases for which treatment (radiation or surgery) is recommended in the judgment of investigator are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to the start of study medication.
2. Concurrent chemotherapy, radiotherapy (other than palliative radiotherapy to lesions that will not be followed for tumor assessment on this study, ie, non-target lesions), biological or investigational agents within 2 weeks of baseline disease assessments;
3. Any surgery (not including minor procedures such as lymph node biopsy) within 4 weeks of baseline disease assessments; or not fully recovered from any side effects of previous procedures;
4. Any clinically significant gastrointestinal abnormalities, which may impair intake, transit or absorption of the study drug, such as the inability to take oral medication;
5. Current enrollment in another therapeutic clinical trial;
6. Any psychiatric or cognitive disorder that would limit the understanding or rendering of informed consent and/or compromise compliance with the requirements of this protocol;

Procedure
Written informed consent was required within 30 days of start of treatment, and prior to any study specific screening procedures.
History and physical exam: General medical history including details of any concurrent illness, oncology history, history of concomitant medications, physical exam including vital signs (pulse, sitting or supine blood pressure, respiratory rate, temperature, weight) and oxygen saturation were done at baseline within 2 weeks of randomization.
ECOG performance status was assessed at screening, baseline, every 2-weeks and end of treatment visit, as per the ECOG scale .
Concomitant Medications was recorded at screening, and continuously throughout trial periods concluding with Post-Treatment Follow-Up Visit. Laboratory studies, (described as follows in footnotes 9-14) may be done up to 72 hours prior to scheduled visits to allow for availability of results at time of patient encounter.
Hematology including WBC and differential; RBC, hemoglobin, hematocrit, and platelet count was done at baseline, every 2-weeks and end of treatment visit.
Blood Chemistry will include BUN, creatinine, sodium, potassium, magnesium, calcium, phosphate, random glucose, LDH, alkaline phosphatase, total protein, albumin, AST, ALT, total bilirubin obtained at baseline, every 2-weeks and end of treatment visit.
Urinalysis to include protein, glucose, leukocyte esterase, blood and microscopic examination of the sediment baseline, every 2-weeks and end of treatment visit.
Coagulation studies to include PT or INR, and PTT were performed at baseline, every 2-weeks and end of treatment visit.
Pregnancy Test for WOCBP was done at baseline within 72 hours of start of dosing. It was repeated at End of Treatment if mandated by institutional policy.

Schedule of Activity

Schedule of Activity	Visit 1 Screening	Visit 2 Enrolment &Baseline	Day 1, week 1,2,3,4,5,6	Between Day 10-14 of Cycle	Between Day 28-30 of Cycle	End of Study (Completion of treatment)	Post – treatment Follow-up Visit	Study Follow-Up Visit 1month	Study Follow-Up Visit 3 months
Informed Consent	X								
PI Physical Assessments	X		X	X	X	X	X	X	X
General Medical History, Physical Examination	X								
ECOG PS5	X	X	X	X	x	X	X	X	X
Inclusion &exclusion criteria	X	X							
Concomitant Medication	X	Collect concomitant medications continuously							
Hematology		X		X	X	X	X	X	X
Blood Chemistry1		X		X	X	X	X	X	X
Urinalysis		X		X	X	X	X	X	X
Coagulation		X		X	X	X	X	X	X
Pregnancy test		X		X	X	X	(X)		
Tumor Assessment (including scans)		X			X (if indication)	X	X		X
Serum Biomarkers	X			X	X	X	X	X	X
Adverse Event	Collect adverse events continuously, including targeted questioning for common adverse events								
Vital Signs (daily before and after treatment)	X (including O2 sat at baseline)		X`	X`	X	X	X	X	
PRO(QLQ-30/ LC13, DQLI)22			X	X	X	X	X		
Patient Status Follow-up			X	X	X	X	X	X	X
SMK-FC 0111	Cycle 1(6weeke) 5 treatments every week								

Safety and Adverse Event Assessments includes tumor-related, treatment-related and unrelated signs and symptoms. Adverse events were documented and Recorded in the CRF AE log upon reporting. Targeted questioning for adverse events was done between Day 10-Day 14 of Cycle with particular attention to any respiratory symptoms, rash or diarrhea and then Day 28 and at End of Treatment Visit. The reporting period for non-serious AE terminated 28 days after the last dose of Trial treatment or upon initiation of a subsequent anticancer treatment, whichever occurred first; the reporting period for serious AE ended 28 days after the last dose of Trial treatment irrespective of the start of any subsequent anticancer treatment.

Patients were followed for adverse events at Post-Treatment Follow-up visit at least 28 (and no more than 35) days after end of treatment, or until all drug-related toxicities had resolved or were deemed irreversible whichever is later. Toxicity grading was by NCI Common Terminology Criteria for Adverse Events Version 3.0.1 (NCI CTCAE 3.0.1.).
Vital Signs: vital signs (to include pulse, sitting or supine blood pressure, respiratory rate, temperature, weight) and oxygen saturation were taken at baseline; vital signs were also taken on Day 1 of cycle, each treatment visit, at end of treatment visit, and at post-treatment follow-up visit. The information was recorded in the patient's chart and CRF; data was recorded as an Adverse Event in the CRF as clinically warranted.

