OFF LABEL PHARMACEUTICAL 'COCKTAILS' FOR CANCER TREATMENT

A4M Integrative Cancer Therapies

Module 6

June 6-8, 2013

Clarithromycin

- Macrolide antibiotic (erythromycin)
- Potent antiinflammatory effect
  ENT,Pulmonary (CF,PB,Asthma,COPD, sinusitis)
- Mechanisms: Inhibits NFkB
  Suppresses TNFa
- Activity: Anti-cachexia
  Anti-angiogenesis Suppresses tumor resistance (via NFkB)
- Where? :
  Myeloma, Waldenstroms Macroglobulinemia
  Lymphoma; marginal zone, follicular, LBCL, Hodgkins
  Lung Cancer (NSCLCa), ?Breast

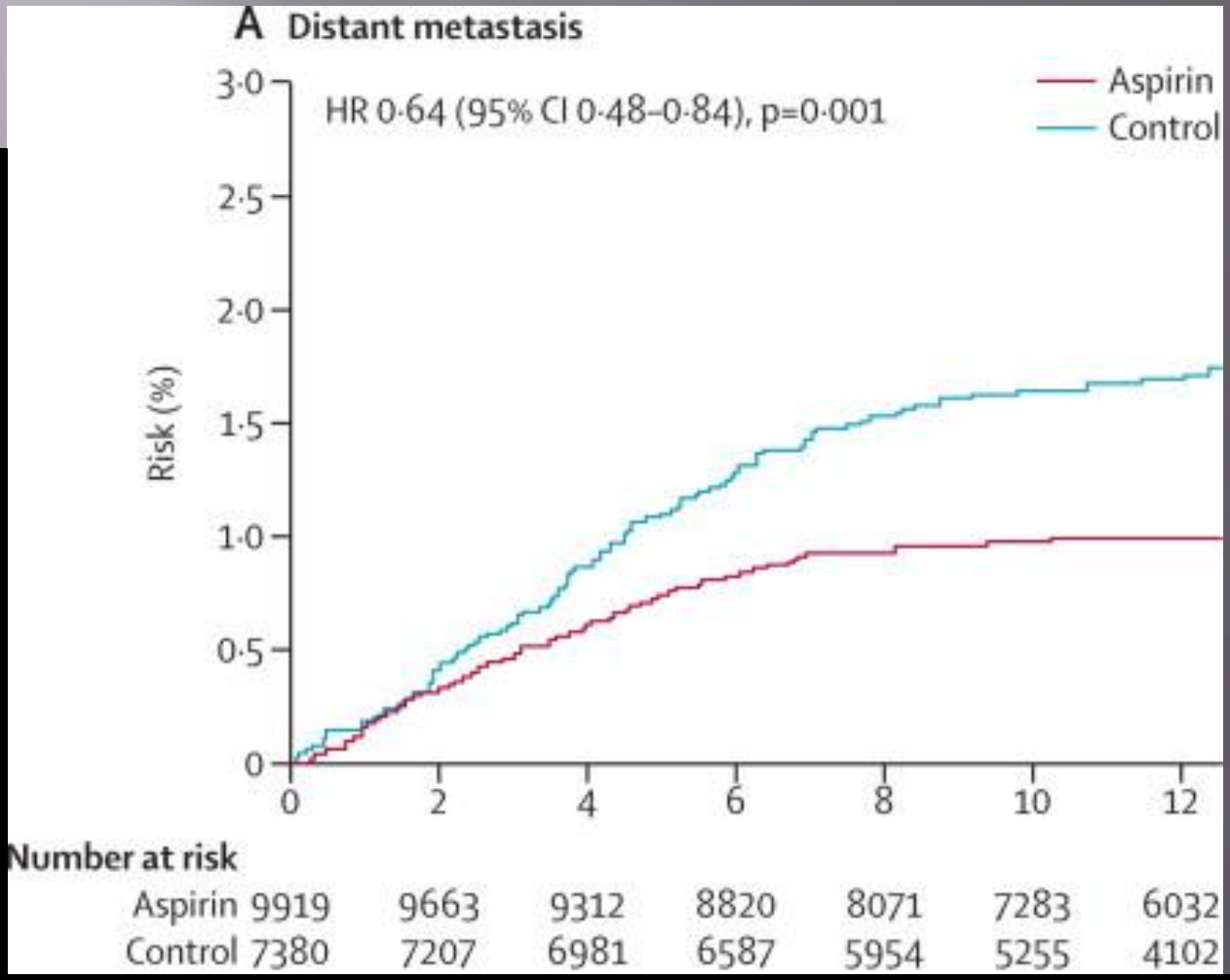
Hiding in plain view: the potential for commonly used drugs to reduce breast cancer mortality

Holmes M, Chen W. Breast Canc Res 2012, 14:216

- Many medications developed for other purposes have other activity
- Increasing evidence that many non-cancer drugs have potential impact on breast cancer survival
- Evidence for both OTC and generic medications **Aspirin and other NSAIDS**
- **Blood Pressure Medications (β-blockers, ACE-I) Lipid lowering agents (Statins) Diabetic medications (metformin)**
- Benefit potentially significant **Metformin (50%), ASA (50%), Statins (30%) β-Blockers- (50+% in TNBC)**

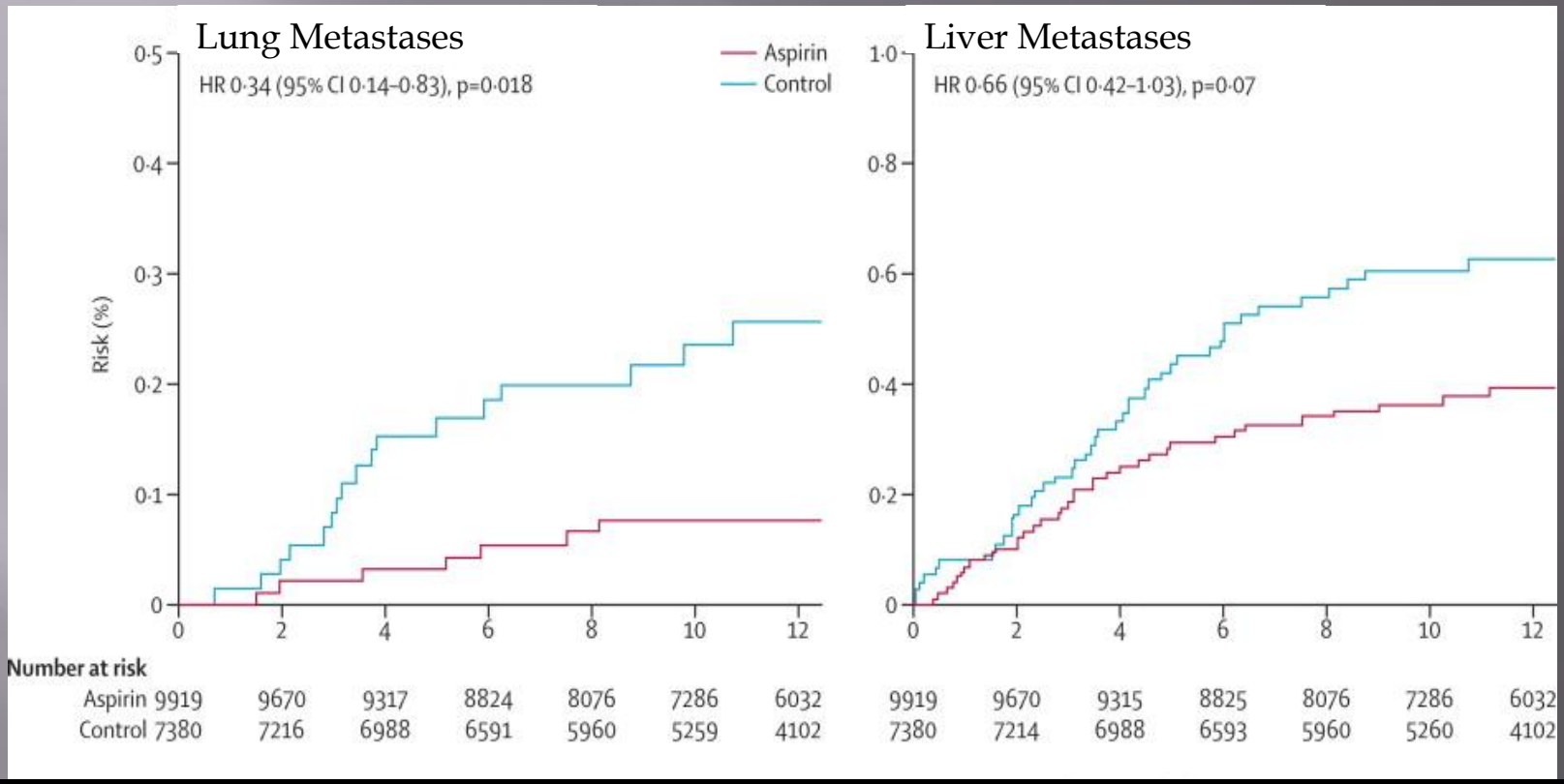
" We advocate that confirmation of these findings in randomized trials be considered a high research priority, as the potential impact on human lives saved could be immense"

