

**Consortium of Academic Health Centers for
Integrative Medicine (CAHCIM) March 27,
2009 Oncology Interest Group Meeting**

**Fermented Wheat Germ
Extract (Aveamar)**

Mate Hidvegi PhD, Ac, Prof (Hon)
Jewish University, Budapest, Hungary

In the 1980's, Albert Szent-Gyorgyi (Nobel Prize for Medicine, 1937 for his discovery of vitamin C and the mechanism of biological oxidation), hypothesized that certain methoxy-substituted benzoquinones, when combined with ascorbic acid, may effectively kill cancer cells. The best natural source for these benzoquinones is a by-product of flour milling: wheat germ, where these molecules are present in form of glycosides. An industrial-scale fermentation process has been developed to break-up these glycosidic bonds, and to make other chemical modifications of the wheat germ extract. The thus resulted standardized fermented product has been shown to possess anticancer, antimetastatic, antiinflammatory and anticachexic properties. The extract - named Avemar - has fulfilled the self-affirmed GRAS status in the USA, and has been approved as a dietary food for special medical purpose (medical food) for cancer patients in countries of the EU. In some countries, Avemar is 100% reimbursed for cancer patients. In the USA this product is available as a dietary supplement in a form of an instant drink mix.

Safety issues. Drug interactions.

The results of toxicological and clinical studies of FWGE demonstrate its safety for its intended use as a dietary supplement ingredient in the United States, and as a medical food for cancer patients in the EU. In acute and subacute toxicity studies using rodents, orally administered FWGE showed that dose levels exceeding the normal recommended oral dosage by up to approximately 25-fold caused no adverse effects. The test substance showed no evidence of mutagenicity or genotoxicity *in vitro* or *in vivo*. Clinical studies using FWGE as a supplement to drug therapy in cancer patients not only showed no evidence of toxicity. There have been no adverse interactions found when FWGE was co-administered with cytostatic drugs, or with targeted drugs, or with hormone drugs used in medical oncology. Overall, it was concluded that FWGE would not be expected to cause adverse effects under the conditions of its intended use as an ingredient in medical foods and dietary supplements.

FWGE has been extensively researched. List of the most important papers in English are shown on the next 3 slides. Readers may also visit the NIH web site: <http://www.ncbi.nlm.nih.gov/sites/gquery> for getting a good list of papers by using the search term: Avemar. Readers may also visit the web site: <http://www.avemarresearch.com/TOC.html>, where papers could be downloaded from.

Hidvegi M, Raso E, Tomoskozi-Farkas R, Paku S, Lapis K, Szende B: The effect of Avemar and Avemar + vitamin C on tumor growth and metastasis in experimental animals. ***Anticancer Research*** 18: 2353-2358. 1998.

Hidvegi M, Raso E, Tomoskozi-Farkas R, Lapis K, Szende B: Effect of MSC on the immune response of mice. ***Immunopharmacology*** 41: 183-186. 1999.

Hidvegi M, Raso E, Tomoskozi-Farkas R, Lapis K, Szende B: MSC, a new benzoquinone-containing natural product with antimetastatic effect. ***Cancer Biotherapy & Radiopharmaceuticals*** 14: 277-289. 1999.

Jakab F, Mayer A, Hoffmann A, Hidvegi M: First clinical data of a natural immunomodulator in colorectal cancer. ***Hepatogastroenterology*** 47: 393-395. 2000.

Boros L. G, Lapis K, Szende B, Tomoskozi-Farkas R, Balogh A, Boren J, Marin S, Cascante M, Hidvegi M: Wheat germ extract decreases glucose uptake and RNA ribose formation but increases fatty acid synthesis in MIA pancreatic adenocarcinoma cells. ***Pancreas*** 23: 141-147. 2001.

Zalatnai A, Lapis K, Szende B, Raso E, Telekes A, Resetar A, Hidvegi M: Wheat germ extract inhibits experimental colon carcinogenesis in F-344 rats. ***Carcinogenesis*** 22: 1649-1652. 2001.

Ehrenfeld M, Blank M, Shoenfeld Y, Hidvegi M: Avemar (a new benzoquinone-containing natural product) administration interferes with the Th2 response in experimental SLE and promotes amelioration of the disease. ***Lupus*** 10: 622-627. 2001.

Fajka-Boja R, Hidvegi M, Shoenfeld Y, Ion G, Demydenko D, Tomoskozi-Farkas R, Vizler Cs, Telekes A, Resetar A, Monostori E: Fermented wheat germ extract induces apoptosis and downregulation of major histocompatibility complex class I proteins in tumor T and B cell lines. ***International Journal of Oncology*** 20: 563-570. 2002.

Nichelatti M, Hidvegi M: Experimental and clinical results with Avemar (a dried extract from fermented wheat germ) in animal cancer models and in cancer patients. ***Nogyogyszati Onkologia*** 7: 180-185. 2002.

Comin-Anduix B, Boros L. G, Marin S, Boren J, Callol-Massot C, Centelles J. J, Torres J. L, Agell N, Bassilian S, Cascante M: Fermented wheat germ extract inhibits glycolysis/pentose cycle enzymes and induces apoptosis through poly (ADP-ribose) polymerase activation in Jurkat T-cell leukemia tumor cells. ***Journal of Biological Chemistry*** 277: 46408-46414. 2002.

Jakab F, Shoenfeld Y, Balogh A, Nichelatti M, Hoffmann A, Kahan Zs, Lapis K, Mayer A, Sapy P, Szentpetery F, Telekes A, Thurzo L, Vagvolgyi A, Hidvegi M: A medical nutriment has supportive value in the treatment of colorectal cancer. ***British Journal of Cancer*** 89: 465-469. 2003.

Tompa A, Kocsis Zs, Marcsek Z, Jakab M, Szende B, Hidvegi M: Chemo-prevention with tamoxifen and Avemar by inducing apoptosis on MCF-7 (ER+) breast cancer cells. 2nd Congress of the World Society of Breast Health, ***Monduzzi***, Bologna, p. 61-66. 2003.

Garami M, Schuler D, Babosa M, Borgulya G, Hauser P, Müller J, Paksy A, Szabó E, Hidvegi M, Fekete Gy: Fermented wheat germ extract reduces chemotherapy-induced febrile neutropenia in pediatric cancer patients. ***Journal of Pediatric Hematology/Oncology*** 10: 631-635. 2004.

Marcsek Z, Kocsis Zs, Jakab M, Szende B, Tompa A: The efficacy of tamoxifen in estrogen receptor-positive breast cancer cells is enhanced by a medical nutriment. ***Cancer Biotherapy & Radiopharmaceuticals*** 6: 746-753. 2004.

Illmer C, Madlener S, Horvath Z, Saiko P, A. Losert, Herbacek I, Grusch M, Krupitza G, Fritzer-Szekeres M, Szekeres T: Immunologic and biochemical effects of the fermented wheat germ extract Avemar. ***Experimental Biology and Medicine*** 230: 144-149. 2005.

Boros LG, Nichelatti M, Shoenfeld Y: Fermented wheat germ extract (Avemar) in the treatment of cancer and autoimmune diseases. ***Annals of the New York Academy of Sciences*** 1051: 529-542 . 2005.

Telekes A, Kiss-Toth E, Nagy T, Qwarnstrom EE, Kusz E, Polgar T, Resetar A, Dower SK, Duda E: Synergistic effect of Avemar on proinflammatory cytokine production and ras-mediated cell activation. ***Annals of the New York Academy of Sciences*** 1051: 515-528. 2005.

Lee SN, Park H, Lee KE: Cytotoxic activities of fermented wheat germ extract on human gastric carcinoma cells by induction of apoptosis. ***Journal of Clinical Oncology*** 23: 4254. 2005.

Bálint G, Apáthy Á, Gaál M, Telekes A, Resetár Á, Blazsó G, Falkay G, Szende B, Paksy A, Ehrenfeld M, Shoenfeld Y, Hidvegi M: Effect of Avemar - a fermented wheat germ extract - on rheumatoid arthritis. Preliminary data. ***Clinical and Experimental Rheumatology*** 24: 325-328. 2006.

Barabas J, Nemeth Z: Recommendation of the Hungarian Society for Face, Mandible and Oral Surgery in the indication of supportive therapy with Avemar. ***Orvosi Hetilap*** 147: 1709-11. 2006.

Saiko P, Ozsvár-Kozma M, Madlener S, Bernhaus A, Lackner A, Grusch M, Horvath Zs, Krupitza G, Jaeger W, Ammer K, Fritzer-Szekeres M, Szekeres T: Avemar, a nontoxic fermented wheat germ extract, induces apoptosis and inhibits ribonucleotide reductase in human HL-60 promyelocytic leukemia cells. **Cancer Letters** 250: 323-328. 2007.

Johanning GL, Wang-Johanning F: Efficacy of a medical nutriment in the treatment of cancer. **Alternative Therapies CME Health and Medical Journal** 13: 56-63, 65. 2007.

Telekes A, Raso E: Changes in the kinase expression panel of K562 human leukemia after Avemar treatment. **Journal of Clinical Oncology** 25(18S): 14143. 2007.

Tejeda M, Gaal D, Szucs I, Telekes A: Avemar inhibits the growth of mouse and human xenograft mammary carcinomas comparable to endocrine treatments. **Journal of Clinical Oncology** 25(18S): 21132. 2007.

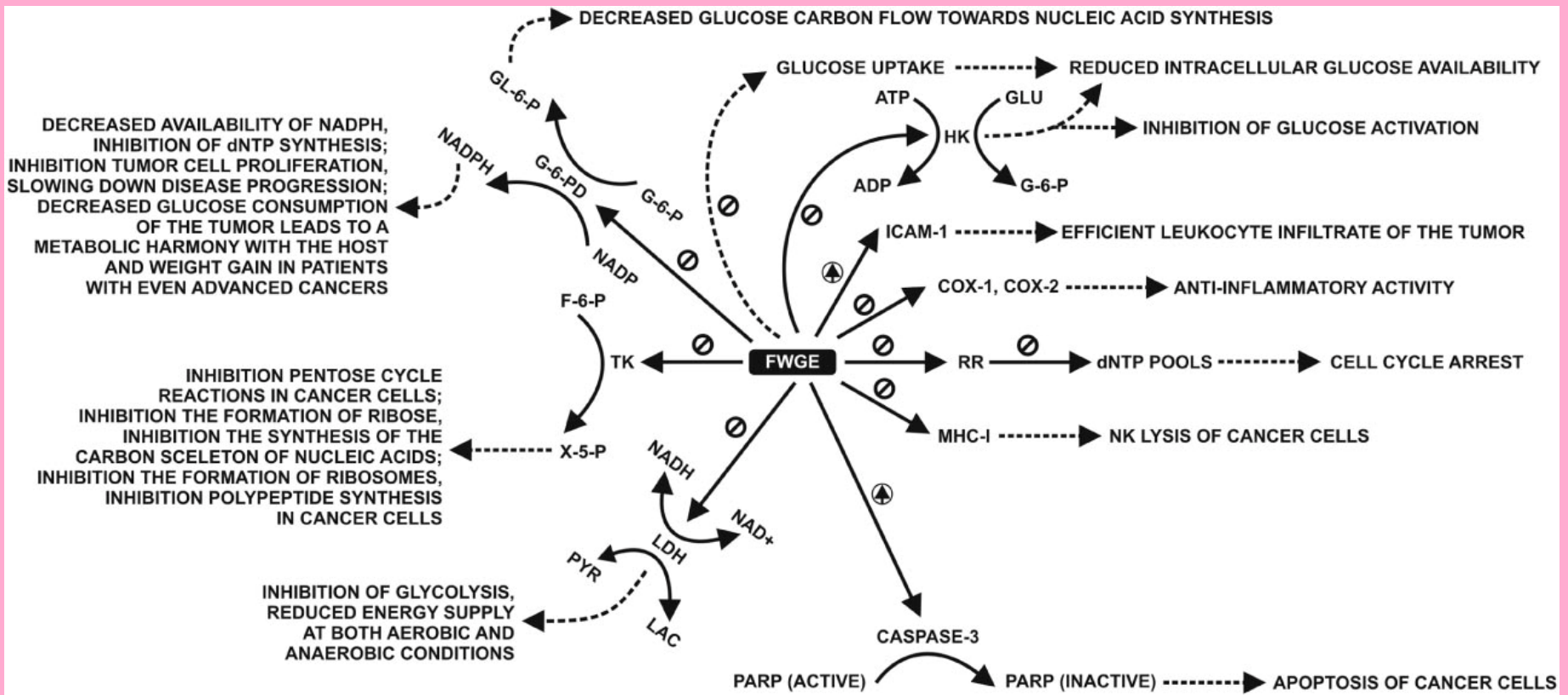
Heimbach J T, Sebestyén Gy, Semjen G, Kennepohl E: Safety studies regarding a standardized extract of fermented wheat germ. **International Journal of Toxicology** 26: 253-259. 2007.

Sukkar SG, Cella F, Rovera GM, Nichelatti M, Ragni G, Chiavenna G, Giannoni A, Ronzani G, Ferrari C: A multicentric prospective open trial on the quality of life and oxidative stress in patients affected by advanced head and neck cancer treated with a new benzoquinone-rich product derived from fermented wheat germ (Avemar). **Mediterranean Journal of Nutrition and Metabolism** DOI 10.1007/s12349-008-0008-4. 2008.

Demidov LV, Manziuk LV, Kharkevitch GY, Pirogova NA and Artamonova EV: Adjuvant fermented wheat germ extract (Avemar) nutraceutical improves survival of high-risk skin melanoma patients. A randomized, pilot, phase II clinical study with a 7-year follow-up. **Cancer Biotherapy & Radiopharmaceuticals** 23: 477-482, 2008.