Subjects Reported Outcomes (PRO): patients completed the EORTC QLQ-C30, its lung cancer module (QLQ-LC13), and the Dermatology Life Quality Index (DQLI) pre-dose at baseline, between Day 12-Day 14 of Cycle , Day 28-30 and at End of Treatment visit. Patients completed the questionnaire immediately upon entering the clinic, PRIOR to being informed at the visit of disease status.

End of Treatment Visit: when a subjects came off study, they were seen for: ECOG assessment, continued evaluation of adverse events and concomitant medications, routine safety and biomarker laboratory studies, and PRO questionnaires. Tumor assessment was scheduled if not done within last 4 weeks.
Post-treatment Follow-up Visit: at least 28 days, and no more than 35 days, after last dose, patients underwent history, physical exam including skin exam, and recording of concomitant medications. Thereafter they were followed at least monthly for resolution of any adverse effects or determination that such effects are irreversible, whichever is later.

Subjects Status Follow-up for Progression, Treatment and Survival: For patients who came off treatment for intolerance or refusal of treatment, follow-up data was 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 monthly basis: date of start of new treatment, type of systemic therapy administered, duration of second line systemic therapy; and survival status.

MATERIALS AND METHODS

Timing of Assessments
All subjects considered for the trial signed an informed consent within 30 days prior to any trial-specific procedures. Baseline assessments were performed within 7 days prior to commencing trial treatment, except tumor imaging , which was performed within 28 days prior to treatment, medical history, which was performed within 14 days, and pregnancy test (if applicable), which was performed within 72 hours prior to treatment. Efforts were made to initiate trial treatment within 3 days of randomization. The first trial treatment was administered on Day 1 of Cycle 1 at which time patients had drug supply available.

Efficacy Assessments
Clinical Efficacy Assessments
Objective tumor response was measured using the Response Evaluation Criteria in Solid Tumors (RECIST)
Baseline imaging tumor assessments was performed within 28 days prior to commencing trial treatment. All measurements were recorded in metric notation using a ruler or calipers.
Post baseline tumor assessments using the same method and technique used to characterize lesions identified and reported at baseline were performed at the end of the study. For patients who discontinue trial treatment for reasons other than disease progression or withdrawal of consent, tumor assessments continued about every 8 weeks until disease progression or initiation of subsequent anticancer treatment. As per RECIST guidelines, patients with documented PR or CR had a confirmatory tumor assessment no sooner than 4 weeks following initial response documentation.
The same method and technique was used to characterize each lesion identified and reported at Baseline, during the trial treatment period, and during follow up.
All Tumor Assessment scans were retained for possible independent radiologic review to be undertaken at Sponsor prerogative.

Tumor-Related Signs and Symptoms
Assessment of Baseline tumor-related signs and symptoms were undertaken within 12-14 days of commencing trial treatment. Tumor-related signs and symptoms were followed at each subsequent visit and were reported on the Adverse Event pages. The CTC grade was recorded at each visit (while present) even if the event improved or remained stable.

Safety Assessments
The following parameters were assessed as described in the Schedule of Activities: Blood Hematology; Blood Chemistry; Urinalysis; Pregnancy Test (serum/urine); Performance Status; Adverse events; particularly those AEs consistent with EGFR TKI toxicity profile (including rash, diarrhea); Concomitant medications.

Patient Reported Outcomes
Subjects Reported Outcomes of HRQOL, and disease/ treatment-related symptoms were assessed using the EORTC QLQ-C30,[23, 24] QLQ-LC13[25] and DLQI.[26, 27]
Patients completed the self-administered questionnaires pre-dose at baseline (Day 1, Cycle 1), between Day 10-14 of Cycle, Day 12 of cycle, and at the end of treatment (either when the patient completed or discontinues treatment). These measures were completed prior to having any tests, and before any discussion of the patient's progress with their physician or other healthcare personnel.

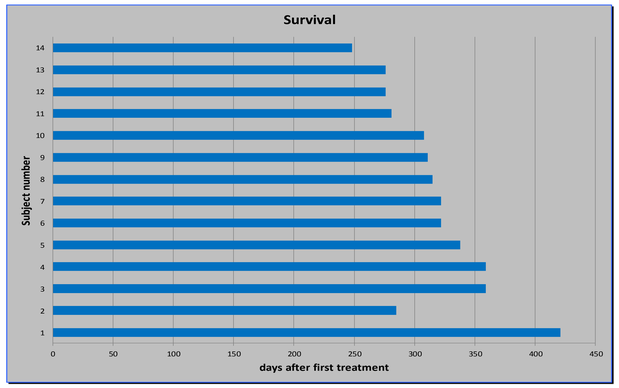
EORTC QLQ-C30
This questionnaire (Version 3.0 – Appendix 2) is comprised of 30 questions in total. Within the 30 questions are 9 multi-item scales and 6 single-item measures. There are 5 functional scales; physical, role, cognitive, emotional and social, 3 symptom scales; fatigue, pain and nausea and vomiting, and also a global health status/QOL scale. There are 5 single item measures assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and a single item concerning perceived financial impact of the disease.[23, 24]

EORTC QLQ-LC13
The QLQ-LC13 (Appendix 4) consists of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy. The 13 questions comprise one multi-item scale for dyspnea and 10 single-item measures assessing symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in the chest, pain in the arm, other pain, and medicine for pain).