Risk Reduction of Metastases by Aspirin

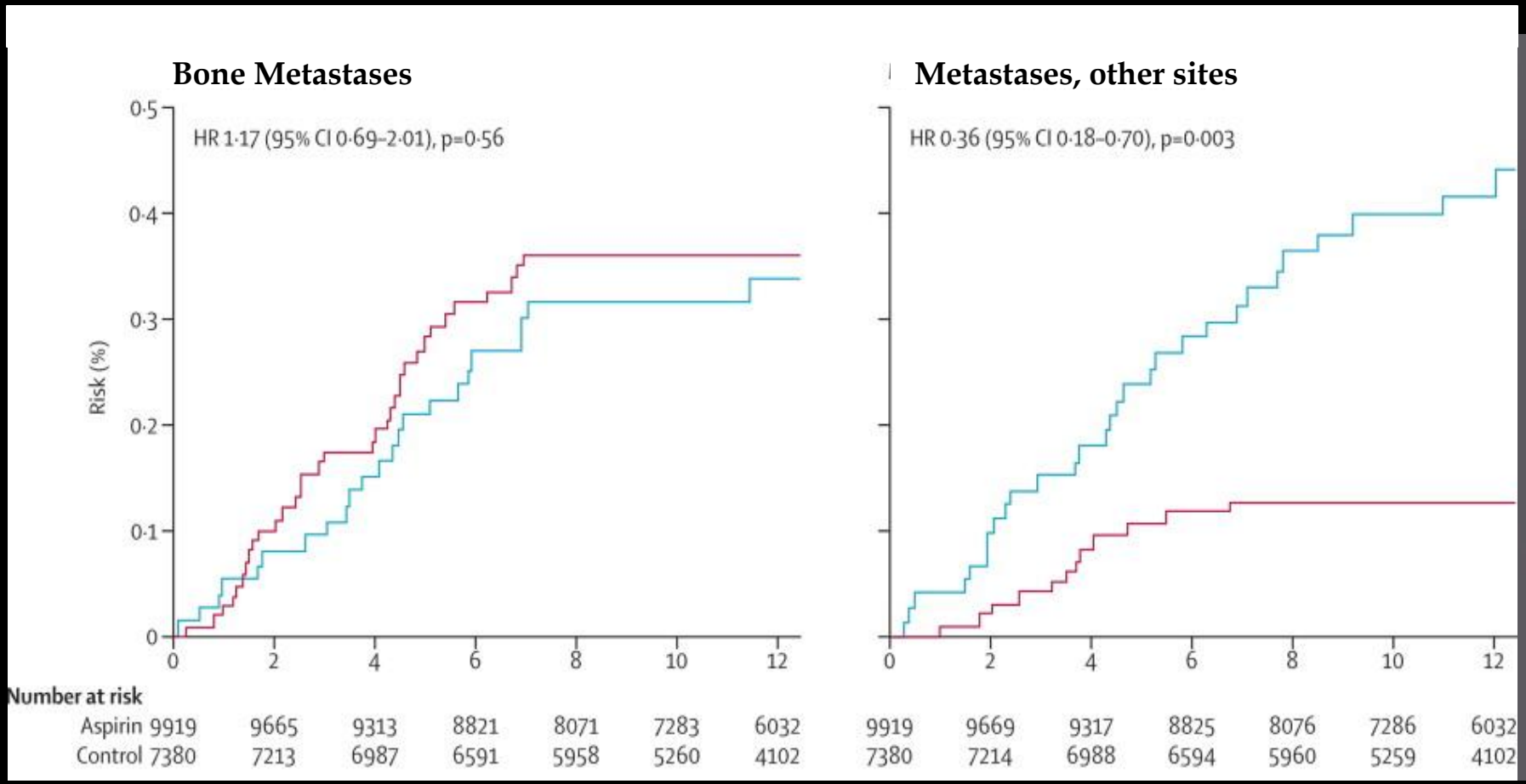


The effect of aspirin on risk of metastasis due to any incident cancer diagnosed during five trials of aspirin versus control Analysis is based on time from randomization to diagnosis of metastasis during or after the trials. Part A shows definite site-specific distant metastasis