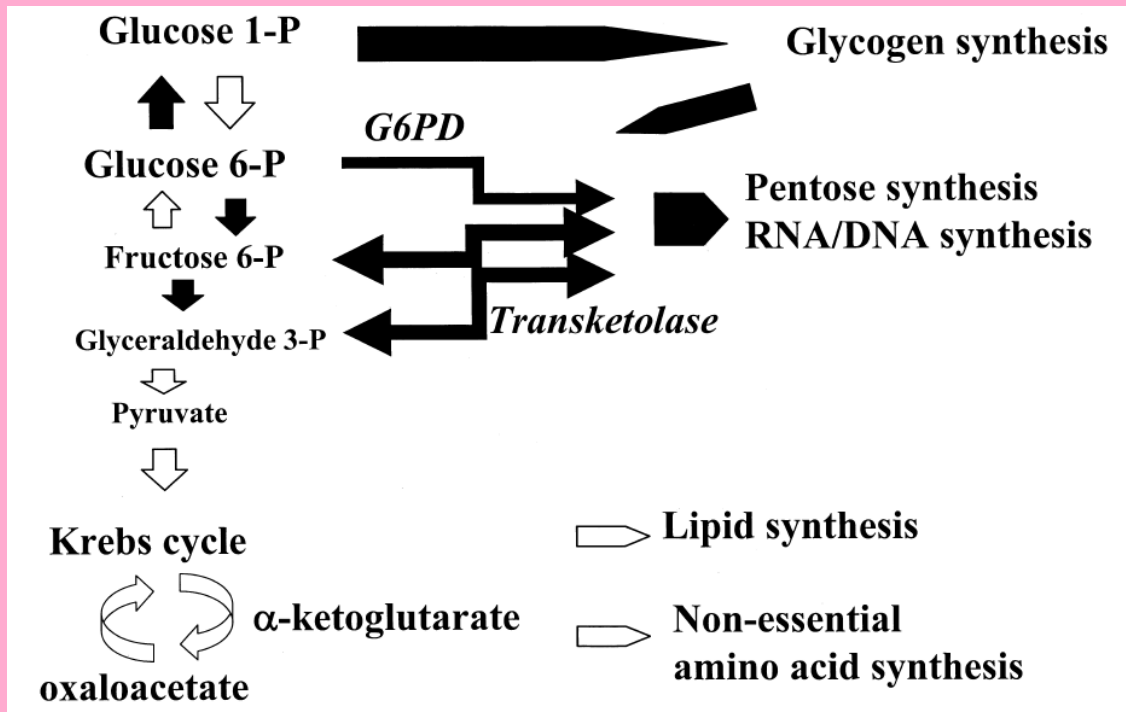
Saiko P, Ozsvár-Kozma M, Graser G, Lackner A, Grusch M, Madlener S, Krupitza G, Jaeger W, Hidvegi M, Agarwal RP, Fritzer-Szekeres M, Szekeres T: Avemar, a nontoxic fermented wheat germ extract, attenuates the growth of sensitive and 5-FdUrd/Ara-C cross-resistant H9 human lymphoma cells through induction of apoptosis. **Oncology Reports** 21: 787-791. 2009.

Brown L and Iyer A: Fermented wheat germ extract (Avemar) in the treatment of cardiac remodelling and metabolic symptoms in rats. **Evidence Based Complementary and Alternative Medicine**. (In press)



Molecular targets of the fermented wheat germ extract (FWGE). By the activation of the caspase-3 downstream proteases, FWGE induces cleavage of poly(ADPribose) polymerase (PARP), which leads to apoptosis of cancer cells. FWGE downregulates the major histocompatibility complex class I (MHC-I) proteins on tumor cells' surface, thus making them targets of natural killer (NK) cells. The extract inhibits the activity of ribonucleotide reductase (RR), the key enzyme of *de novo* DNA synthesis. FWGE also inhibits cyclooxygenase (COX)-1 and -2 and thus has anti-inflammatory activity. It has also been shown that FWGE upregulates the expression of intercellular adhesion molecule-1 (ICAM-1) on the endothelial cell. It is known that endothelial cells of the vasculature of human solid tumors have a decreased expression of ICAM-1 compared to normal endothelial cell tissue, and this phenomenon can be considered as a tumor-derived escape mechanism since the development of an efficient leukocyte infiltrate of the tumor is impaired. FWGE decreases glucose (GLU) uptake both directly and by inhibiting glucose activation via the inhibition of hexokinase (HK), the catalyst of activation by phosphorylation. FWGE also inhibits pentose cycle enzymes involved in direct glucose oxidation (glucose-6-phosphate dehydrogenase, G-6-PD) and nonoxidative glucose utilization (transketolase, TK) toward nucleic acid synthesis. These inhibitions result in decreased glucose consumption of cancer cells and thus the progression of the neoplastic disease slows down. The extract further inhibits the enzyme lactate dehydrogenase (LDH), which results in decreased glycolytic flux and reduced energy supply of tumor growth at both aerobic and anaerobic conditions (Warburg-effect). In contrast, FWGE treatment is about 50× less effective in peripheral blood lymphocytes in inducing biological effects, which provides a comfortable therapeutic window for FWGE to apply in patients as a supplemental treatment modality with minimal or no toxic side effects.

The proliferating metabolic phenotype of tumor cells



Proliferating metabolic phenotype of tumor cells is characterized by high rates of nucleic acid synthesis through the nonoxidative steps of the pentose cycle and decreased recycling of ribose carbons back into glycolysis.

Inhibition of transketolase or G6PD results in cell cycle arrest, and the subsequent limited availability of glucose substrates for nucleic acid synthesis results in tumor cell apoptosis.

drives the cancer phenotype.

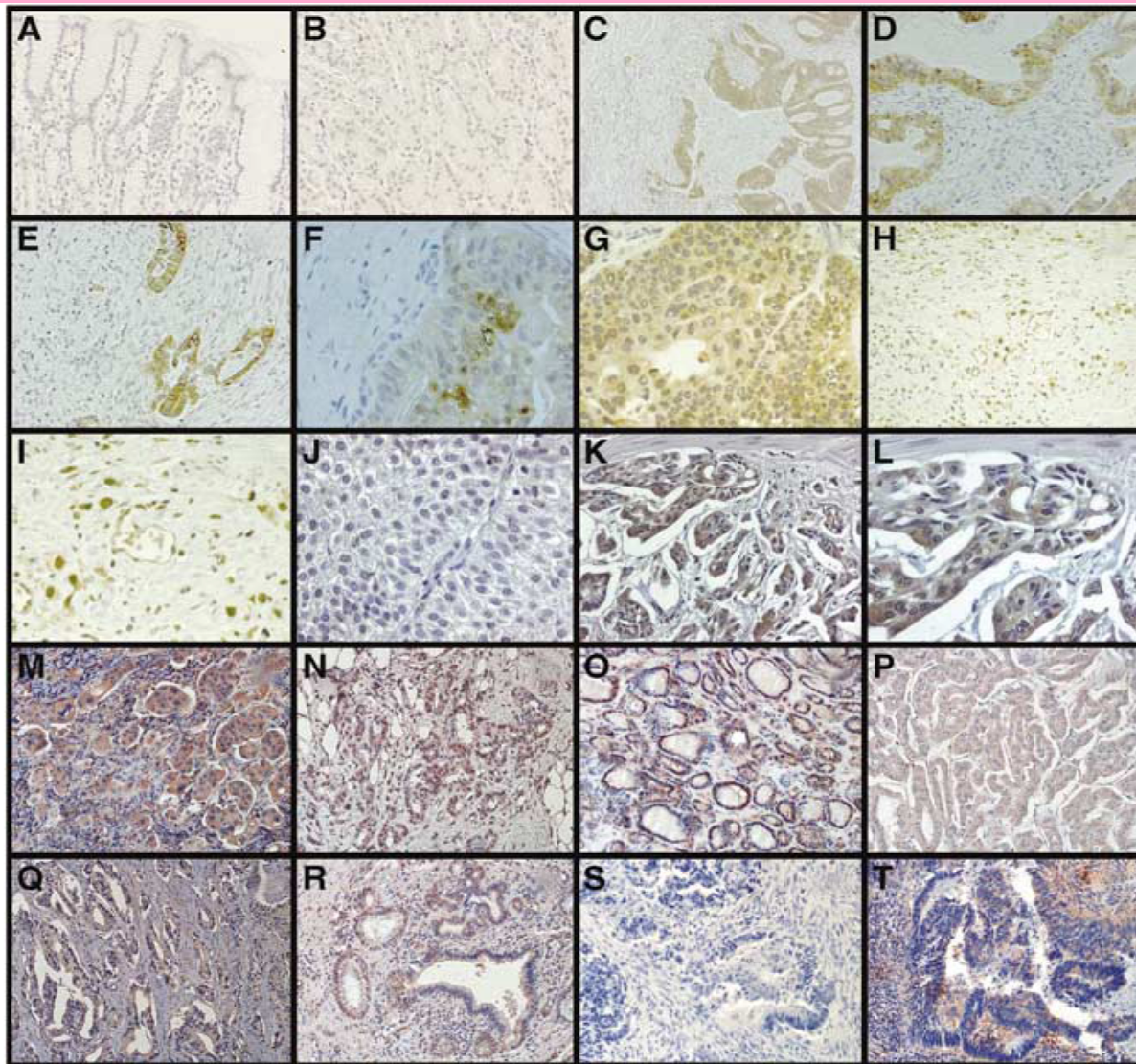
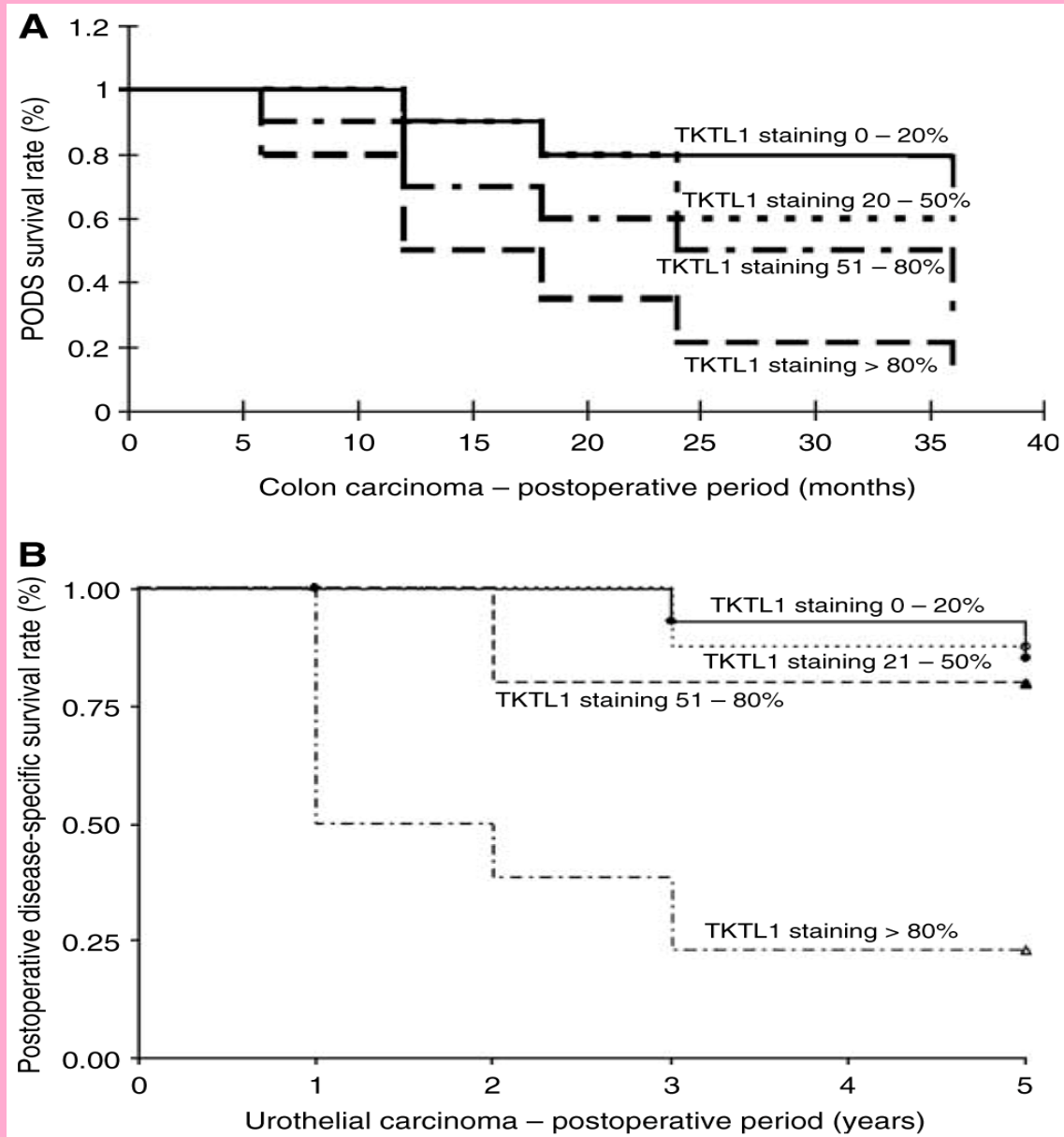


Figure 2 Expression of TKTL1 in normal and carcinoma tissues. Specimens of a gastric carcinoma (**C–G**) and corresponding normal tissue (**A, B**); (**A, B**) no expression of TKTL1 in normal tissue. (**C–G**) Strong cytoplasmic expression in tumour tissue, but no expression in the surrounding stroma cells. Note the elevated expression within the inner region of the tumour (**F**). (**H, I**) Nuclear TKTL1 expression in a poorly differentiated gastric carcinoma. (**J**) No expression of TKTL1 in a superficial, Ta bladder carcinoma. (**K, L**) Strong TKTL1 cytoplasmic expression in an invasive, poorly differentiated bladder carcinoma. Strong TKTL1 upregulation in carcinomas of the lung (non-small-cell lung carcinomas; **M**), breast (**N**), thyroid (follicular thyroid carcinoma (**O**), papillary thyroid carcinoma (**P**)), prostate (**Q**), and pancreas (**R**). No expression of TKTL1 in a noninvasive colon carcinoma (**S**), and strong expression in an invasive colon carcinoma (**T**). Anti-TKTL1 was revealed by diaminobenzidine tetrahydrochloride (DAB; brown staining) (**A–L**) and 3-amino-9-ethylcarbazole (AEC; red staining) (**M–T**).