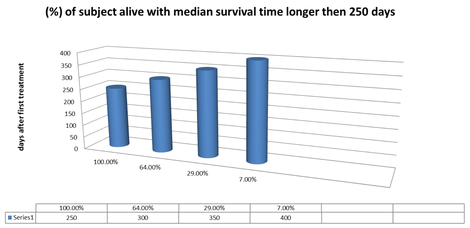
DLQI
The Dermatology Life Quality Index questionnaire (Appendix 5) consists of 10 questions and is designed to be a simple but sensitive method to measure the disability caused by skin diseases. The aim of the questionnaire is to measure how much the patient's skin problem has impacted their life over the previous week. The majority of the questions are answered on a 4-point Likert scale ranging from 'Very much' to 'Not at all'. It is usually completed in one to two minutes.

RESULTS

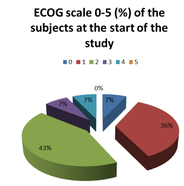
Total 14 subjects with advance metastatic breast cancer were consented to the study. Average age 55(40-70); all female; 93% Caucasian.
4/14 declined routine treatment prior to enrolling in the study, 10/14 had used all available treatment and were considered incurable.
After cycle I (6 weeks): 11/14 (79%) had 1-3 point improvement in ECOG rating. 10/14 (71%) had 1-5 point improvement in EORTC (scale 1-7) rating. 4/14 gained weight (1-5 lbs.). 6/14 (43%) remained the same. 4/14 (28.5%) lost weight (1-2 lbs.). 8/14 (57%) had reduction in pain levels (1-9 pt. on scale of 1-10). 6/14 (43%) entered with no pain and maintained the same level. 6/14 (43%) entered study on pain medication. 5/6 (83%) no longer needed pain medication at the end of cycle 1. 3/14 (21%) are disease free with normal physical exam, review of systems and imaging, 5/14 (36%) have significant reduction in quantity and/or size of the largest tumor, 2/14 (14%) have reduction in quantity and/or size of the largest tumor, 4/14 (29%) no progression of disease,
3/14(21%) went home after cycle I, 11/14(89%) continue with the treatment.
6 (43%) subjects received two cycle (12 weeks) treatment , 5 (36%) subjects received 5 cycles (30 weeks) treatment.

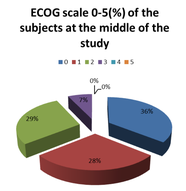


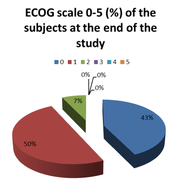
13/14 (93%) are alive with median survival 307 days, (44 weeks -11 months) from first day of treatments, (14/14 (100%) with median survival 250 days. 9/14 (64%) past 300 days survivor from first day of treatment and (43 weeks). 3/14 (21%) past 350 days of survival from first day of treatment. 1/14 past 400 days). 1/14 died after 285 days from first treatment.

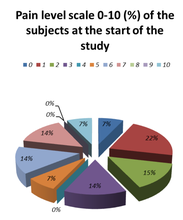


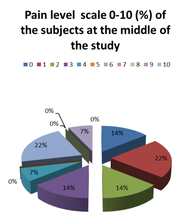
RESULTS

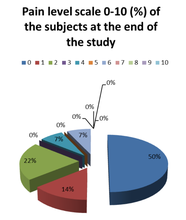


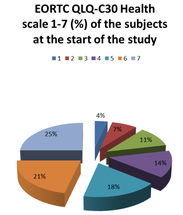


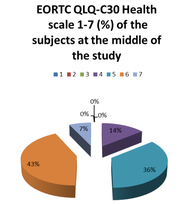


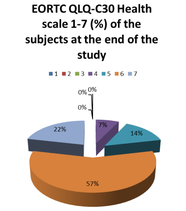


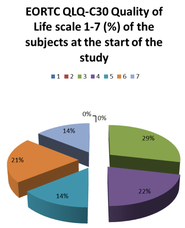


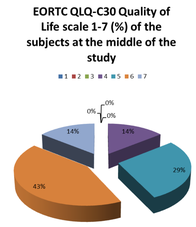


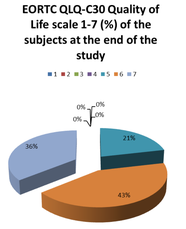












CONCLUSION

Overall, all subjects have tolerated the SMK treatment well, no adverse events have been reported related to the product, responses have been documented to the treatment 100%. All subjects develop hyperpigmentation.
All subjects quality of life significantly improved.

SMK is a very promising treatment for all types of metastatic breast cancer.

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