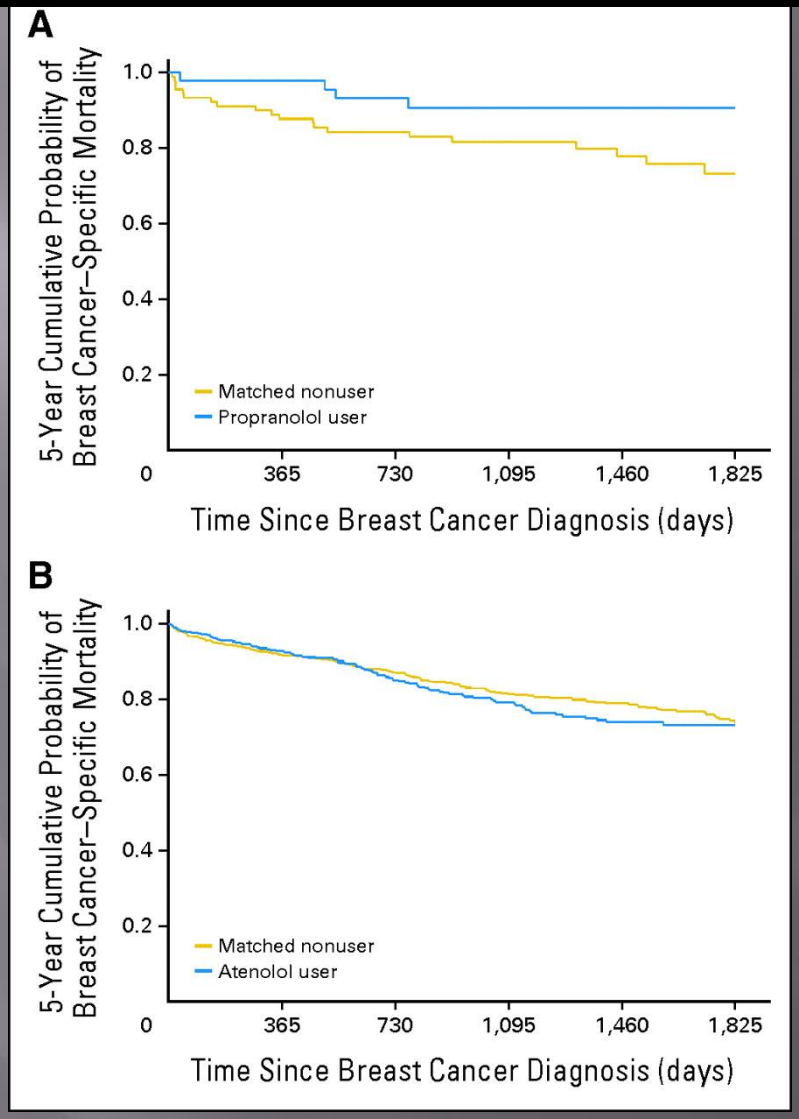
Risk Reduction of Metastases of Aspirin, by Site - I



Risk Reduction of Metastases of Aspirin, by Site - II



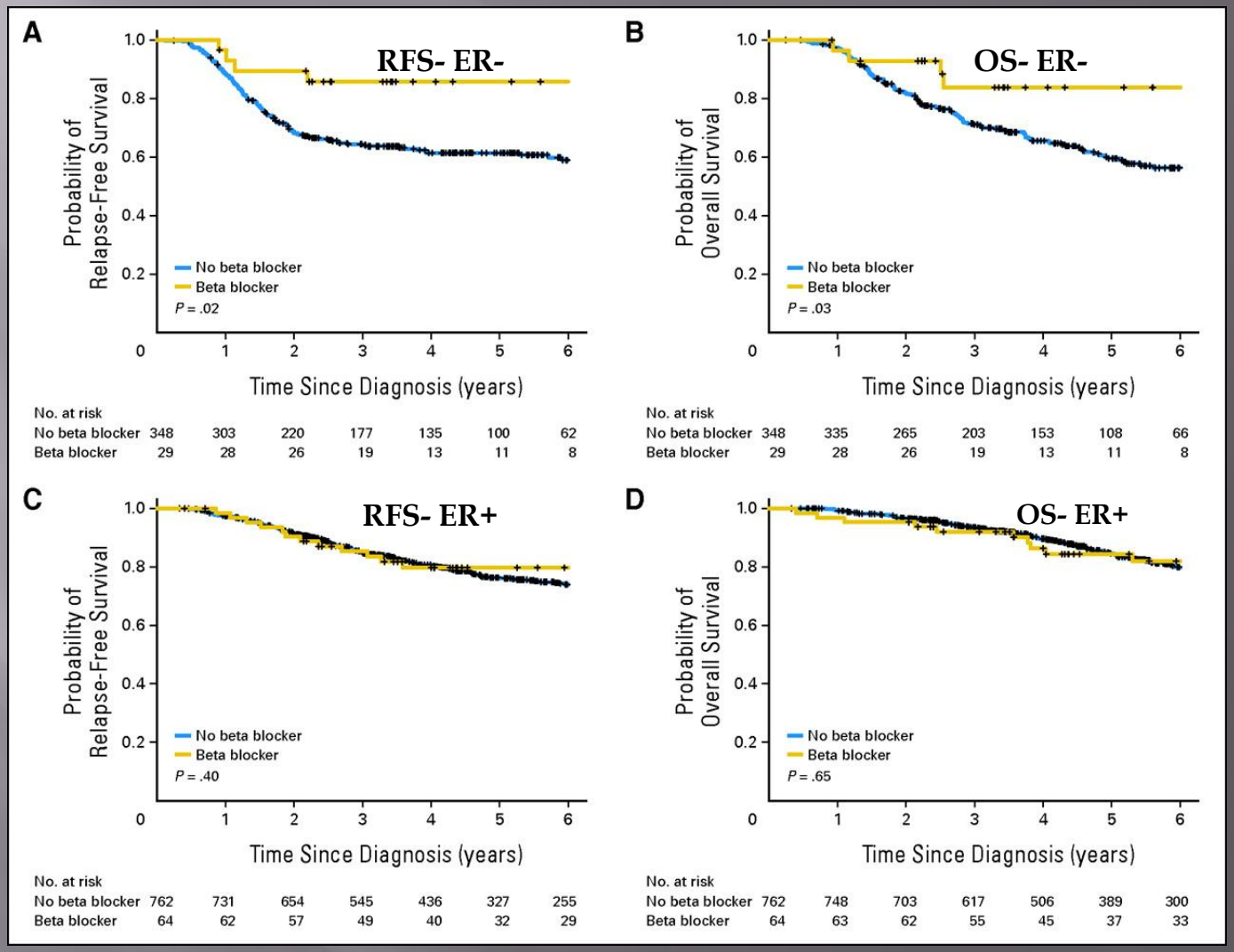
Beta-Blockers Reduce Breast Cancer Mortality



Five-year cumulative probability (unadjusted) of breast cancer–specific mortality in propranolol users (A) or atenolol users (B) versus matched nonusers.

Barron T I et al. JCO 2011;29:2635-2644

Beta-Blocker Use Is Associated With Improved Relapse-Free Survival in Patients With Triple-Negative Breast Cancer



(A) Relapse-free survival (RFS) and (B) overall survival (OS
(B) in patients with triple-negative breast cancer.
and with estrogen receptor–positive breast cancer