Activity of transketolase determines the survival of cancer patients.

British Journal of Cancer (2006) 94, 578 – 585



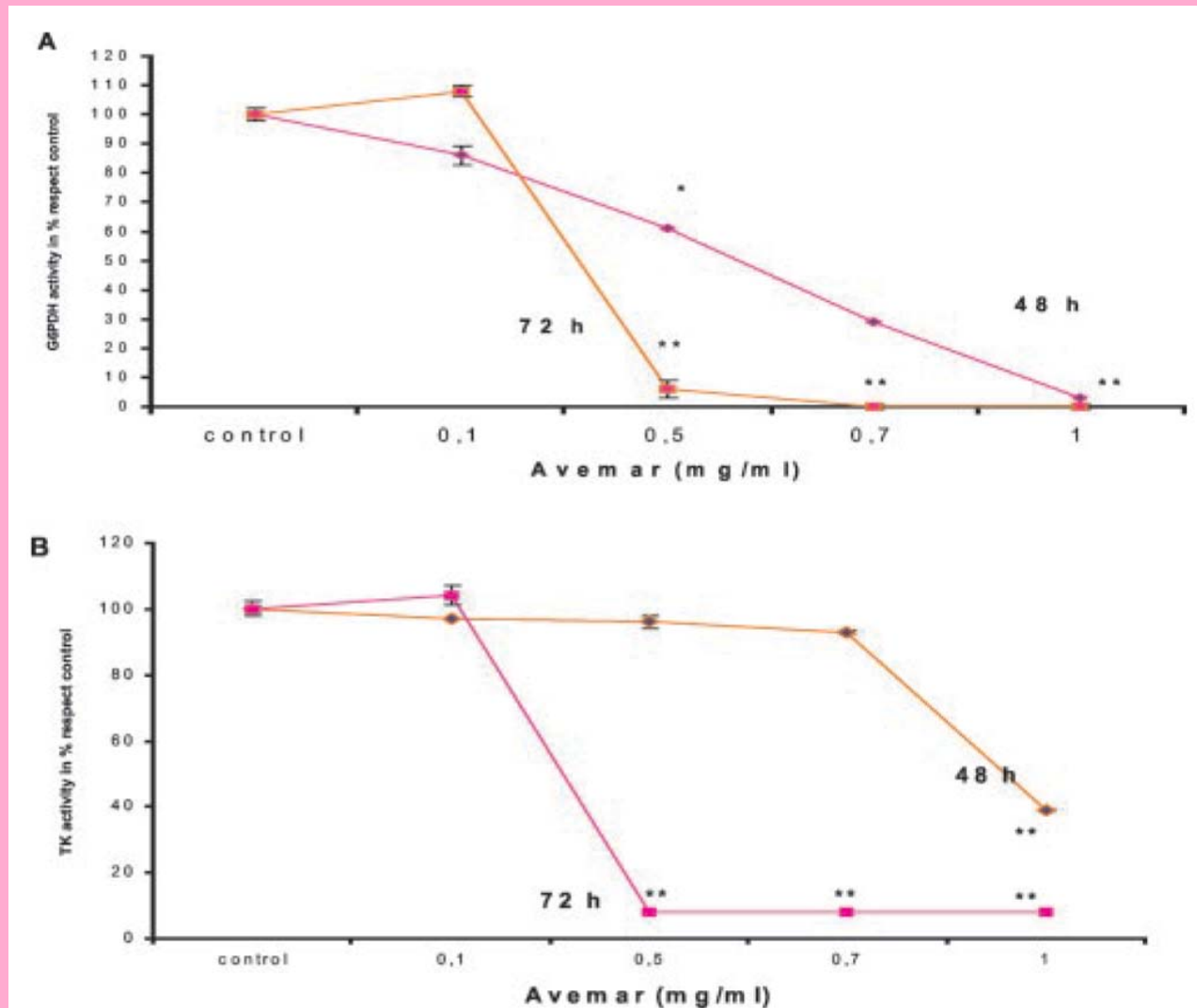
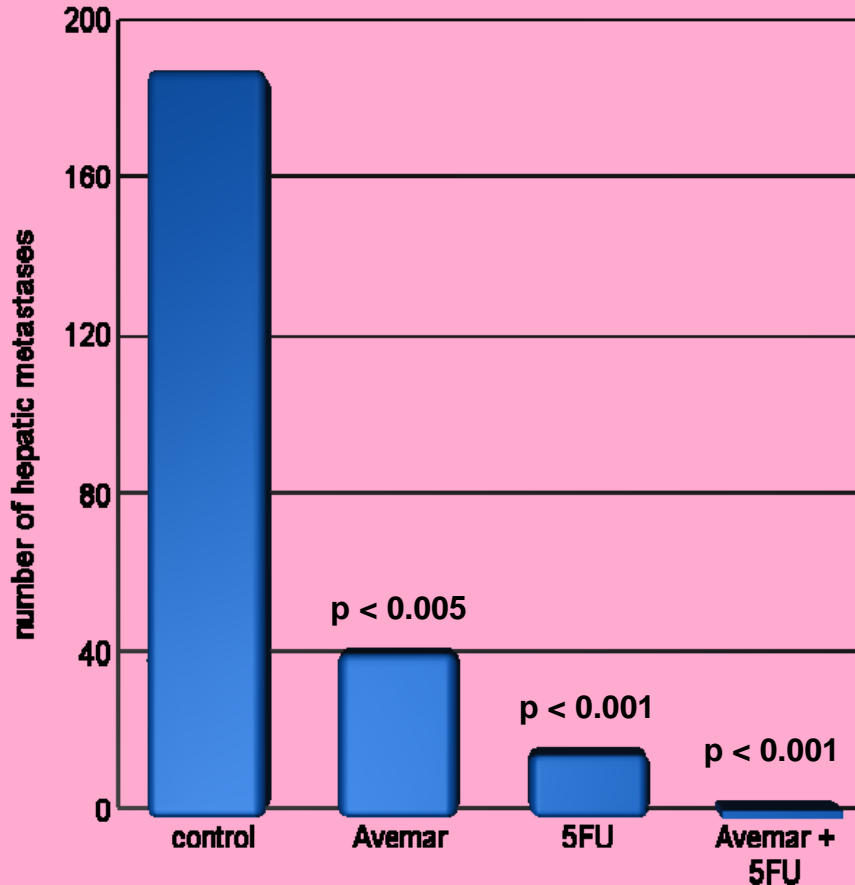


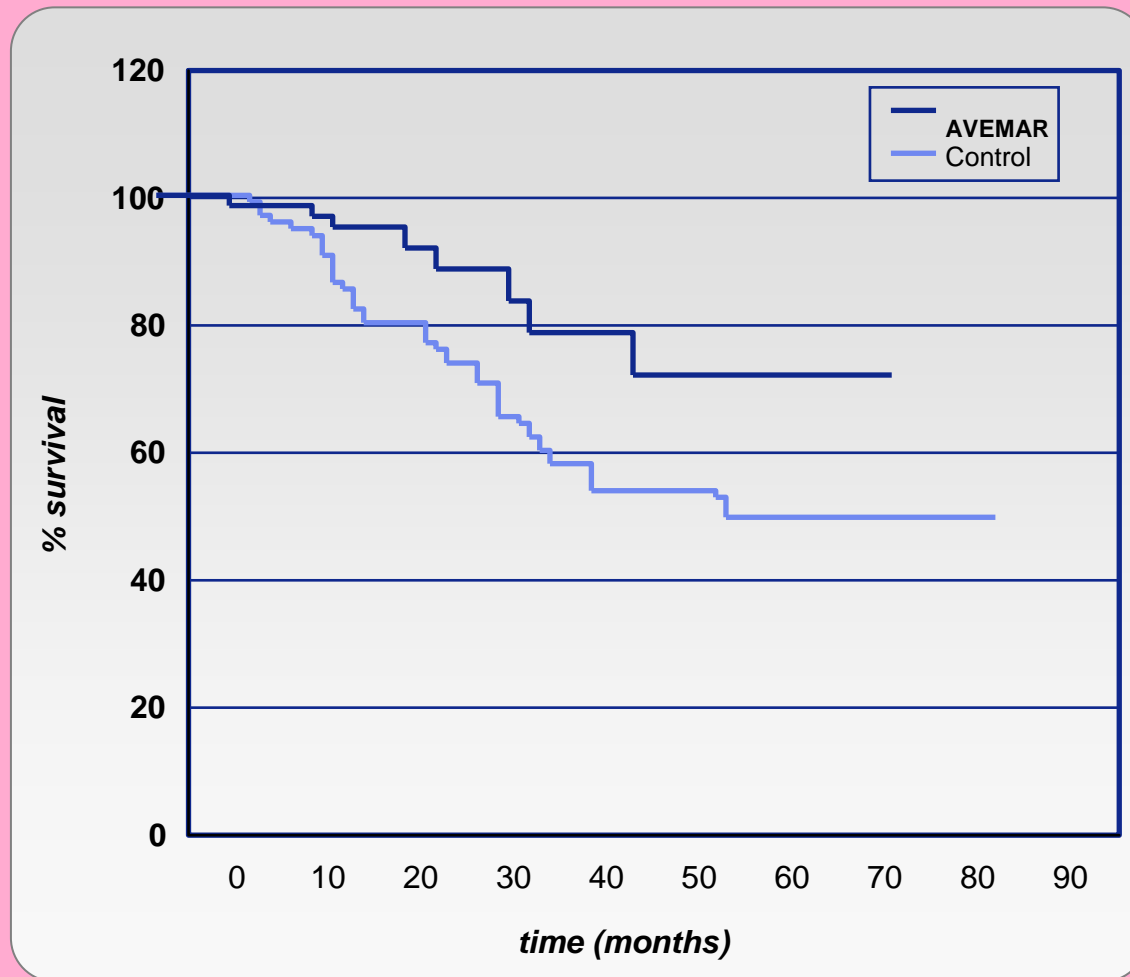
FIG. 5. Jurkat leukemia cell G6PDH (A) and transketolase (B) enzyme activities in response to 48 and 72 h of Avemar treatment. Avemar inhibited both G6PD and transketolase in a dose- and time-dependent manner. Mean \pm S.E.; $n = 9$; *, $p < 0.05$; **, $p < 0.01$.

Inhibiting Colorectal Metastases in Mice

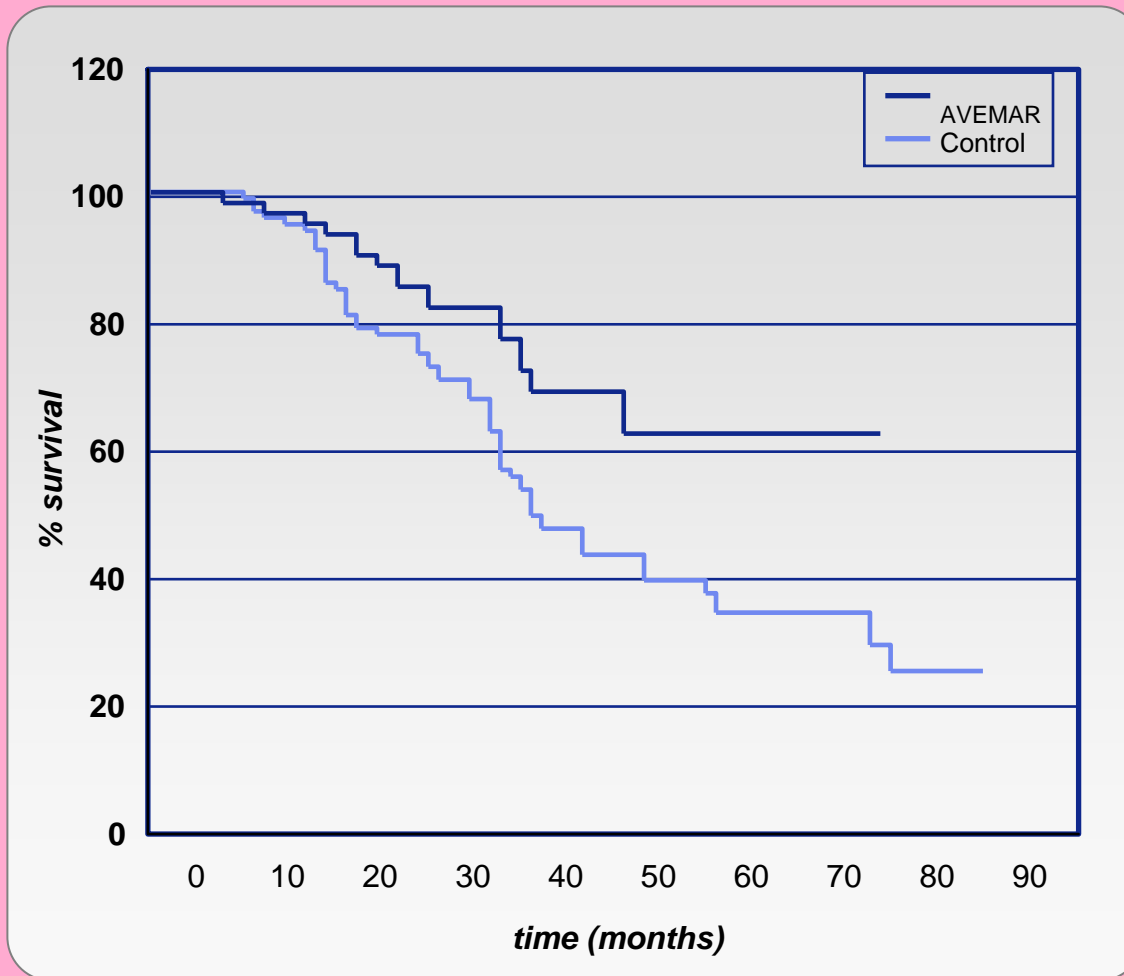


- Both Avemar (3 g/kg/d) and 5-Fluorouracil (1 mg/kg/d) significantly reduce the number of liver metastases of C38 colorectal murine carcinoma
- Avemar + 5FU in combination show a still greater efficacy

