



# Breast Cancer Update

Issue 59 February 2008

- Breast Cancer Symposium Report
- HER2 Testing
- ICS Initiatives
- ANZ BCG Trial Activation Status and Accrual Reports



# BREAST CANCER UPDATE

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This newsletter is produced by The Cancer Council Victoria's Breast Cancer Committee and sent to health professionals interested in management of breast cancer(s). The Victorian Cooperative Oncology Group's advisory committees on breast, gastrointestinal, gynaecological, head & neck, lung, skin and urological cancers also produce twice yearly cancer updates.

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\*\*\*\*\* **Last Issue – No. 58 – July 2007** \*\*\*\*\*

***The articles in the Breast Cancer Update have been published to contribute to professional debate and exchange. The opinions expressed are not necessarily those of The Cancer Council Victoria.***

## Editorial

*Dr Jacquie Chirgwin  
Medical Oncologist  
Box Hill / Maroondah Hospitals*

In welcoming you to our January Breast Cancer Newsletter, I would like first to pay tribute to the wonderful work and support for VCOG that Susan Fitzpatrick has provided over many years. It has always been a pleasure to work with her and she has personally provided me in many ways with wise words of advice in many areas. It is very sad to see her leave the Cancer Council, but I am sure she will shine in whatever she takes on next! My thanks and best wishes to her.

We have a somewhat slimmed down edition, this time. This is due to some unforeseen circumstances which have resulted in several of the planned articles being deferred. So we shall look forward to these next time – they include a report of the issues experienced by young women with breast cancer, and a report on a rehabilitation program for patients recovering from adjuvant treatment for early breast cancer.

We do have some interesting articles, including a summary by Stephen Fox, on the complexity of HER-2 testing. Elise Davis has summarized the work that the ICS are undertaking in Breast Cancer, and I have written a long (my apologies) article on the San Antonio Breast Cancer Symposium, December 2007. I continue to think these summaries provide an excellent method to keep everyone up to date with the latest breast cancer results and controversies. I am very

keen for our advanced trainees to routinely write these articles, as I believe it contributes to the value they experience in attending these large international meetings. I am therefore asking that you nominate your trainee if you know they are attending an important breast cancer meeting. Please contact me by e-mail to let me know: [chirgwin@tpg.com.au](mailto:chirgwin@tpg.com.au) In the July issues we will have reports on the EBCC meeting in Berlin, the IBCSG meeting that follows this in Budapest, ASCO and the ANZ BCTG 30<sup>th</sup> Anniversary meeting being held in Wellington, New Zealand. With regard to this last meeting, I can particularly recommend it (I have been a member of the steering committee); I know there are to be some fine celebrations as well as high quality invited speakers.

I also recommend to you the various small reports on a diverse range of breast cancer related topics that are reprinted from elsewhere – NBCC, TCCA, COSA, Wongi Yabber etc. These little snippets also go a long way towards keeping you well posted on what is going on around the traps!

As always, I am very keen to receive articles on topics you think will be interesting for the readers – please e-mail to me; the deadline for the next publication is 31<sup>st</sup> July.

Regards

Jacquie

### Contributions Welcome

The Breast Cancer Update welcomes contributions – conference reports, review of an area of interest, reviews of recent journal articles, clinical trial updates.

	<b>Deadline</b>	<b>Issue Date</b>
Mid-year issue	1 June	1 July
Year-end issue	1 November	1 December

Contributions should be forwarded to:

The Editor, Breast Cancer Update  
C/- Victorian Cooperative Oncology Group  
The Cancer Council Victoria  
1 Rathdowne Street  
CARLTON VIC 3053  
[vcog@cancervic.org.au](mailto:vcog@cancervic.org.au)

Susan Fitzpatrick has announced her decision to leave the Cancer Council after 24 years of service, first as assistant to Prof Dick Lovell and then, from 1997, as Executive Officer of VCOG/CCRC in her own right.