Melhem-Bertrandt A et al. JCO 2011;29:2645-2652

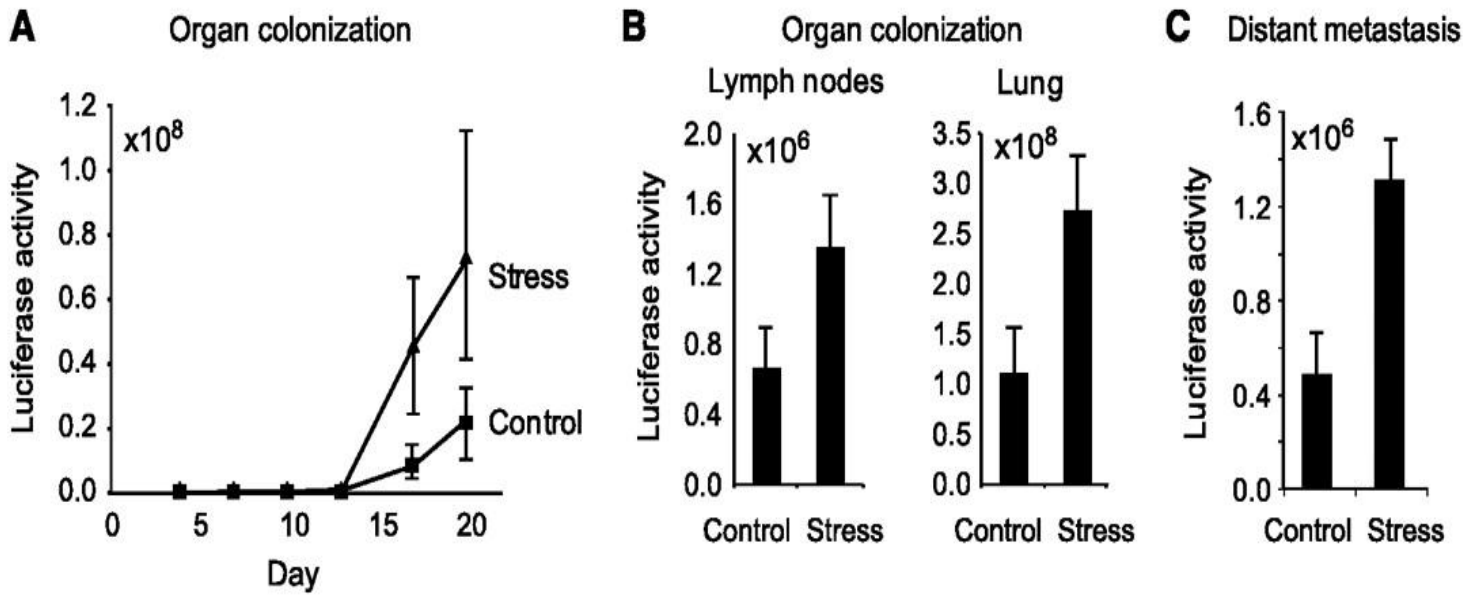
Why β-Blockers reduce risk?

Inhibits β-adrenergic pathways of SNS

Insight into importance of stress and cancer

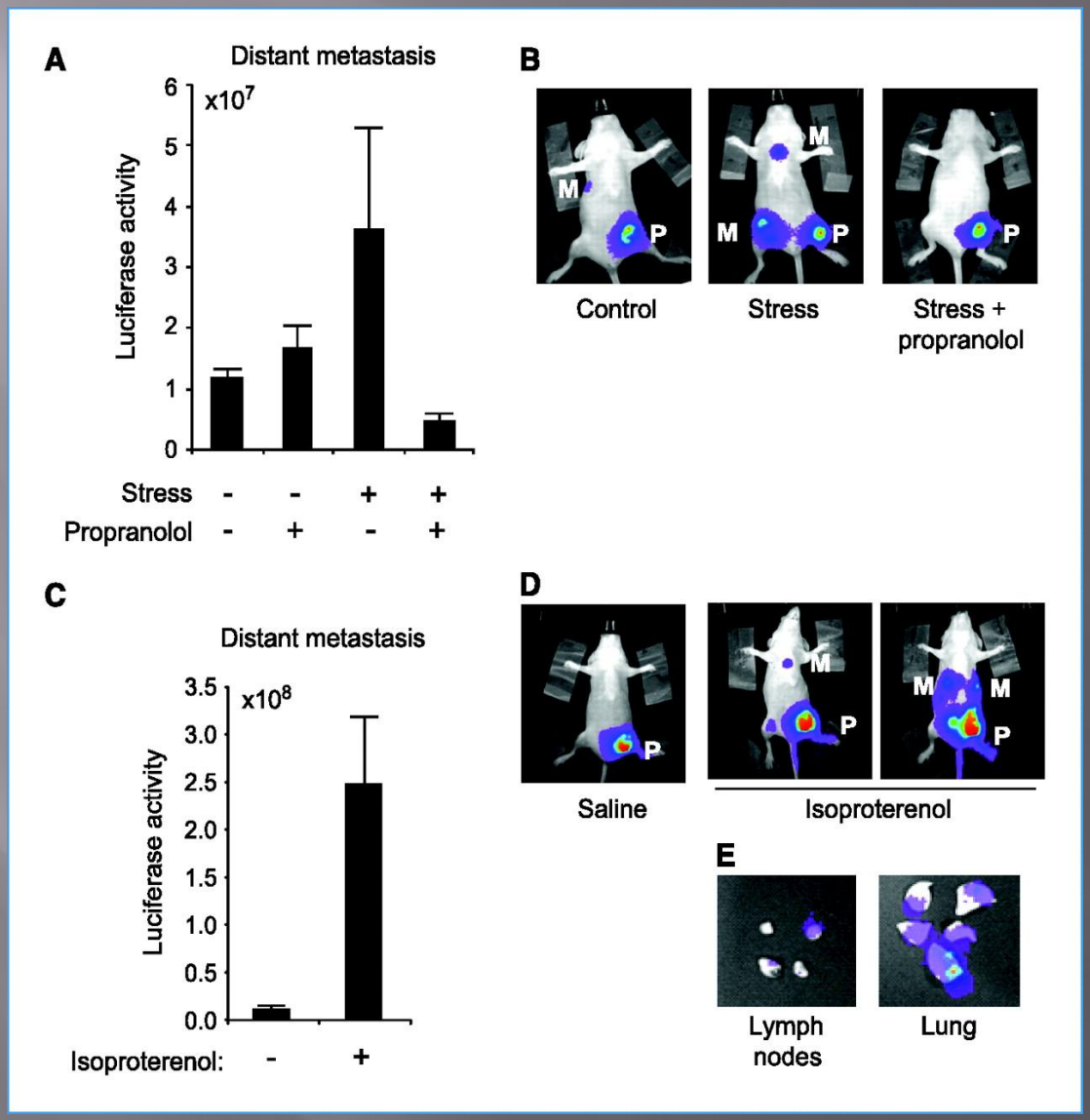
Adrenergic activation
Increases tumor invasiveness
Increases metastases

Effect of stress on colonization of metastatic target tissues.



Sloan E K et al. Cancer Res 2010;70:7042-7052

Role of the SNS in stress-induced metastasis.



Sloan E K et al. Cancer Res 2010;70:7042-7052

Metformin (↑AMPK ↓IGF-1 &c-MYC) (↓mTOR)

- Metformin: elicits anticancer effects through the sequential modulation of DICER and c-MYC. Nat Commun. 2012 May 29;3:865. doi: 10.1038/ncomms1859.
- Is synthetically lethal with glucose withdrawal in cancer cells. Cell Cycle. 2012 Aug 1;11(15):2782-92. Epub 2012 Aug 1.
- Potentiates the effects of paclitaxel in endometrial cancer. Gynecologic Oncology 125 (2012) 458–469
- Together with the mTOR inhibitor everolimus (Affinitor) sensitize breast cancer cells to the cytotoxic effect of chemotherapeutic drugs. Anticancer Res. 2012 May;32(5):1627-37.
- Inhibits P-glycoprotein expression via the NF-κB pathway through AMPK activation. Br J Pharmacol. 2010 Nov 3. doi: 10.1111/j.1476-5381.2010.01101.x.

Metformin in cancer prevention

- Dr. Dario Alessi's research (U. of Dundee) involving data from patient records over ten years, have shown that patients on metformin showed anywhere between a 30-40% protection against all forms of cancer, compared to diabetics not on metformin. Diabetics on metformin show lower cancer incidence than non-diabetics.