BJC (2003) Colorectal Cancer Survival Probability Curve (Kaplan-Meier estimate)



BJC (2003) Colorectal Cancer Progression-Free Probability Curve

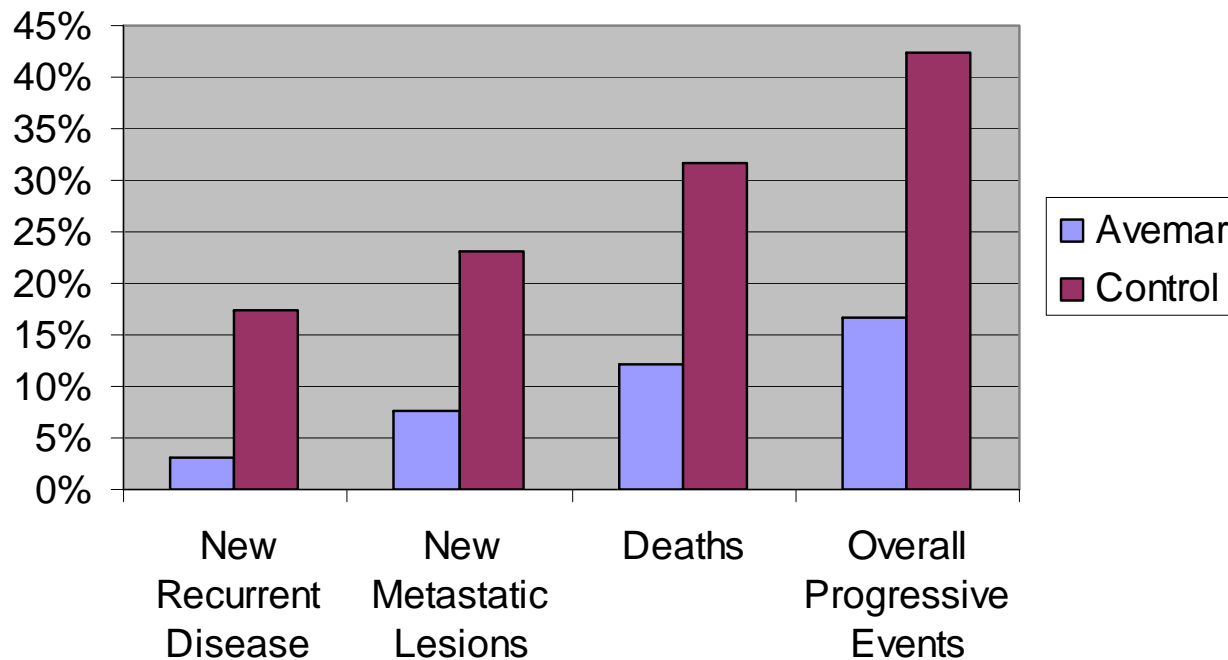


Progression is any of the following events:

- death
- new metastasis
- relapse

Colorectal Cancer – clinical trial

Table 2. Occurrence of progression-related events (End Point Analysis)



British Journal of Cancer (2003), 89:465-469

Double-Blind, Multicenter Clinical Study

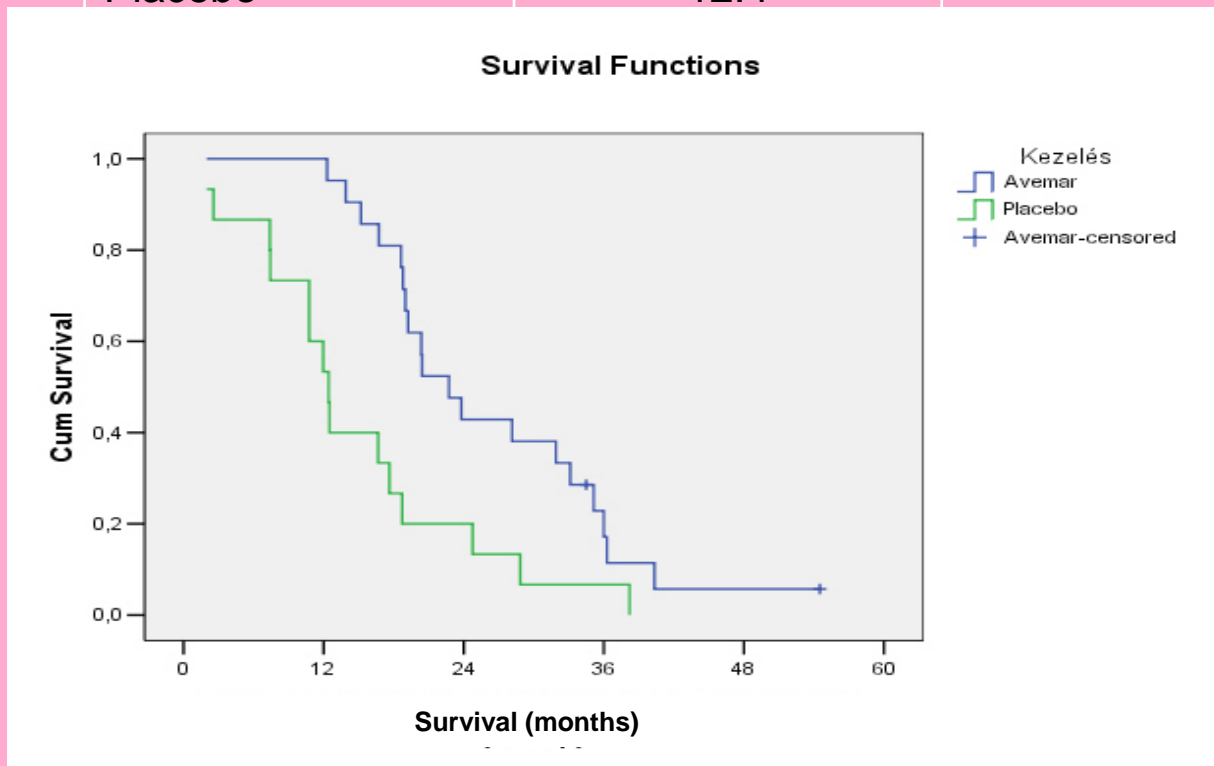
**AVEMAR in metastatic
colorectal cancer**

**Department of Medical Oncology
Chaim Sheba Medical Center
University of Tel-Aviv**

**Gastrointestinal Cancers Unit
Department of Medical Oncology
Ichilov Medical Center
University of Tel-Aviv**

Kaplan-Meier survival analysis FWGE in metastatic colorectal cancer (double-blind study, Israel)

	Survival time median (months)	95 % confidency interval of the median of the survival time
AVEMAR	22.7	17.6 – 27.9
Placebo	12.4	10.2 – 14.6



**Log Rank test
 $p=0.04$**
Survival of the patients in the Avemar group is significantly longer than that in the placebo group.

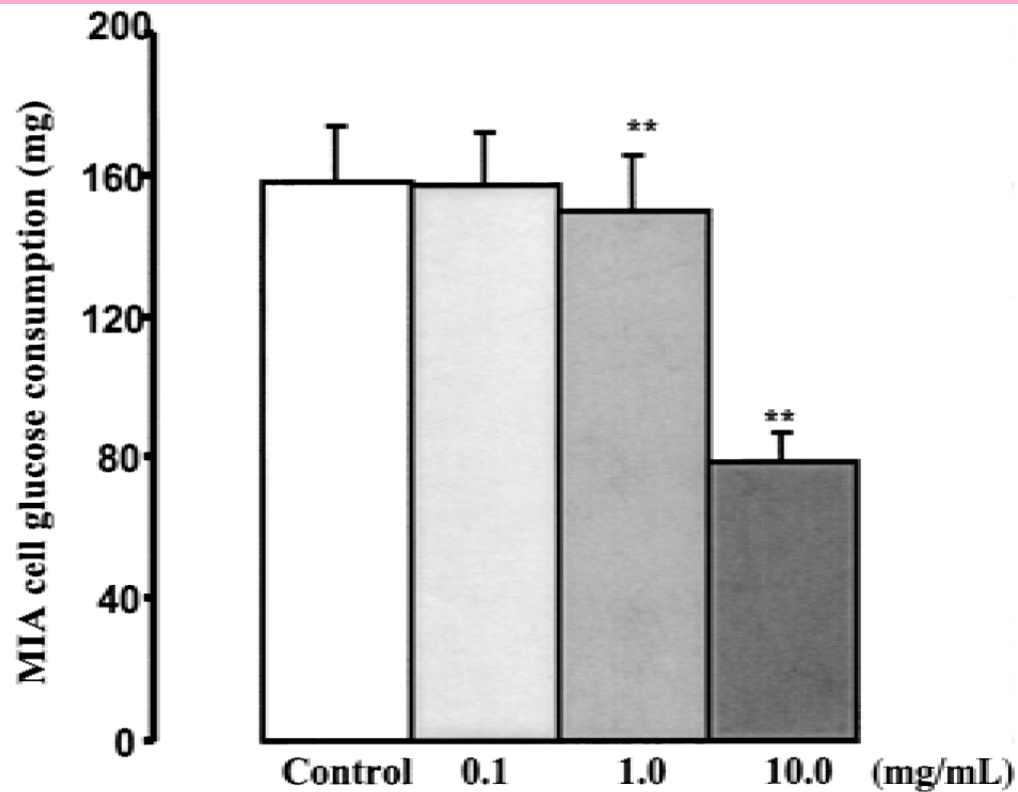


FIG. 1. Glucose consumption of MIA pancreatic adenocarcinoma cells in response to increasing doses of fermented wheat germ extract (Avemar) treatment after 72 hours of culture. Glucose consumption (measured in milligrams) was estimated by the difference in media glucose content between Avemar-treated and control cultures. MIA cell glucose consumption was significantly inhibited in the presence of either 1 mg/mL ($*p < 0.05$) or 10 mg/mL ($**p < 0.01$) Avemar ($x + SD$; $n = 6$).

Treatment	Number of lung metastases average±SD
Control group	20,0±6,0
MSC 3g/kg/day p.o.	4,0±2,1*
DTIC 60 mg/kg/day i.p.	7,0±4,3*
MSC+DTIC	0,1±0,1**

*<0,01

**p<0,001

Figure 5. Effect of the therapeutic composition (MSC+DTIC) on the number of lung metastases of B16 melanoma inoculated into the muscle of the hind leg.

Cancer Biotherapy Radiopharm 14: 277-289, 1999

First Institute of Pathology and Experimental Cancer Research,
School of Medicine, Semmelweis University, Budapest, Hungary

FWGE as Adjuvant in Stage III Melanoma

Cancer Biotherapy and Radiopharm, August, 2008

- Site: Blokhin Cancer Center of the Russian Medical Academy, Moscow
- Design: open, prospective, randomized Phase II
- Objective: Avemar's effects on disease outcome in high-risk melanoma patients
- Follow-up: 7 years

Table 3. Survivals of stage III cutaneous melanoma patients.