Metformin with neoadjuvant chemotherapy for breast cancer

- MDA: 2,529 women with early-stage breast cancer . Of these patients, 68 were diabetic but not taking metformin and 87 were diabetic and taking the drug. The researchers found that the pathologic complete response (pCR) rates in the breast cancer patients taking Metformin was 24 percent, vs 8% in those not on metformin.

Metformin candidates

- Metformin can be safely given as an off-label adjunctive treatment in cancer patients, especially breast, ovarian, colorectal, prostate, pancreas and perhaps in glioma patients who have Type 2 diabetes, metabolic syndrome, elevated circulating insulin levels, or are obese, or even simply those who cannot or do not adhere to a low carb low fat diet.

Gossypol

- Polyphenolic compound from seeds, stem, and roots of cotton plant, being developed as a male contraceptive. Available thru compounding pharmacies.
- Anti-cancer activity in animals reported from Russia in the 1960s

Gossypol (cont'd)

- Gossypol promotes apoptosis of breast, bladder, lymphoma, leukemia (CML and CLL), myeloma, prostate, colorectal, alveolar cell lung, glioma, pancreas, melanoma, nasopharyngeal, and head and neck squamous cell cancers. A preponderance of the research reported on efficacy against hematologic cancers and prostate cancer.

Gossypol activities

- Besides direct anticancer action, it enhances anti-tumor activity of chemotherapy against lymphoma, modulates multi-drug resistance gene expression in human breast cancer cells, and enhanced breast cancer sensitivity to Tamoxifen as well as Adriamycin.

Gossypol clinical evidence

- Phase I/II clinical trial of Gossypol against refractory metastatic breast cancer was carried out at MSKCC (Van Poznak C, et al. *Breast Cancer Res Treat*, 66:3, pp. 239-248). Doses were in the 30-50mg per day range with 30% of patients experiencing fatigue, 15%, nausea/vomitting, and diarrhea in 10%. Antitumor activity was seen with a 15% response/stability rate.

In Phase I and Phase II trials, AT-101 has demonstrated single-agent cytoreductive activity in several cancers, including chronic lymphocytic leukemia (CLL), non-Hodgkins lymphoma (NHL), and prostate cancer. Phase II combination trials were conducted in several cancers, including hormone-refractory prostate cancer and non-small cell lung cancer (with Taxotere® [docetaxel]), B-cell malignancies (with Rituxan® [rituximab]), small cell lung cancer (with Hycamtin® [topotecan]), glioma (with Temodar® [temozolomide], +/- radiotherapy) and esophageal cancer (with docetaxel, 5-fluorouracil and radiotherapy).

Gossypol: Summary

- This is a fairly low toxicity and inexpensive natural derivative that can be used in combination with chemotherapy or other anti-apoptotic agents for a wide-range of cancers but appear especially promising for prostate, breast and B-cell hematologic malignancies. The main concern here is side-effects which include fatigue, nausea/vomitting, diarrhea, and ileus.

Gossypol: Summary (cont'd)

- Side-effects can be managed by individualized dosing and schedule adjustments. The long-term concern of infertility in males should be considered in young male patients. The lack of bone marrow suppression makes it a good agent to combine with chemotherapies.

Statins

- As a class, statins have diverse biological effects including improving endothelial function, stabilizing atherosclerotic plaques, attenuating oxidative stress and inflammation, immuno-modulation, as well as inhibiting the thrombogenic response. Many of these actions are executed via modulation or inhibition of post-translational protein prenylation/isoprenylation.
- immunomodulatory, antiangiogenic and anti-inflammatory effects of statins all contribute to anti-cancer potential

Statins

- In the early 2000s, there was actually a concern that statin use may be associated with an increased risk of cancer, but analyses of several large statin studies in cardiovascular diseases dispelled the concern. Human studies can be generally divided into the use of statins as a chemopreventive to prevent cancer or as an adjuvant to treat actual cancer. While a lot of effort in terms of direct studies and meta-analyses have been devoted to finding a correlation of statin use and cancer incidences, and while risk reductions of 48% – 90% were found for breast, colon and prostate cancers in retrospective case-control studies, these are by no means a final reliable statistic.

Statins-br ca prevention

- Breast Cancer, primary prevention: In a review by Kochhar and team of 40,421 females, statin use was associated with a 51% risk reduction of breast cancer after controlling for age, smoking, alcohol use, and diabetes (J Clin Oncol 23: 7S, 2005 [suppl, abstr 514]).
- Secondary prevention: Kwan et al. observed that breast cancer patients who took statins after diagnosis were less likely to have had recurrences than were patients who did not take statins (Breast Ca Res Treat. 2008 Jun;109(3):573-9).
- In 2008, Kumar et al. made the interesting observation that women on statins who develop breast cancers develop less aggressive cancers which are of lower grade and less invasive (Cancer Epidemiol Biomarkers Prev. 2008 May;17(5):1028-33.)

Statins-breast ca Rx

- Garwood et al. from UC San Francisco performed a perioperative ‘window’ trial of fluvastatin in 40 women with a diagnosis of DCIS or stage 1 breast cancer. Patients were randomized to high dose (80 mg/day) or low dose (20 mg/day) fluvastatin for 3-6 weeks before surgery and the research team found that the short treatment caused measurable favorable biologic changes by reducing tumor proliferation in high-grade, stage 1 breast cancer but not DCIS (Breast Ca Res Treat. 2010 Jan;119(1):137-44).

Statins-potential synergy with anti-cancer agents

- Statins may influence the efficacy of many other anti-cancer or potential anti-cancer agents, either via biological synergism or by affecting the blood levels of some agents. Although most of the studies represent *in vitro* work, such insights set a potential foundation for rational planning of a cocktailed approach against cancer. Some representative research illustrating statin synergy potentials are as follows:

Statins-potential synergy with anti-cancer agents (cont'd)

- - potentiates sorafenib (Nexavar) cytotoxicity (Cancer Lett. 2010 Feb 1;288(1):57-67)
- - synergizes with , the cox-2 (Celebrex) inhibitor, against colon cancer (Int J Oncol. 2009 Nov;35(5):1037-43; also Int J Cancer. 2010 Feb 15;126(4):852-63)
- - synergizes with sulindac (NSAID) against colon cancer (Gastroenterology. 1999 Oct;117(4):838-47)
- - synergizes with gamma tocotrienols against breast cancer (Exp Biol Med (Maywood). 2009 Jun;234(6):639-50)

Statins-potential synergy with anti-cancer agents (cont'd)

- - synergism with paclitaxel (Taxol) chemotherapy in K52 and HL60 cell lines (Mol Cancer Ther. 2001 Dec;1(2):141-9)
- - potentiates cisplatinum against MmB16 melanoma in rodent model (Gastroenterology. 1999 Oct;117(4):838-47)
- - potentiation anti-tumor effects of pamidronate (bisphosphonate) in vitro and in vivo (Int J Oncol. 2007 Jun;30(6):1413-25)

Statins-potential synergy with anti-cancer agents (cont'd)

- - synergizes with zoledronic acid (Zometa, a bisphosphonate) against myeloma (Anticancer Drugs. 2006 Jul;17(6):621-9)
- - enhances trastuzumab (Herceptin) in breast cancer cell lines (Breast Cancer Res Treat. 2007 Jul;104(1):93-101)
- - potentiates the effect of saquinavir against Daudi and Raji human lymphoma cells (Oncol Rep. 2004 Dec;12(6):1371-5)
- - synergism with tamoxifen (Cardiovasc Res. 2004 Nov 1;64(2):346-55)

Statins- summary

- Notwithstanding occasional contradictory reports of statins increasing the risk of cancer, given the safety (simvastatin is available as an OTC in the U.K.) and low cost of statins, plus the wide array of studies and accumulating data showing a protective effect of statins against cancer development and recurrence, statins should be seriously considered as part of a cocktailed approach for primary and secondary cancer prevention (especially for colon, breast, lung and prostate – where the data are strongest).

Statins-summary (cont'd)

- Statins should also be seriously considered as a cornerstone ingredient to combine synergistically with other compounds such as gamma tocotrienols, cox-2 inhibitors, bisphosphonates etc for added effects in cancer treatment. Not all statins are the same however, and some (e.g. lipophilic statins such as simvastatin) may work better against certain cancers than others (e.g. hydrophilic statins such as pravastatin). Dosage may be important as well.

Statins-summary (cont'd)

- Unfortunately, because most of the statins have patents that are expired or near expiration, there is a lack of incentive on the part of drug companies to conduct large scale clinical trials using these agents against cancer, so it is not clear that we will gain much more useful clinical insight in the near future, but strong reasons to consider adding statins to most cancer preventative or treatment cocktails unless side-effects are an issue in an individual patient.

Amino-Bisphosphonates as anti-cancer agents

- Aredia (pamidronate disodium) Zometa (zoledronic acid) Fosamax (alendronate) Actonel (risedronate) and Boniva (ibandronate)
- It was originally thought that bisphosphonates are useful in bone metastases because of the ability of these agents to inhibit bone resorption; newer understanding leads us to knowledge that these drugs are really direct anti-cancer agents as well

Amino-bisphophonates

- Inhibit farnesyl pyrophosphate synthase, a key enzyme in the mevalonate pathway, in turn inhibiting the prenylation of small G-proteins such as Ras, Rap1, Rho and Rab, reduces the signals they mediate, and thereby prevents the growth, adhesion/spreading, and invasion of cancer cells.

Amino-bisphosphonates (NBPs)

- Cause direct cell cycle disruption and induce apoptosis.
- This direct apoptotic effect of NBPs such as Zometa has now been reported in breast, prostate, myeloma, leukemia, colon cancers. Moreover, NBPs also independently inhibit cancer cell invasiveness, and exert anti-angiogenic effects as well via a variety of potential mechanisms.

NBPs-limitations of current formulations

- half-lives of the drugs are very short in the blood (no more than an hour or two), the maximum concentration achieved is also up to 100 fold less than what was demonstrated to cause cancer apoptosis (self-destruction) in the test tube experiments, although concentrations are adequate for anti-invasive effects. These drugs tend to concentrate in the bones though, which explains why they are effective for controlling cancer metastatic to the bone.
- Further potential may lie in strategies such as encapsulating the NBPs in liposomes and exploiting the NBP's synergisms with other agents.

NBPs- synergy with other agents

- NBPs have been reported to be synergistic with various cytotoxic agents, cox-2 inhibitors, imatinib, bortezomib, rapamycin, ATRA (retinoic acid), thalidomide, histone deacetylase inhibitors (HDACs), and interferon beta on growth inhibition.
- Also have immunomodulatory properties-stimulating and expanding cytotoxic gamma-delta T lymphocytes--NBPs combined use with low dose Interleukin 2 (IL-2) to induce gamma-delta T cells as immunotherapy against a variety of cancers

NBPs--summary

- direct anticancer can be broadened to more cancer types as primary treatment used in a combinatorial manner if the latest research on gamma-delta cell therapy is confirmed and its combined use with other potentially synergistic agents should be actively explored.
- Based on principles of molecular action, MMP inhibitors such as the tetracyclines and statins should be synergistic with NBPs as well. Baulch-Brown from Australia already demonstrated Zometa synergism with Lescol (Fluvastatin) against myeloma in vitro
- (Leuk. Res.. 2007 Mar;31(3):341-52), and similar results were obtained with Zocor by a German group (Anticancer Drugs. 2006 Jul;17(6):621-9). BPH-715 is 200x more potent as an anti-cancer than current NBPs.
- current research seems to point to Zometa as being more powerful but it has to be administered parenterally. Ibandronate (Boniva) is worth exploring for application because it can be given orally and has a better safety profile, although less data is available

Adjuvant Clodronate for breast cancer

- In a pioneering double-blind controlled study of Clodronate in treating breast cancer metastatic to the bone, Canadian researchers Paterson et al. (1993) noted reduced bone-related morbidity in treated patients and recommended that Clodronate be further investigated for potentially reducing bone metastasis as an adjuvant treatment for those who are at risk

Adjuvant Clodronate for breast cancer

- Diel et al. (1998) from the University of Heidelberg published a landmark trial in the New England Journal of Medicine on the subject and found in the 302 patient randomized trial that adjuvant clodronate at 1600 mg a day reduced not only bone metastases in breast cancer, but reduced other organ metastasis as well as the risk of death.

Adjuvant Clodronate for breast cancer

- Subsequently, a Finnish study published in 2001 unexpectedly showed a decrease in survival in clodronate treated breast cancer patients, thus confounding the topic. With accumulating evidence in favor, the FDA issued an approvability letter in 2005 for the use of clodronate as an adjuvant treatment in breast cancer.
- Finally in 2006, a larger randomized double-blinded placebo controlled multi-center study of over one thousand patients over 5 years confirmed reduced skeletal metastasis as well as possibly favorable survival in breast cancer patients (esp those with Stage II or III disease rather than Stage I) receiving clodronate as adjuvant over the initial 2 years.

Adjuvant Clodronate for breast cancer

- the drug is not commercially available in the US and not FDA approved despite its approvability, and these all hinder more wide-scaled use of the drug.
- unlike other bisphosphonates, the risk of ONJ with clodronate is extremely low at 0 – 0.5% (rare cases reported only) after taking it for 2 years (see Mayo Clin Proc 2007; 82:516-522)

Adjuvant Clodronate for breast cancer- summary

- Given some of the favorable trial results above and the very safe and relatively inexpensive (under $200 per month from Canada) nature of the drug, in addition to its benefit in reducing bone loss in breast cancer patients simultaneously receiving anti-estrogen therapy, Clodronate may be seriously considered as adjuvant treatment for Stage II and III breast patients.
- It is not available in the US, but can be obtained from Canada, Mexico, Europe and Asia. Newer generation bisphosphonates may have more potent anti-cancer potential, but this is as yet unknown.
- There is an ongoing SWOG clinical trial of oral clodronate vs oral ibandronate vs IV zometa post treatment of stages I, II, or III breast cancer, started 2005, planned to end 2015.

Gamma-Delta T-cell Immunotherapy (amino-bisphosphonates+IL-2)

- **γδ T cells** or "gammadelta" T cells are unique to primates and represent a minority white cell in our blood (0.5-5%); yet they play an essential role in sensing 'danger' by invading pathogens as they expand dramatically in many acute infections and may be a key fighter in cancer as well.