	Groups	FWGE	Control
Progression-free survival (PFS)³	Number of patients	26	26
	Patients without progression	15 (57.7%)	7 (26.9%)
	Median [CI ¹] (months)	See note ²	8.5 [7.2-9.8]
	Mean [CI] (months)	55.8 [39.8-71.7]	29.9 [15.3-44.5]
Overall survival (OS)⁴	Patients alive	17 (65.4%)	10 (38.5%)
	Median [CI ¹] (months)	See note ²	25.7 [11.3-40.1]
	Mean [CI] (months)	66.2 [53.1-79.4]	44.7 [30.2-59.2]
	5-year survival rate (%)	61.5	36.7

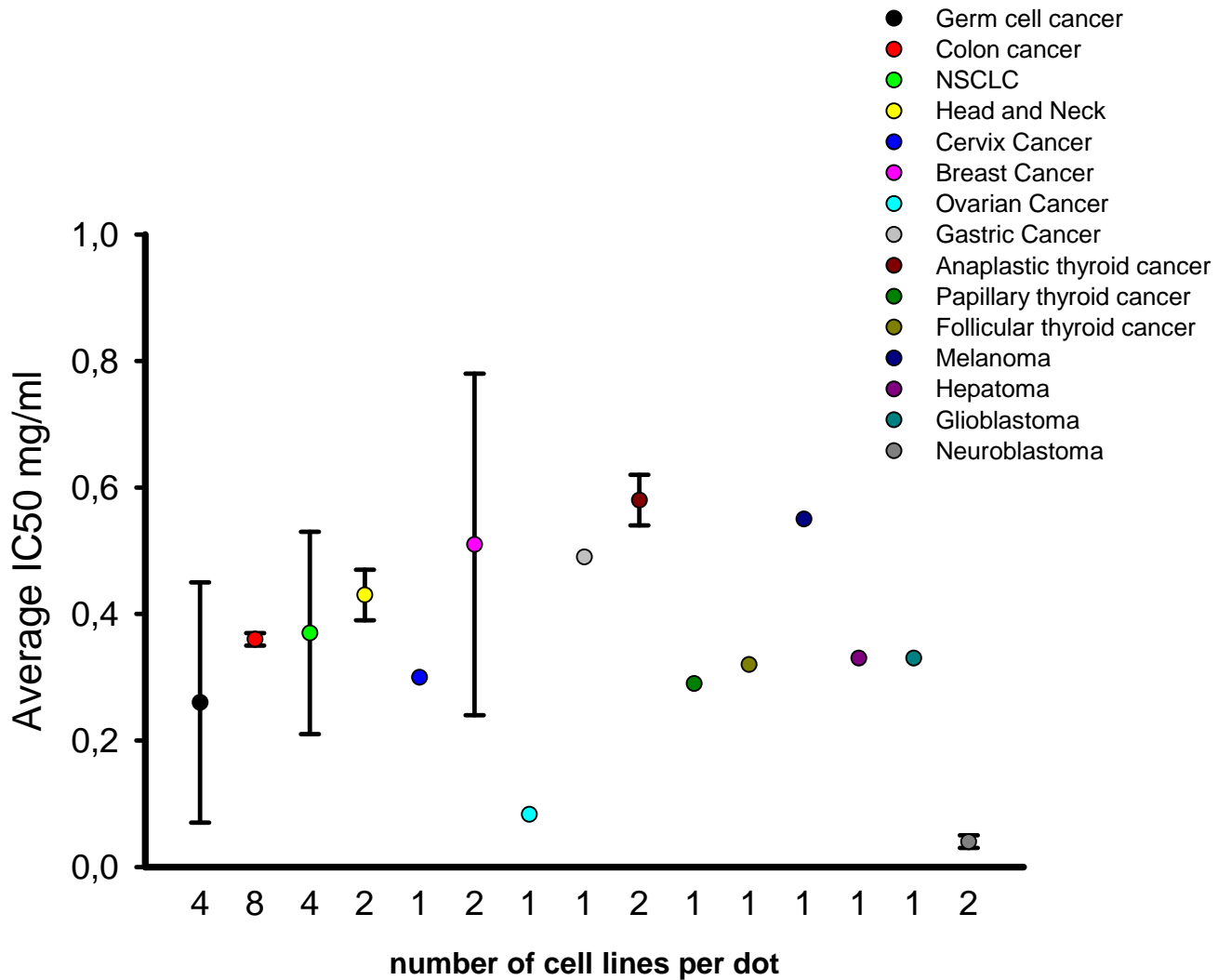
¹ 95% confidential interval.

² Median can not be defined if the cumulative survival ratio is less than 50%.

³ Log Rank–test: chi-square [1] = 6.08; P = 0.0137

⁴ Log Rank–test: chi-square [1] = 4.72; P = 0.0298

Average IC50 of Avemar in different Cancer types



FWGE in Head and Neck Cancer

N= 45 (44 planocellular, 1 adeno cc)

Results – after 1 year

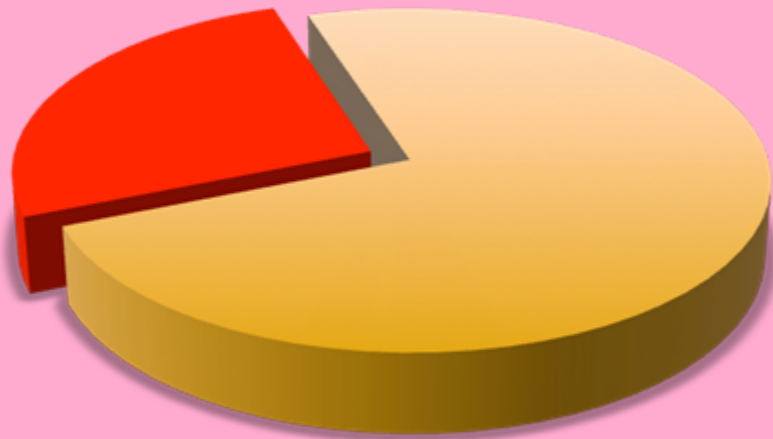
	AVEMAR®	Control	
Mortality	0/23	1/22	N.S.
New recurrence	1 (4.3%)	12 (54.5%)	p<0.001
New metastasis	1 (4.3%)	4 (22.7%)	N.S.
Progression event	2 (8.7%)	17 (77.3%)	p<0.001

FWGE in Head and Neck Cancer

N= 45 (44 planocellular, 1 adeno cc)

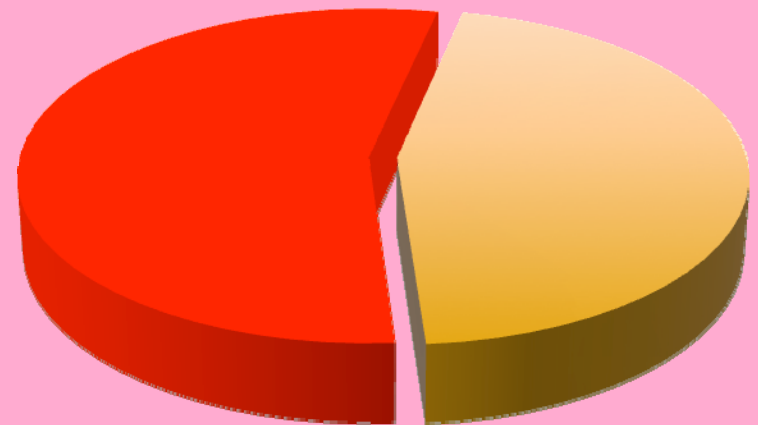
Results – *after 5 years*

Avemar group



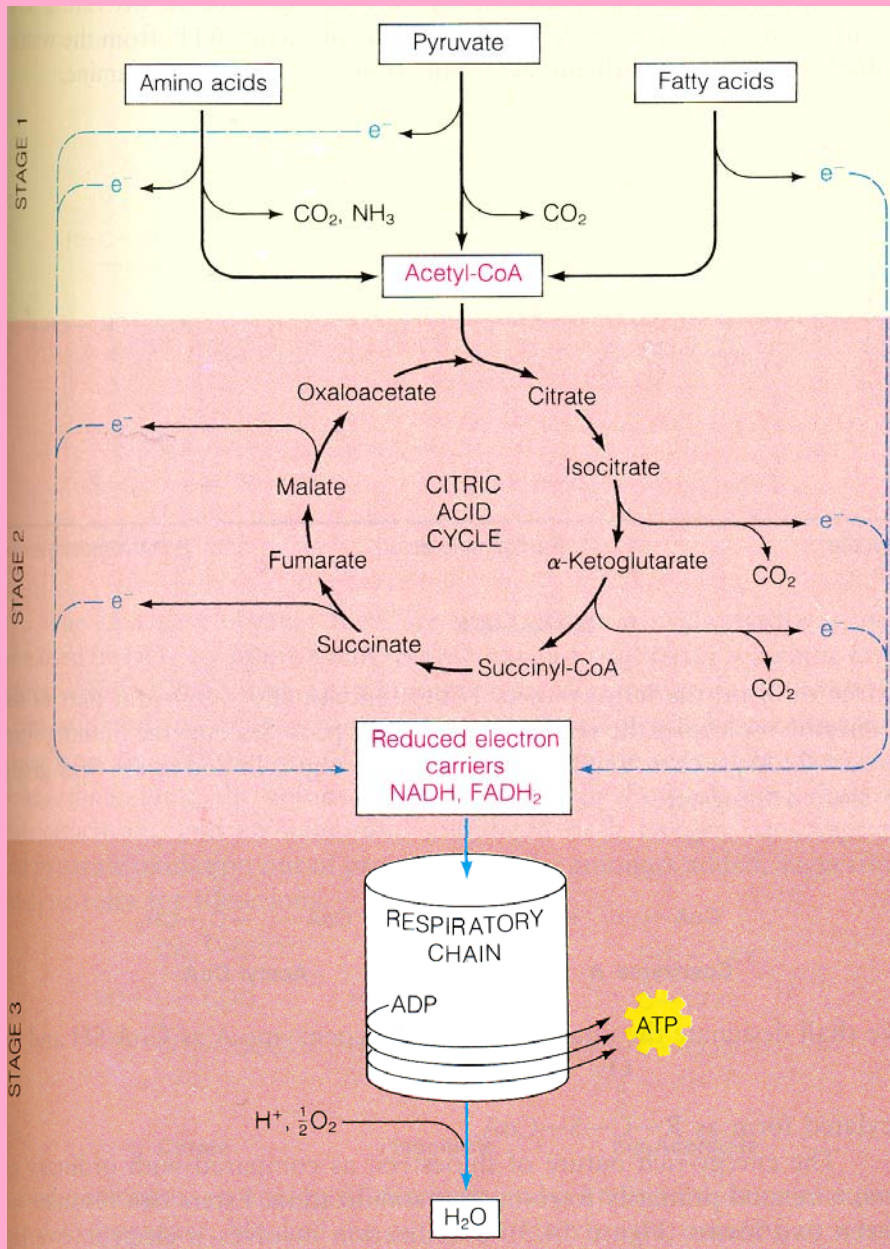
■ Died ■ Alive

Control group



■ Died ■ Alive

Healthy cell respiration



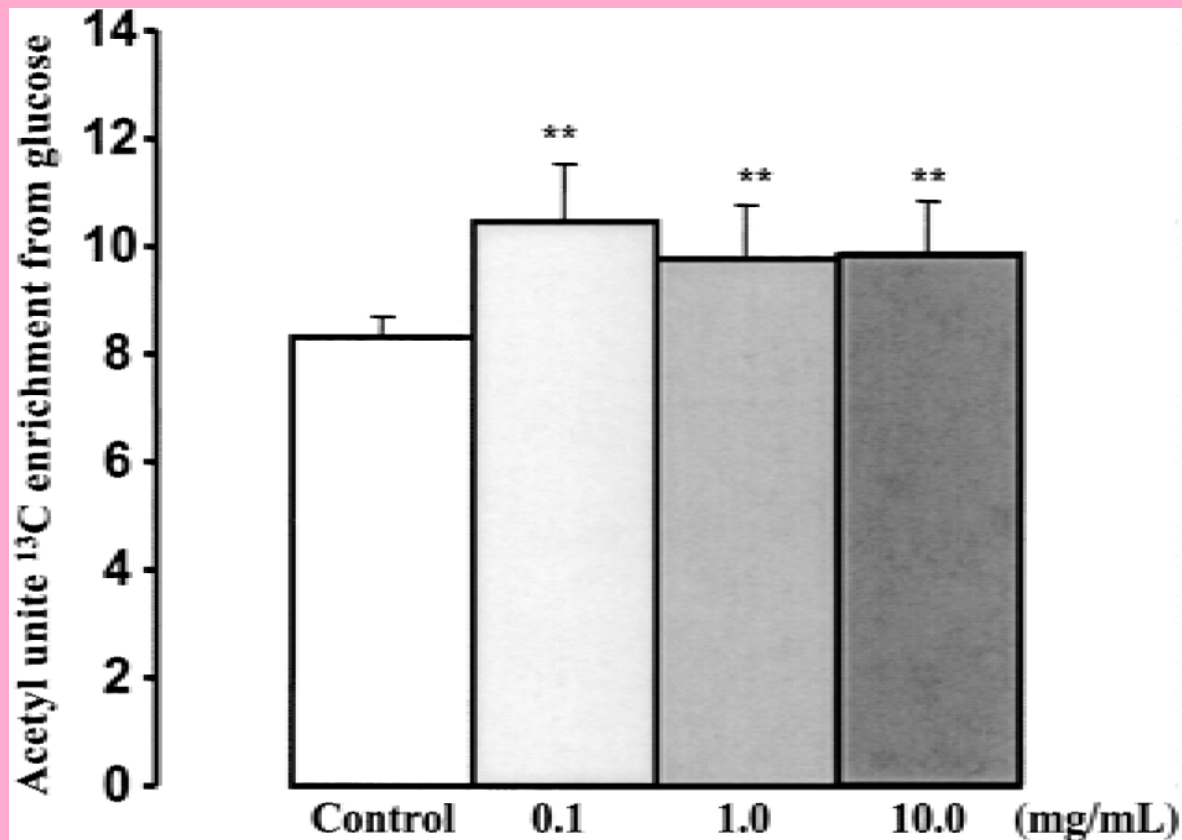


FIG. 9. Acetyl-CoA ¹³C enrichment in MIA pancreatic adenocarcinoma cells in response to increasing doses of fermented wheat germ extract (Avemar) treatment after 72 hours of culture. ¹³C enrichment of acetyl units used for lipid synthesis also shows a significant increase with all doses of Avemar treatment ($\bar{x} + SD$; $n = 9$; * $p < 0.05$, ** $p < 0.01$).

The new strategy in medical oncology means to turn cancer into a chronic, manageable disease by normalizing the proliferative metabolic phenotype of cancer cells, and helping the patients' natural anti-cancer defence mechanisms to fight with the proliferation, propagation and dissemination of cancer cells.

Effects of combinations of FWGE with tamoxifen, exemestane (Aromasin) and anastrozole (Arimidex) on the growth of breast cancer

Tejeda M, Gaal D, Szucs I, Telekes A:
Avenar inhibits the growth of mouse and
human xenograft mammary carcinomas
comparable to endocrine treatments.
J Clin Oncol 2007; 25(18S):21132.