G-D T-cell immunotherapy

- mammals have two innate immune defense systems: an *adaptive immune system* unique to vertebrates in which lymphocytes participate with recognition of peptide antigens and which can be defined by memory of the target; and a more ancient *innate immunity* which is cell based (macrophages, monocytes, NK cells, NKT cells, dendritic cells) and *which has no memory* once demobilized.
- The gammadelta cells can be thought of as unconventional T cells at the interface between and linking the two immune systems, and contribute to the elimination of infections or cancers by direct and indirect killing as well as modulation and stimulation of other immune cells (eg macrophages and NK cells) and the secretion of cytokines, notably interferon gamma and TNF-alpha.

G-D T-cell immunotherapy

- Gammadelta cells share with alphabeta T cells certain functions such as cytokine production and potent cytotoxic (cell killing) activity but **gammadelta cells recognize different sets of antigens**, usually in a non-MHC-restricted fashion, and cancers are highly susceptible to gammadelta T-cell mediated lysis which led to the proposal that gammadelta T cells can be used for cancer immunotherapy (See Kabelitz D, *Potential of human gammadelta T lymphocytes as immunotherapy for cancer*, Int J Cancer 2004 Dec 10;112(5):727-32).
- Unlike conventional T lymphocytes which recognize peptide antigens, this "alternative" T cell's ability to recognize tumor cell ligands not seen by conventional alphabeta T cells is one property that makes them intriguing. The other unique property is the way they recognize antigens circumvents the ability to of cancer cells to eventually elude detection.

G-D T-cell immunotherapy

- most epithelial tumors (including melanomas, pancreatic adenocarcinomas, squamous cell carcinomas of the head and neck, and lung carcinoma – See Scan J Immunol, 2007;66(2-3):320-8) were susceptible to allogeneic gammadelta T-cell lysis and in the case of an established ovarian carcinoma, to autologous gammadelta T-cell killing

- efficient killing of cancer stem cells by gammadelta T cells (Todaro M, et al. J Immunol. 2009 Jun 1;182(11):7287-96).

G-D T-cell immunotherapy

- Pioneering work by the Italian team Casetti et al. elegantly demonstrated that **co-stimulation simply with interleukin 2 plus amino -bisphosphonates induced up to 100-fold increases in the numbers of peripheral blood Vgamma9Vdelta2 T cells in animals**.
- Together with a German team led by Wilhelm et al. this laid the ground work for subsequent clinical endeavors in this field (Casetti R et al. Drug-Induced Expansion and Differentiation of V 9V 2 T Cells In Vivo: The Role of Exogenous IL-2, J Immunol 2005;175(3):1593-8).

G-D T-cell immunotherapy

- In 2005, Bennouna et al. presented a phase I trial of 18 BrHPP (Phosphostim) and low dose IL-2 treated patients with solid tumors in a poster session at ASCO (JCO, 2005; 2005 ASCO Annual Meeting Proc 23(16S), Pt II of II:2536).

G-D T-cell immunotherapy

- The same team from Palermo also reported positive results in a small trial in May of 2010 of using zoledronic acid with low dose IL-2 in 10 “therapeutically terminal, advanced metastatic” breast cancer patients. Treatment was well tolerated and there was a statistically significant correlation of clinical outcome with peripheral Vgamma9Vdelta2 T cell numbers, with three patients who sustained robust peripheral Vgamma9Vdelta2 cell populations after treatment responding with declining cancer markers and partial remission or stable disease (Meraviglia S, et al. Clin Exp Immunol. 2010 May 10)

G-D-T-cell immunotherapy

- *British Journal of Cancer* (2011) **105**, 778–786. doi:10.1038/bjc.2011.293
- **Background:**
- Adoptive transfer of *ex vivo* expanded autologous Vγ9Vδ2 T cells may be of therapeutic benefit for cancer because of their potent direct cytotoxicity towards tumour cells, synergistic cytotoxicity when combined with aminobisphosphonates and enhancement of antibody-dependent cell-mediated cytotoxicity.

G-D-T-cell immunotherapy

- **Methods:**
- To determine the feasibility and clinical safety of therapy with *ex vivo* expanded, activated Vγ9Vδ2 T cells in combination with zoledronate, we enrolled 18 subjects with advanced solid tumours into a phase I clinical study. Administered indium^{111}-oxine-labelled Vγ9Vδ2 T cells were tracked in a cohort of patients.

G-D-T-cell immunotherapy

- **Results:**
- Administered Vγ9Vδ2 T cells had an activated effector memory phenotype, expressed chemokine receptors predictive of homing to peripheral tissues and were cytotoxic *in vitro* against tumour targets. Adoptively transferred Vγ9Vδ2 T cells trafficked predominantly to the lungs, liver and spleen and, in some patients, to metastatic tumour sites outside these organs. No dose-limiting toxicity was observed, but most patients progressed on study therapy. However, three patients administered Vγ9Vδ2 T cells while continuing previously ineffective therapy had disease responses, suggesting an additive effect.

G-D-T-cell immunotherapy

- **Conclusion:**
- Therapy with aminobisphosphonate-activated Vγ9Vδ2 T cells is feasible and well tolerated, but therapeutic benefits appear only likely when used in combination with other therapies.

G-D-T-cell immunotherapy-summary

- the ability to use fairly straightforward medicines such as the amino-bisphosphonates and interleukin-2 off-label to dramatically expand these cells in a patient without serious side-effects opens the way to a practical immunotherapy. The fact that there is laboratory data showing efficacy against leukemia/myeloma and also human experience which is positive for some solid tumor (prostate, breast, lung and kidney) cancer types gives hope that this treatment can be broadly deployed against an array of cancers, both hematologic and solid tumors. Research finding that the therapy can efficiently kill cancer stem cells is also exciting. Very likely most effective with very low disease burdens.

Ursodeoxycholic acid (Actigall, URSO) for chemoprevention

- Ursodiol or Ursodeoxycholic (Actigall, URSO) is a naturally derived bile acid that decreases the amount of cholesterol produced by the liver and absorbed by the intestines. Interestingly, ursodiol is found in large quantities and the major therapeutic ingredient in bear bile, which is an established if controversial member of traditional Chinese medicine's pharmacopoeia.
- Ursodiol helps break down cholesterol that has formed into stones in the gallbladder and is also hepatoprotective. Ursodiol also increases bile flow, which is why it is useful in cholestatic conditions such as biliary cirrhosis. Since the 1980's, Urso has been in widespread clinical use for biliary conditions.