Female, 8 week old (22-23 g) inbred BDF1 mice (Animal Facility, National Institute of Oncology, Budapest, Hungary) were used. The mice were kept under SPF conditions in plastic cages (3-4 per cage), fed with semi-synthetic rodent pellets (Charles River) and filtered tap water, ad libitum.

ER+ MXT mouse mammary carcinoma, obtained from NCI, Bethesda, MD, was maintained in the Animal Facility by serial transplantations. Under Nembutal anesthesia, three mm³ pieces of the tumor tissue were injected subcutaneously into the dorsal skin of the mice.

Tumor volume was determined by measuring two diameters (L and D) of the tumor using a caliper and applying the formula: V (volume) = $L \times D^2 \times \pi/6$. Measurements were done on day 7, 9, 11, 14, 16, 18, 21, 23 and 25 after tumor inoculation. Spontaneous death of the animals, as well as any clinical signs of toxicity were registered.

FWGE (Avemar) was donated by the Inventor and, tamoxifen and Arimidex by Astra Zeneca, and Aromasin by Pfizer, respectively.

All treated and control groups consisted of 7 mice.

FWGE monotherapy to determine optimal dose

The daily doses of FWGE applied via gastric tube were 1.5, 3.0, 4.5 and 6.0 g/kg, BW, respectively. FWGE was dissolved in 0.7% saline. Aliquots of 0.1 ml FWGE solutions were prepared for each dose. Treatment was started 7 days after tumor inoculation, when tumors became palpable, and was applied 10 times for 12 days with two-day pause after the fifth treatment. Physiological saline was given using a gastric tube (0.1 ml daily) as negative control.

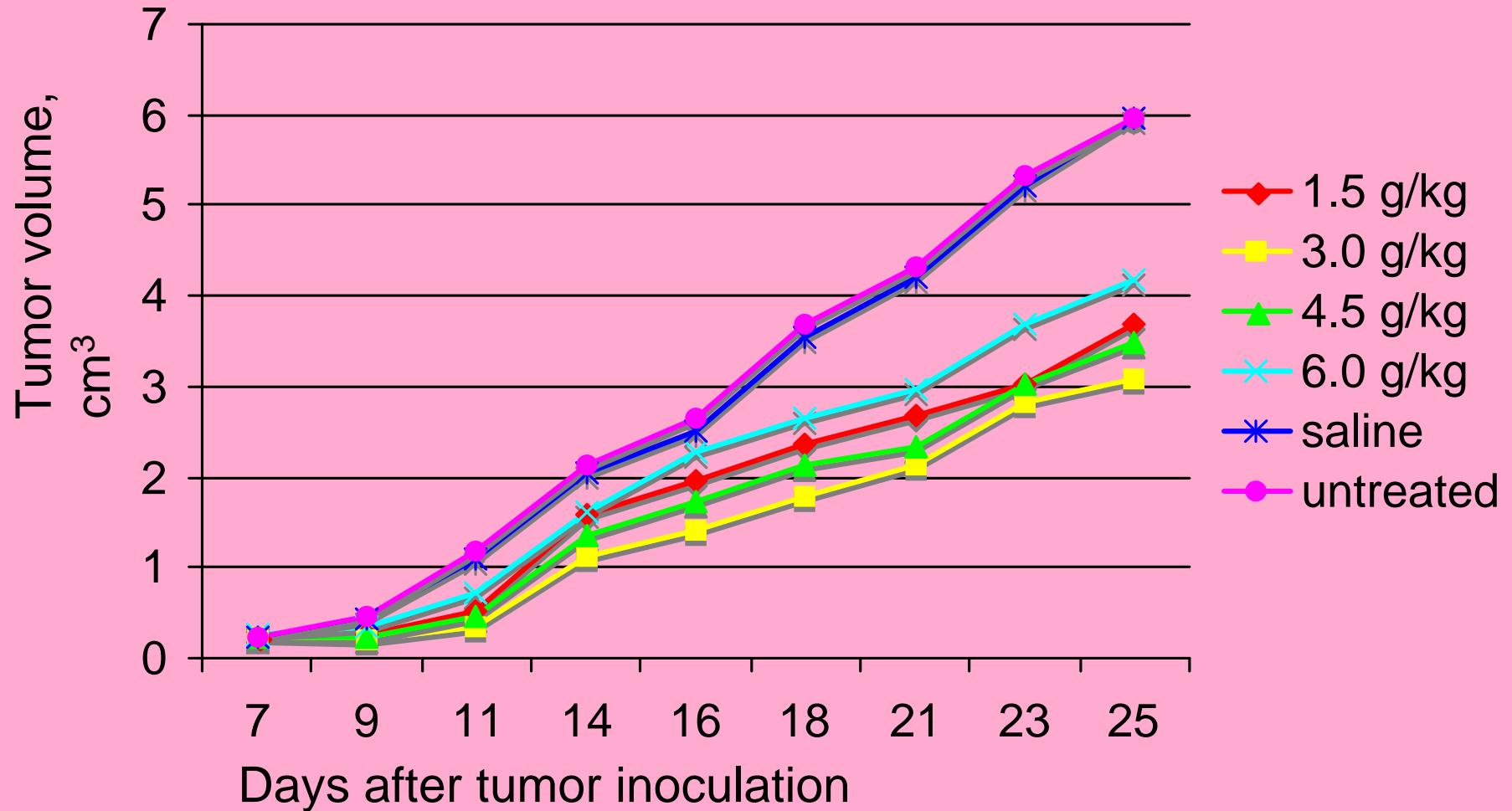
Combination treatment

The orally instilled dose of 3.0 g/kg FWGE was **combined** with the subcutaneous injection of 0.5 mg/kg tamoxifen, the intraperitoneal injection of 5 mg/kg Arimidex and the intraperitoneal injection of 10 mg/kg Aromasin, respectively. At the same time, **monotherapies** with 3 g/kg orally instilled FWGE, subcutaneously injected 0.5 mg/kg tamoxifen, intraperitoneally injected 5 mg/kg Arimidex and intraperitoneally injected 10 mg/kg Aromasin were also performed. All compounds were dissolved in physiological saline solution (aliquots of 0.1 ml for FWGE and 0.25 ml for the other compounds). The control mice received 0.25 ml physiological saline intraperitoneally. All treatments started 7 days after tumor inoculation and applied 10 times, for 12 days, with two-day pause after the fifth treatment.

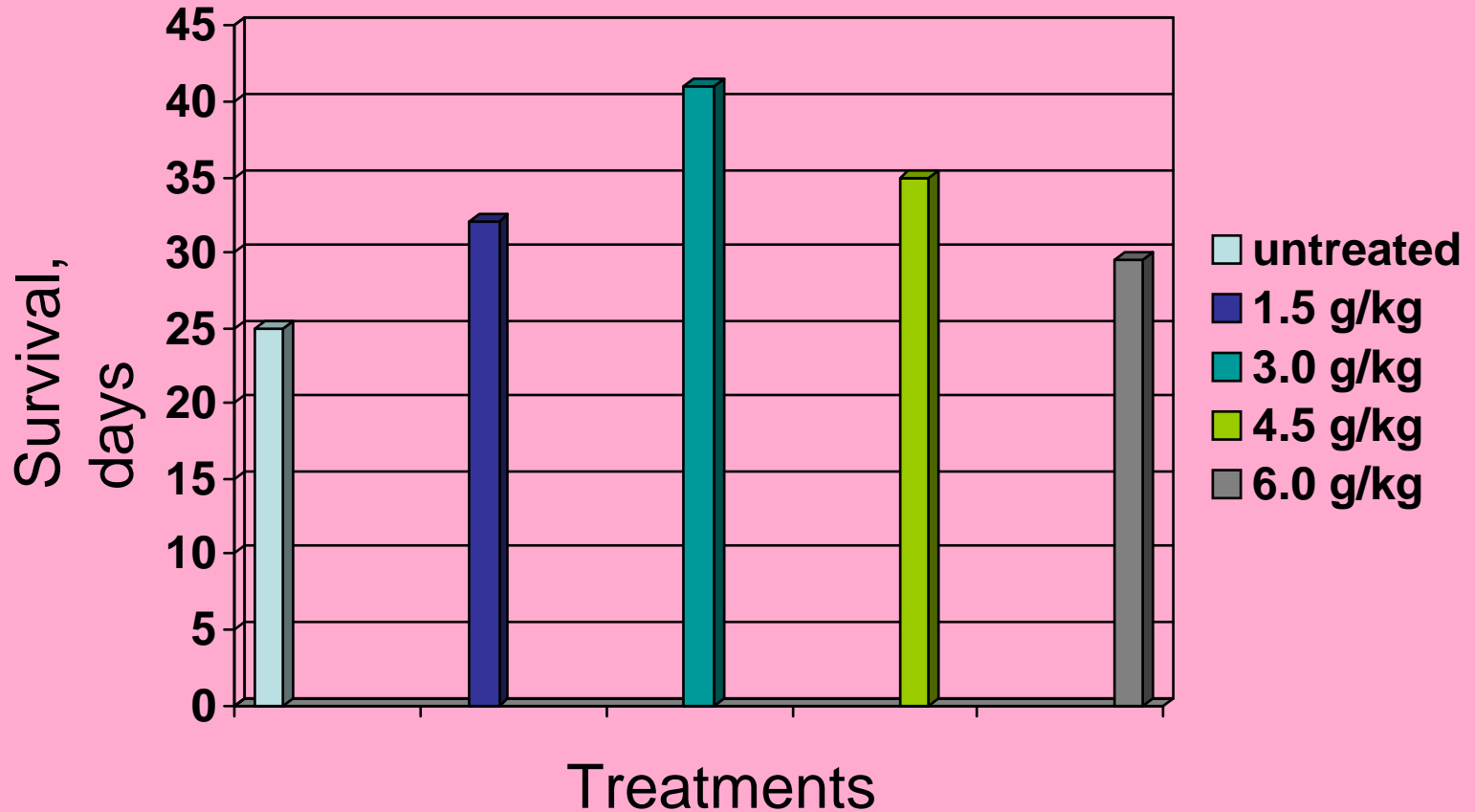
Dose dependent efficacy of FWGE monotherapy

All doses of FWGE significantly inhibited tumor growth. The highest per cent of inhibition was found after the application of 3.0 g/kg FWGE, which corresponded to the recommended single daily human dose. The average survival times were also prolonged by FWGE treatments.

Effect of FWGE monotherapy on the growth of MXT breast cancer



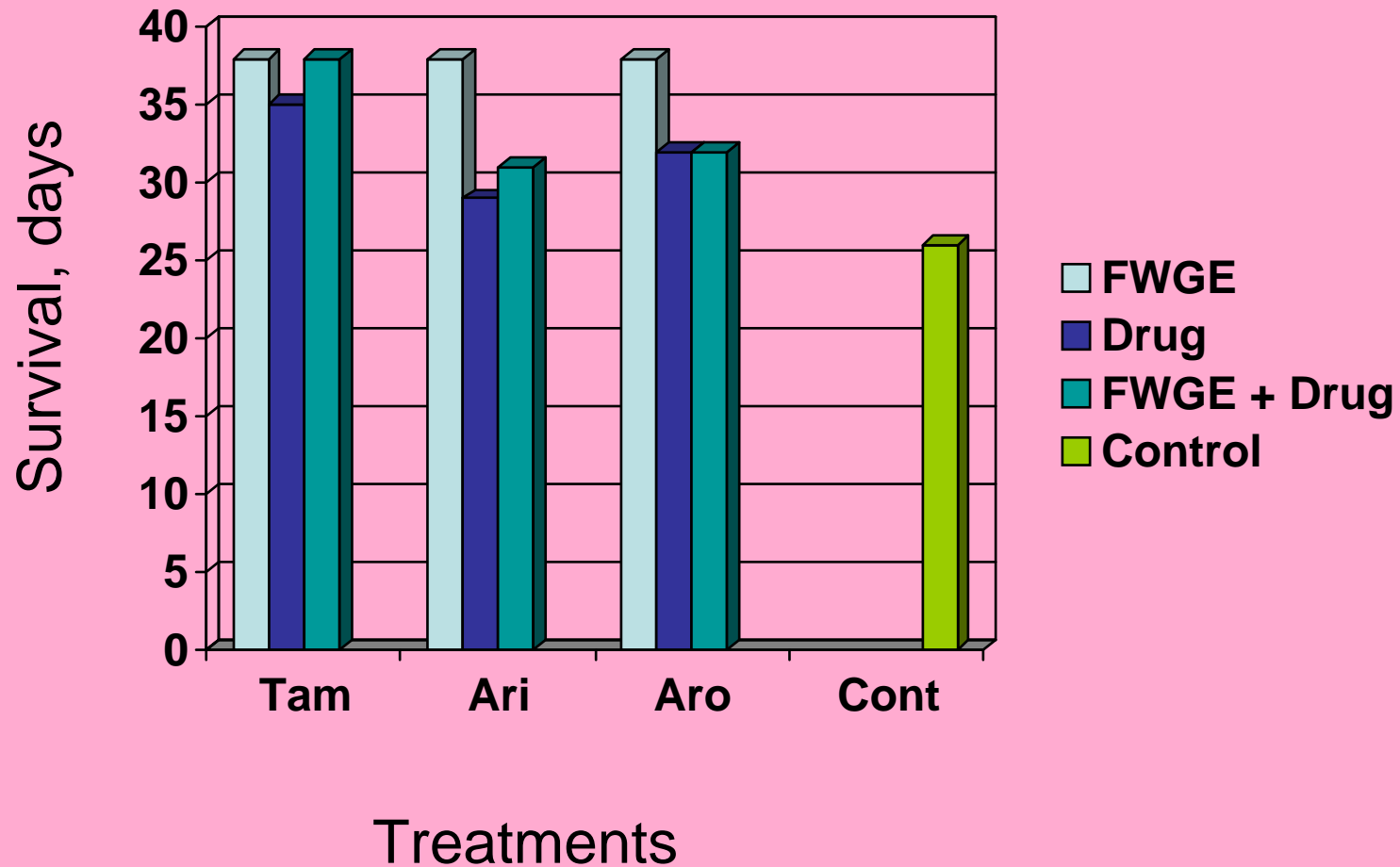
Effect of FWGE monotherapy on the survival of mice having MXT breast cancer