Off Label Pharmaceuticals for Cancer

Agent	Therapeutic Daily Dose
Celebrex	200-400 mg. (<COX-2)
Rapamycin	1 - 2 mg. (<mTOR/PI3K)
Tetrathiomolybdate (TM) (Tetracycline antibiotics also anti-angiogenic)	40-200 mg. (copper chelator) Minocycline 200 mg bid Doxycycline 100 mg bid
Noscapine	500-2000 mg. (anti-mitotic, microtubule-interfering agent)
Disulfiram	125- 250 mg. (multi anti-cancer)
Valproic acid	500-750 mg. (<HDAC)

Off Label Pharmaceuticals for Cancer Cont'd…

Agent	Therapeutic Daily Dose
Hydroxychloroquine	400-800 mg. (<CXCR4)
LMW Heparin	(anti-thrombotic/anti-angiogenic)
Baclofen	5 mg. bid (>GABA, antagonist to β-adrenergic cascade) Liver/pancreatic/breast cancer
Naltrexone (Low-dose)	1.5 to 4.5 mg at bedtime (opioid antagonist, upregulated the expression of the opioid growth factor & its receptor) Ovarian cancer
3-Bromopyruvic Acid and sodium dichloroacetate	Inhibits Glycolysis

Celebrex (COX-2 inhibitor)

- Celebrex (celecoxib), is a promising chemopreventive Arber et al.: N Engl J Med 2006;355:885-895; Bertagnolli et al.: N Engl J Med 2006;355:873-895
- Besides down-regulating COX-2, celebrex selectively affects genes & pathways involved in inflammation and malignant transformation in tumors. Digestion 84 (3), 169-184 (May 2011)
- Botanical and Nutritional co-administration can significantly improve response. Curcumin, ginger, boswellia, andrographis, Chinese Skullcap, bromelain, addition of B-6, Magnesium, and Zinc as well.
- Celebrex often effective for cancer-related pain relief, especially for bone metastases.
- DOSE: 100-200 mg. 2x daily, which can be taken with Cimetidine 200-400 mg.)-Don't use in sulfa allergic pts!

Celebrex

- **Synergist with Herceptin & EGFR Targeting Drugs**

  Mediates antitumor effects through the inhibition of PI-3/Akt signaling independently of COX-2. Mol Pharmacol. 2006 Nov;70(5):1534-41. Epub 2006 Aug 3.
- Enhances the anti-cancer effects of xeloda while reducing side effects (esp hand-foot syndrome). J Cancer Res Clin Oncol. 2010 Nov 27.
- Curcumin and celebrex synergistically inhibit cancer. Digestion. 2006;74(3-4):140-4. Epub 2007 Jan 15.
- N-3 fatty acids (EPA/DHA) are also synergistic with celebrex (Nutr Cancer. 2007;59(1):14-20. J Periodontol. 2008 Oct;79(10):1934-4)

Rapamycin
(Antibiotic-soil Organism from Easter Island)

- Targets mTOR (mammalian target of rapamycin), which has a direct linkage to the phosphatidylinositol-3'-kinase (PI3K)/PTEN-AKT (serine/threonine-specific protein kinase) survival pathway (Int J Oncol. 2004 Apr;24(4):893-900)
- PI3K-AKT-cells that express the active form of AKT are sensitive to rapamycin
- Synergistic with EGF receptor inhibitors against non-small-cell lung, pancreatic, colon, and breast tumors. (Int J Biochem Cell Biol. 2008 Jul 23)

Rapamycin (continued)

- Grapefruit doubles the bioavailability (via inhibition of small intestinal 3A4) - can use half dosage - less drug, less cost, and less toxicity without losing effectiveness (100th Annual Meeting in Denver in a session on "Late-Breaking Research: Clinical Research 1: Phase I-III Clinical Trials," Poster Section 27on April 20, 2009)

Rapamycin
Synergistic with Herceptin

- With herceptin, significantly increased anti-tumor efficacy compared to either drug alone in Her II neu over expressing breast cancer cells. (Int J Cancer. 2007 Jul 1;121(1):157-64, Breast Cancer Res 2005, 7, Urology. 2007 Mar;69(3):596-602.:41-42)
- Many cancers that over-express Her II neu and PI3K also over-express EGF (Her I), and may respond better to the multi-kinase Her I and II inhibitor, **Tykerb (Lapatinib),** which is the first Her II neu targeted drug to be validated in a preclinical model for activity against Her-2+ brain metastases of breast cancer. (J Natl Cancer Inst. 2008 Aug 6;100(15):1092-103. Epub 2008 Jul 29)

Rapamycin
Synergistic with Herceptin (continued)

- The loss of PTEN activates PI3K - mTOR, so PTEN regulation is also key in Her II neu cancers. (Biochim Biophys Acta. 2008 Mar 4, Gynecol Endocrinol. 2008 May;24(5):239-49.)

Rapamycin Fed Late in Life Extends Lifespan in Mice

- Inhibition of the TOR signaling pathway by genetic or pharmacological intervention extends lifespan
- Extends median and maximal lifespan of both male and female mice when fed beginning at 600 days of age
- On the basis of age at 90% mortality, rapamycin led to an increase of 14% for females and 9% for males.
  (Nature 460, 392-395, 16 July 2009)

Chloroquine & chemotherapy

- Chloroquine potentiates the anti-cancer effect of 5-fluorouracil BMC Cancer. 2010 Jul 15;10:370.
- Chloroquine sensitizes breast cancer cells to chemotherapy Autophagy. 2012 Feb 1;8(2):200-12. Epub 2012 Feb 1.
- Hydroxychloroquine enhances TKI against CML August 2011, Vol. 4, No. 4, Pages 369-371 , DOI 10.1586/ehm.11.34
- Hydroxychloroquine enhances TKI Tarceva against NSCLCa. J Thorac Oncol. 2012 Aug 8.

Tetrathiomolybdate

- In cancer patients has shown to reduce the serum levels of Interleukin (IL)-6, IL-8, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) http://clincancerres.aacrjournals.org/content/9/5/1666.log
- TM lowering of Cp also inhibits NFk-B. Lowering Cp to low normal range during chemotherapy can improve chemosensitivity. TM increases platinum uptake by ovarian cancer cells.
- Lowering Cp <15 after obtaining CR and maintaining for 3 years induces angiogenic blockade, and subsequent tumor (and tumor stem cell) dormancy of some sort.

Noscapine (Opium alkaloid)

- Commonly used antitussive agent available in Europe, Asia, and South America.
- A tubulin-binding agent, increases the time that cellular microtubules spend idle in a paused state
- Inhibits Bcl-2 expression
- Crosses the blood-brain barrier

Noscapine

- Noscapine was able to inhibit cancer at doses which produced little or no toxicity, including no adverse effects on the primary immune response (Ke Y et al. Cancer Immunol Immunother. 2000 Jul;49(4-5):217-25). More recently, Newcomb et al. from New York also demonstrated potential anti-angiogenic activity of Noscapine as an alternate anti-cancer mechanism (Int J Oncol. 2006 May;28(5):1121-30)

Noscapine

In Vivo

- Noscapine inhibits murine lymphoid tumors, human breast and bladder in nude mice murine (Ye, 1998), prolonged survival in melanoma (Landen et al. Cancer Res. 2002 Jul 15;62(14):4109-14), crosses the blood brain barrier and inhibited implanted C6 glioma in the rat model (Landen, Clin Cancer Res. 2004 Aug 1;10(15):5187-201), and has potent anti-cancer activity in the non-small cell lung cancer model Cancer Chemother Pharmacol. 2008 Dec;63(1):117-26).

Noscapine-summary

- Potentially useful against CLL leukemia/lymphoma/myeloma, prostate cancer, non-small cell lung cancer, glioma (administered alone or in combination with chemo and/or radiation to enhance cytotoxicity), hormone resistant breast cancer, or perhaps co-administered with taxanes.
- Distinct advantages include i) oral bioavailability, ii) encouraging experimental data, iii) low toxicity, iv) low cost, and v) synergistic potential with other modalities and drugs.