Combination therapy with tamoxifen, Arimidex, Aromasin and FWGE

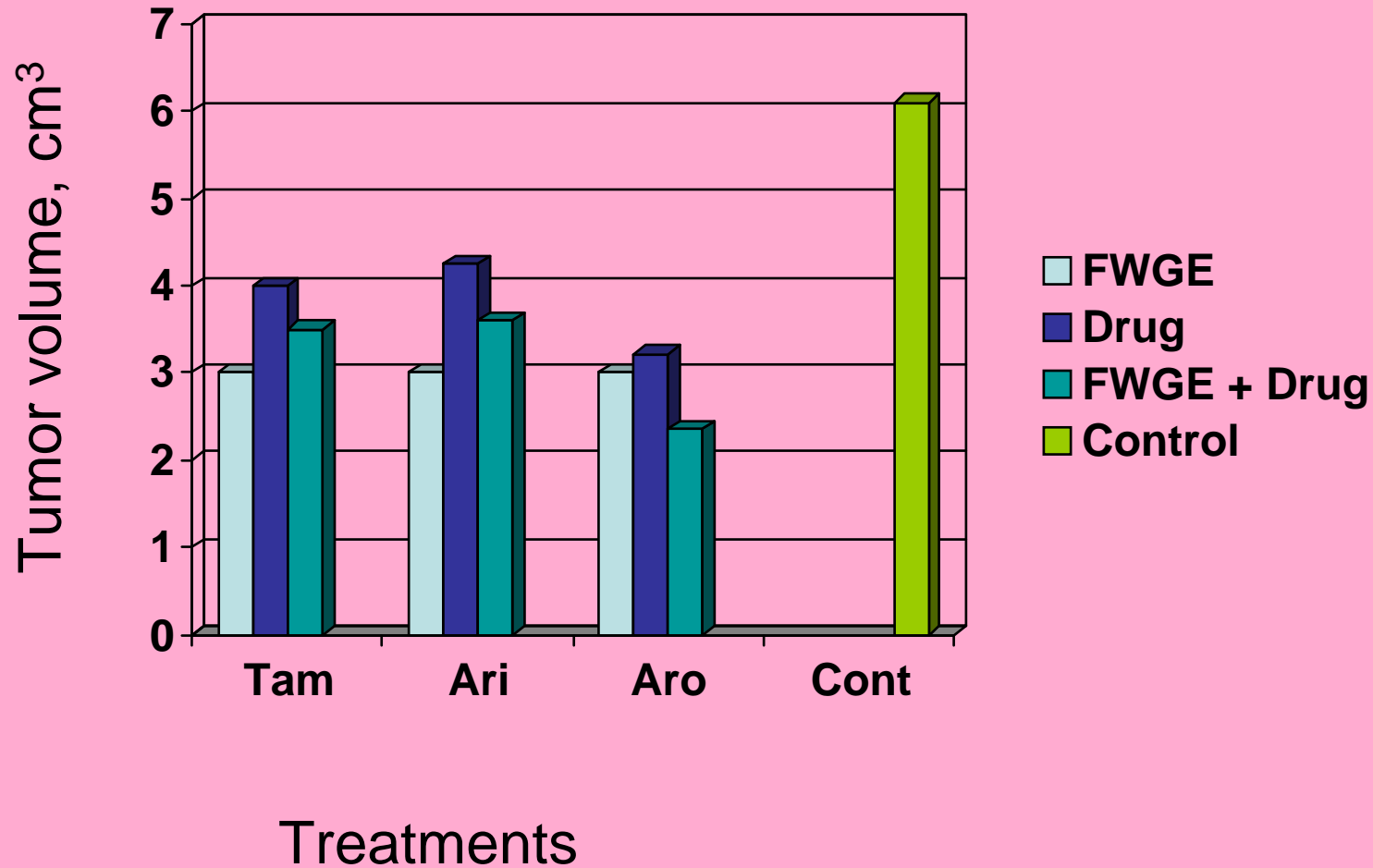
In this experiment monotherapy with Tamoxifen, Arimidex and Aromasin resulted prolongation of survival, though these values were not significant compared to the control. FWGE treatment significantly ($p < 0.025$) prolonged survival of tumor-bearing mice. Combination of FWGE with the drugs resulted similar or greater life span prolongation as had been achieved by the drugs on their own.

Effect of FWGE-drug combinations on the survival of mice having MXT breast cancer



The tumor volumes of mice, taken at day 25 after tumor inoculation, show that all monotherapies and FWGE-drug combinations resulted in decrease of tumor volume compared to the control. FWGE monotherapy proved to be the most effective among the monotherapies. The effects of combinations on the tumor volume exceeded that of the drugs on their own. Combination of FWGE with Aromasin resulted in 60.4% inhibition of tumor growth.

Effect of FWGE-drug combinations on the growth of MXT breast cancer



T47/D ER+ human breast cancer xenograft

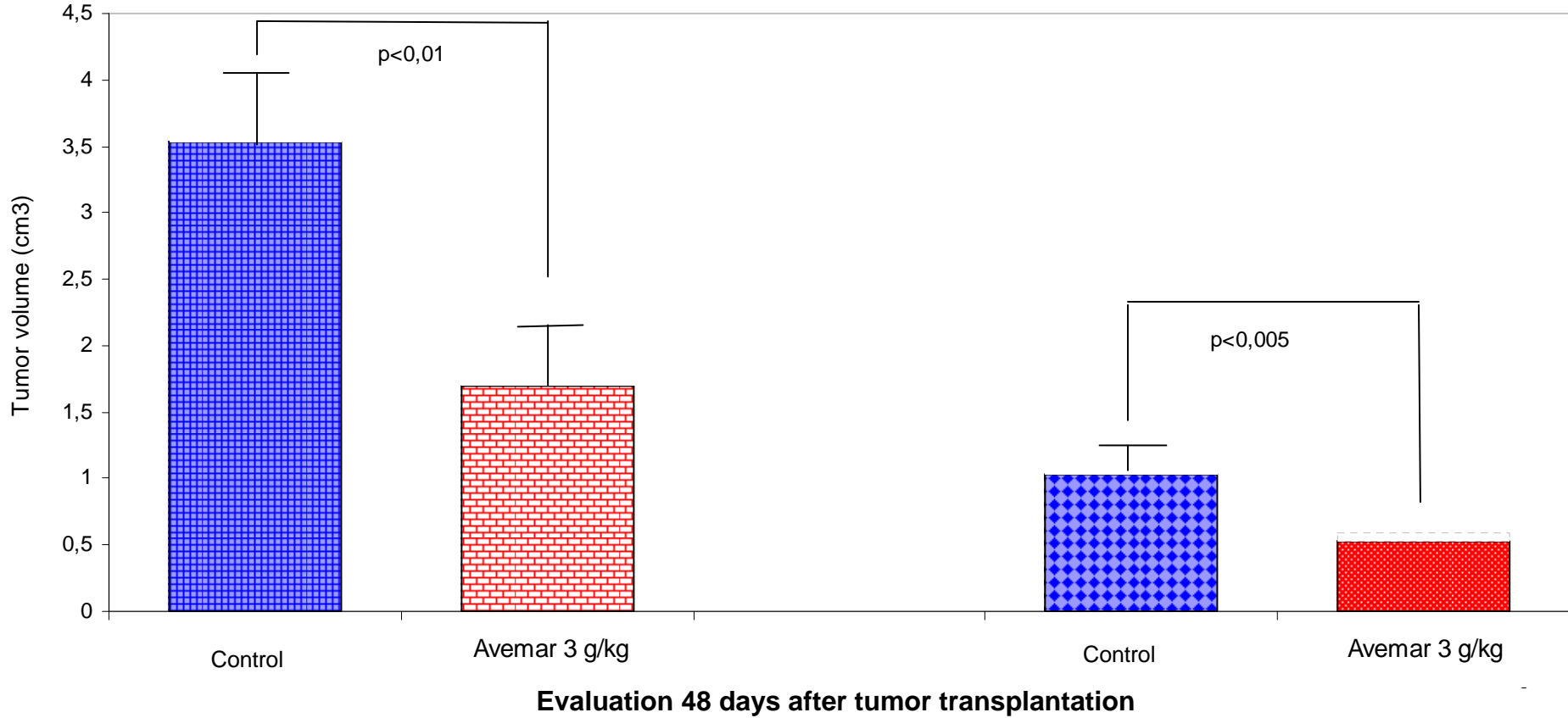
In xenograft models, FWGE produced 50% tumor growth inhibition compared to control, and was more effective than the other monotherapy treatments: Aromasin (26%), Arimidex (25%) or tamoxifen (42%). Combined treatment with FWGE always improved efficacy within the range of 3–10%.

Comparative efficacy of FWGE on the growth of MDA-MB-231 estrogen receptor negative (ER⁻), and T-47/D hormone sensitive, estrogen receptor positive (ER⁺) human breast carcinoma xenografts in mice. (American Type Culture Collection (ATCC), Rockville, MD)

EFFECT OF AVEMAR ON ESTROGEN RECEPTOR POSITIVE AND NEGATIVE TUMOR IN XENOGRAFT MODEL

MDA-MB-231 (ER⁻)

T-47/D (ER⁺)



Conclusions

The tumor growth inhibitory effect of FWGE on ER positive MXT mouse breast carcinoma as well as in T47/D human xenograft models are comparable (equal or better) to standard endocrine treatments. FWGE certainly did not reduce the effect of endocrine treatments. FWGE showed similar efficacy (50% inhibition of growth) when ER+ and ER- human breast cancer xenograft were compared.

The antitumor activity of FWGE was not dependent on the estrogen receptor status.

Inclusion of FWGE into the treatment protocols of both ER+ and ER- breast cancers can be recommended.

QOL1: Breast Cancer (Szeged)

- Endpoints: chemotherapy side effects + body mass
- 39 patients; average length of FWGE therapy: 19.3 months
- Results
 - Side effects of chemotherapy:
 - 38.5% no changes;
 - 25.6% improved;
 - 35.9% completely disappeared
 - Body mass:
 - average increase = 7.4% ($p < 0.001$)

QOL2: Breast Cancer (Szeged)

- Endpoint: quality of life (EORTC QLQ-C30 questionnaire)
- 55 patients; average length of AVEMAR therapy: 32.2 mos.
- Results:
 - Improvement in functional scales:
 - physical functions ($p < 0.05$)
 - emotional functions ($p < 0.001$)
 - global state of health ($p < 0.01$)
 - Improvement of symptomatic scales:
 - fatigue ($p < 0.01$)
 - nausea and vomiting ($p < 0.01$)
 - insomnia ($p < 0.01$)
 - constipation ($p < 0.01$)

QOL3: Lung cancer (Natl. Inst of Pulmonology)

- Endpoint: quality of life in advanced stage (EORTC QLQ-C30 questionnaire)
- 17 patients; average length of AVEMAR treatment : 7.9 months
- Results:
 - global state of health ($p < 0.01$)
 - fatigue ($p < 0.05$)

Fermented wheat germ extract accelerates the regeneration of thrombocytes and reticulocytes in sublethally irradiated or cyclophosphamide treated mice

Irradiation: Mice were irradiated under a ^{60}Co gamma source (dose rate: 0.2697 Gy/min) with an accumulating dose of 3.5 Gy.

Cyclophosphamide (Cytosan, Bristol-Meyers, 200 mg cyclophosphamide + 150 mg mannitol per ampoule) was dissolved in saline and injected in a dose of 200 mg/kg body weight (0.1 ml/10 g body weight, LD_{10}). Control mice were injected at the same time with 0.2 ml saline.

Blood samples were taken from the tail veins. Leukocytes and thrombocytes were counted using a hemocytometer. Reticulocytes were supravitaly stained with brilliantkresylblue. Reticulocytes/1000 red blood cells were scored.

Bone marrow stem cell colony forming potential was tested and expressed as colony forming units in spleen: CFU-S in lethally irradiated isologous recipients.

Bone marrow granulocyte-macrophage progenitors (CFU-GM) were assayed in a soft gel system containing 30 per cent fetal calf serum, 10 per cent conditioned medium of WEHI 3-B cells as IL-3 source, McCoy 5A medium, 5×10^5 bone marrow cells and 0.3 per cent agar in a final volume of 1 ml/Petri dish.

Effects of Avemar administration

Leukocyte count after 4 days of radiation exposure was approximately 30 per cent of controls which increased to 50 per cent then remained at this level for the remaining observation period (21 days). Thrombocyte count showed a significant increase by day 7 which reached the control values at day 21.

Reticulocyte regeneration also started earlier in Avemar than in distilled water treated irradiated groups. Postirradiation thrombopenia was significantly less pronounced in the Avemar treated group.

In cyclophosphamide treated mice, thrombocyte count showed a more rapid recovery in the Avemar treated group than in the control.

The same effect of Avemar on platelet regeneration was observed in cyclophosphamide treated and in irradiated mice where Avemar also significantly increased platelet regeneration.

Clinical significance

The clinical significance of these observations is that Avemar increases bone marrow cell regeneration and platelet activity which substantially contribute to the restoration of normal immune functions after irradiation- or chemotherapy treatments in cancer.

Besides their role in preventing hemorrhages and extended tissue damage, platelets are an important source of various inflammatory cytokines.

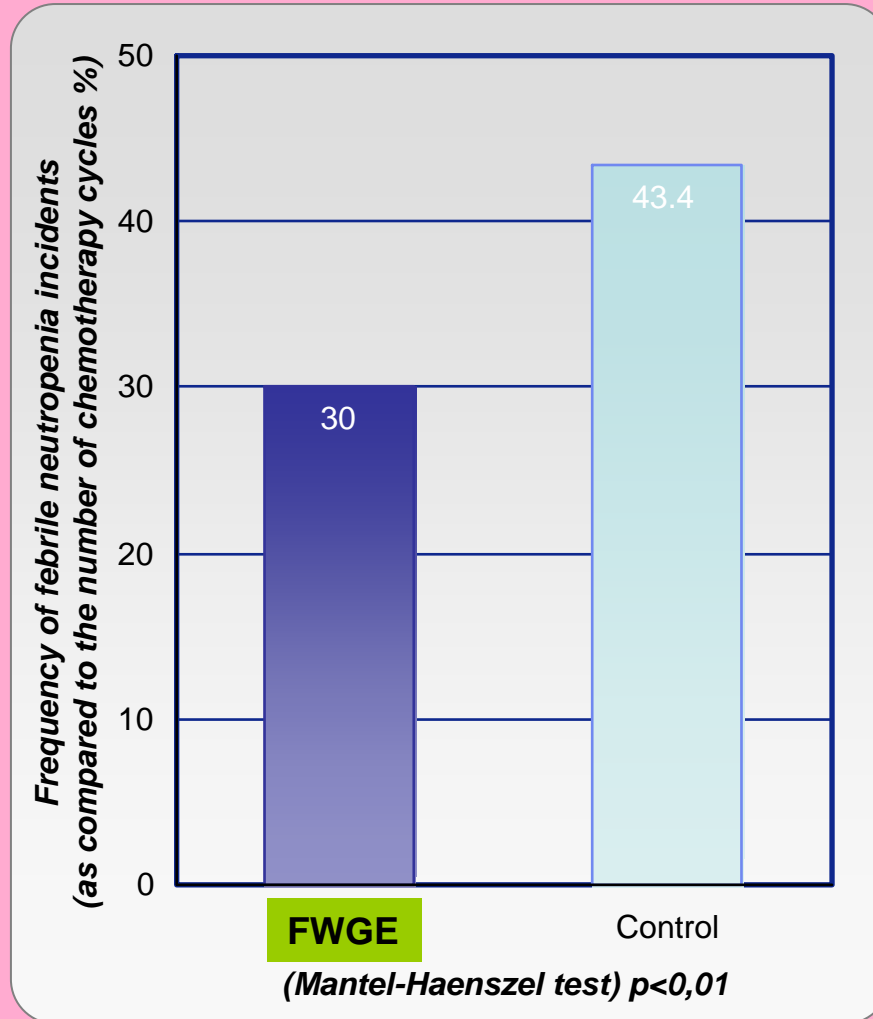
The rapid reticulocyte regeneration, which we observed after Avemar treatment, may also contribute to the increased oxygenation and a more complete regeneration of vital organs that are adversely affected by high dose chemotherapy and/or radiation during the treatment of cancer.

Avemar Against Febrile Neutropenia in Childhood Cancers

Journal of Pediatric Hematology-Oncology, 2004

- Site: Clinics of Pediatrics No. II Budapest University (Prof. Gy. Fekete)
- Design: open, prospective, randomized
- Objective: Avemar effect on chemotherapy-related febrile neutropenia
- No of patients: 22 (11 matched pairs)
- (histology, site, diagnosis, age, clinical stage)
- Follow-up: 3 years

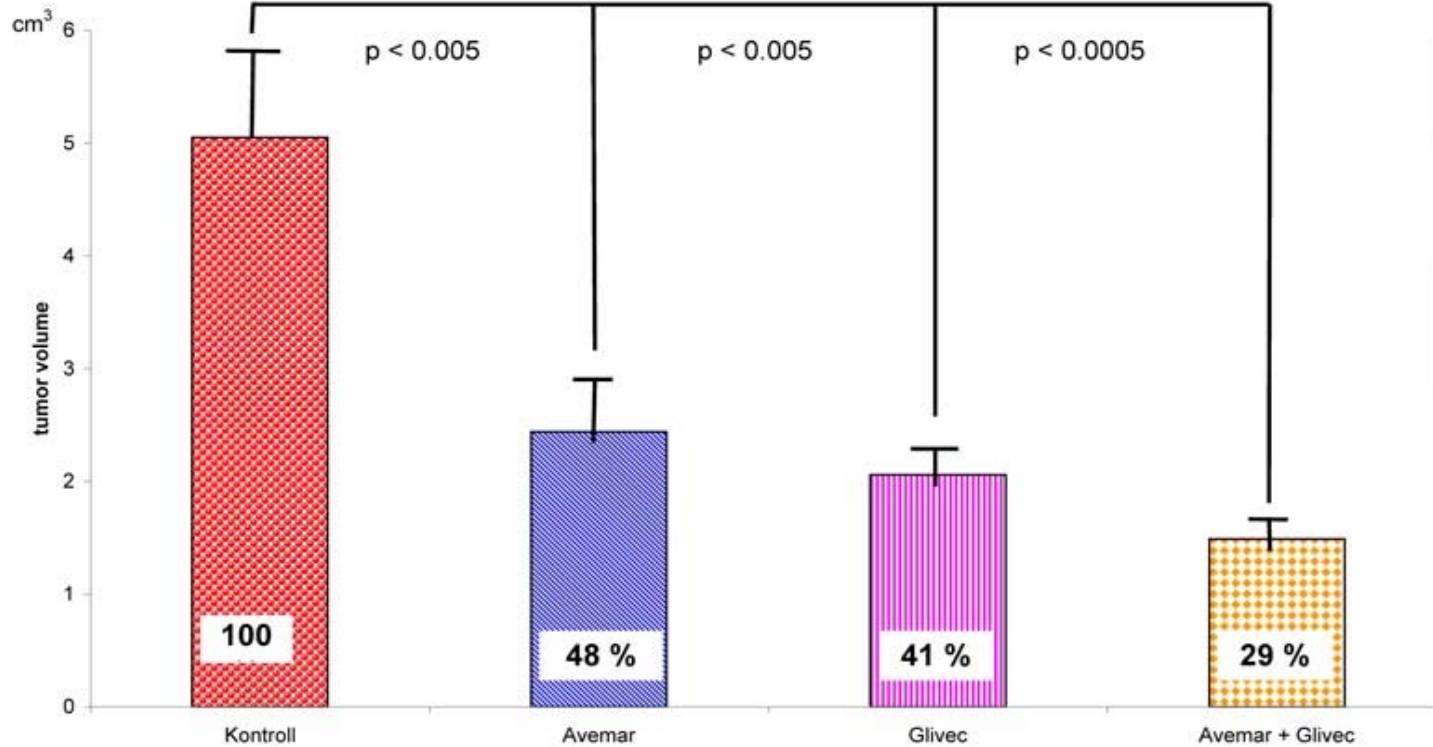
Febrile neutropenia ratio of episodes/cycle (%)



ONGOING CANCER CLINICAL TRIALS WITH FWGE

Avemar and Gleevec on K562 human leukemia cells implanted into mice

Relative tumor volumes after 13 days of final treatments



Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings (Post-Meeting Edition).
Vol 25, No 18S (June 20 Supplement), 2007: 14143
© 2007 American Society of Clinical Oncology

Abstract

Changes in the kinase expression panel of K562 human leukemia after Avemar treatment

A. Telekes and E. Rásó

National Institute of Oncology, Budapest, Hungary

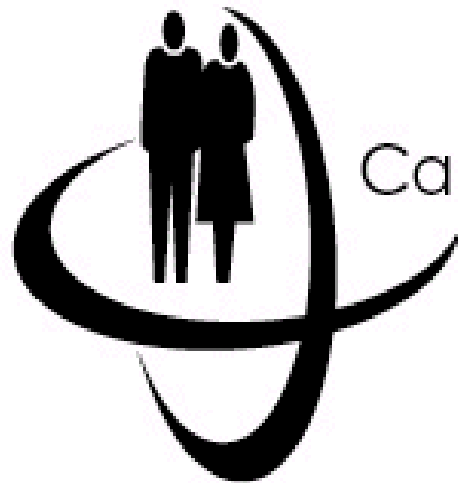
14143

Background: The positive effect of the wheat germ extract Avemar has already been proved in cancer. Compared to the control group significantly longer survival times were achieved in both *in vivo* experiments and clinical studies. Inhibition of cell growth was also detected in K562 human leukaemia cell line *in vitro*. Avemar given p.o.(3 g/kg) resulted in significant increase of the survival time compared to the control group ($p < 0.005$ Mann-Whitney) in i.v. implanted K562 xenograft model, which was practically the same as the effect of Gleevec treatment. Since, the mechanism(s) of action of Avemar is still not properly characterized a kinase expression panel in K562 *in vitro* model was examined. **Methods:** K562 cells (8×10^5 cell/ml), were treated with Avemar (500 $\mu\text{g/ml}$) and mRNS from 3–3 parallel samples and their appropriate controls were isolated 24, 48 hours after the treatment and 24 hours after washing the cells previously treated with Avemar for 48 hours. To determine the kinase expression pattern Kinase OpenArray™ plates were used, having over 500 kinase genes with controls in quadruplicates in each plate. Changes in expression was declared if the average value was over 1 (2-fold change in mRNA copy number) and the standard deviation was relatively small ($2 \times \text{STDEV} = \text{AVERAGE}$). **Results:** We have found 16 kinases which expression has temporary or durable (maintained for 24 hour after washing) decreased (e.g.: CCL2, ABR, FLT1, EphB6, TGF α) and 30 which expression has increased (e.g.: CPT1B, IRE1, ITK, RON, LTK, EphB2, FASTK). **Conclusions:** Our result demonstrated that many of the kinases which expression was altered by Avemar treatment is known to participate in cell cycle, cell migration, apoptosis and signal transduction. Thus, our results might shed light on the main mechanism(s) of action of Avemar and raise the possibility to identify the active substance(es) of this natural extract.

No significant financial relationships to disclose.

AVEMAR PLUS IMATINIB (GLEEVEC) IN CML

DEPARTMENT OF HEMATOLOGY,
SAN MARTINO UNIVERSITY HOSPITAL,
GENOVA, ITALY



Cancer Treatment
Research Foundation

Study 1 of 1 for search of: avemar[Return to Search Results](#)[Full Text View](#)[Tabular View](#)[Contacts and Locations](#)[Related Studies](#)

Efficacy of FWGE in Combination With Hormone Therapy for the Treatment of Hormone-Refractory Prostate Cancer Patients

This study is currently recruiting participants.

Verified by Sheba Medical Center, March 2008

Sponsored by:	Sheba Medical Center
Information provided by:	Sheba Medical Center
ClinicalTrials.gov Identifier:	NCT00411853

► Purpose

We propose in this study to treat hormone refractory prostate cancer (HRPC) patients., with a novel preparation of fermented wheat germ nutriment (FWGE), in combination with the 1st line hormone therapy, the gonadotropin releasing hormone (GnRH), which stopped being effective. The study will be conducted during two years with 60 patients. The efficacy will be assessed in terms of clinical and serological response and by specific questionnaires.

This concept is based on previous reports regarding other diseases such as colon cancer, where the addition of a new drug to a drug which previously had failed, improved the patients' survival, the quality of life and the clinical parameters. In addition, preclinical data have shown activity of that regimen in prostate cancer cell lines and in animals' models.

FWGE exhibits a wide variety of mode of actions, in a wide range of malignant tumors. It increased the natural immune responses while decreasing the systemic inflammation often present in cancer patients. It reduced the growth of human prostate tumor xenograft in mice and prolonged their survival. It delayed disease progression, increased overall survivals, improve quality of life and reduce oxidative stress.

The long-term goal of this research is that the addition of FWGE to a drug which previously had failed, would slow down disease progression in patients with advanced and thus refractory cancers, improving the patients' quality of life, their clinical parameters and survival.

Condition	Intervention	Phase
Hormone Refractory Prostate Cancer	Drug: Fermented Wheat germ extract	Phase II

[MedlinePlus](#) related topics: [Cancer](#) [Prostate Cancer](#)

[U.S. FDA Resources](#)



In Memoriam

o. Univ. Prof. Dr. Dr.h.c. Hermann Esterbauer

(30 July 1936–7 January 1997)

Professor Dr. Dr.h.c. Hermann Esterbauer, an internationally renowned biochemist, died on January 7, 1997, in Graz, Austria. At the time of his death Prof. Esterbauer was Head of the Department of Biochemistry at the Karl-Franzens-University in Graz and was acting chairman of the special collaborative research effort "SFB Biomembranes and Atherosclerosis."

Hermann Esterbauer, born on July 30, 1936, in the Austrian town of Ach, began his scientific career as a University assistant in the Department of Physical Chemistry at the Karl-Franzens-University in Graz (1963–1968). He then joined the newly founded Department of Biochemistry in Graz as a University Assistant under the department's first chairman, Prof. E. Schauenstein. After obtaining his *venia docendi* in 1970, Prof. Esterbauer continued his scientific training through successive post-doctoral fellowships