Susan learnt the job under a master and applied her exemplary organisational skills to the multitude of meetings, newsletters and other tasks involved in the most reliable way. She leaves VCOG in a healthy vibrant state, which we are committed to nurturing and growing in the future. VCOG is one of The Cancer Council's most important functions; it keeps us in close contact with clinicians, developments in treatment and with a hotline to the treatment system.

I'd like to thank Susan for all the work she has done over so many years to ensure that these links are strong and that VCOG members benefit from the relationship as much as The Cancer Council does.

I will continue to oversee the work of VCOG/CCRC and Dorothy Reading, Senior Strategic Consultant in my office will act as a point of contact.

Prof David Hill AM, PhD  
Director, Cancer Council Victoria

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## SAN ANTONIO BREAST CANCER SYMPOSIUM

### December 13<sup>th</sup> – 16<sup>th</sup> 2007

*Jacquie Chigion*

Melbourne's "four seasons in a day" habit clearly came with us to San Antonio. We arrived late evening to a sticky 27°C, concerned that T-shirts would have to be purchased the next day. Fortunately we awoke the next day to a wet and windy 9°C (which did not really improve for the rest of the week), much more suited to the contents of the suitcase. Indeed this morning, my last day here, is below freezing.

There seemed to be less new data this year, but there were still many many interesting posters and several overviews of concepts by some of the world's experts, which again just add that little further angle, facilitating that next round of innovations.

I will cover four main areas in this report:

- Some trial results/updates
- Bone density and AI's
- Some of the concepts and ideas
- Posters

#### Trial Results

#### **1. 100 month ATAC efficacy and safety results**

32 months have passed since the previous ATAC update. There are now 46,000 women years of follow up and 1704 events, an increment of nearly 40%. Compliance with Anastrozole was 88% and with Tamoxifen 87%. The mean

age of the population is now 72yrs.

The absolute disease free survival benefit of A vs T has increased from 2.8% at 68 months, to 4.8% at 100 months. The recurrence rate in the Tamoxifen arm is 21.8% vs 17% in the Anastrozole arm. This increasing separation of the curves, after treatment has been completed is the first demonstration of a "carryover" effect for an AI, as previously demonstrated in the 5 years after adjuvant Tamoxifen. The difference in time to distant recurrence is now also statistically significant (2.4% absolute benefit), as is a reduction in contralateral breast cancer (1.7% absolute benefit). Overall survival remains equivalent with a HR of 0.97, although there is a numerically lower number of deaths in the Anastrozole arm (351 vs 380).

There were no unexpected or concerning long term side effects. Although fracture rate was 30% higher during Anastrozole treatment (318 vs 211), this difference did not continue once treatment was ceased (103 vs 99). AMI and CVA were not statistically significantly different in the two arms (although the number of CVA's on Tamoxifen was slightly higher – 37 vs 21).

It was suggested that the lack of OS benefit was due to the fact that a survival benefit in this population may not be evident until after 10 yrs

of follow up (it took 10 yrs to demonstrate the OS benefit of Tamoxifen vs placebo), as well as the fact that the number of deaths from other causes is increasing as the ATAC population ages.

**2. ATLAS (at long last....?)**

This was presented by Richard Peto on behalf of Christina Davies who was unable to attend due to a back injury. It was accompanied by quite a lot of smoke and mirrors...

Initially a number of “excuses” for the data were noted:

- Only 59% of the population were known ER+; 41% were untested
- 2 yrs post randomization, compliance in the continued Tamoxifen arm was 83%, and 4% of the no treatment arm were taking Tamoxifen
- Due to these reasons, it was estimated that only around 72% of the “real” benefit of Tamoxifen could be expected to be demonstrated

Results were as follows (11,500women):

Years 5-9:	42,000 women yrs	1353 recurrences	3% annual rate
Years 10-14:	8,000 women yrs	211 recurrences	3% annual rate
Recurrences:	700 Tamoxifen	800 No Tamoxifen	
HR:	years 5-9	0.88	p=0.05
	years 10-14	0.77	p=0.12

It was noted that the initial recommendation to cease Tamoxifen after 5 years was based on small patient numbers –around 1600 pts in the ECOG, Scottish and NSABP B14 longer vs shorter adjuvant Tamoxifen studies, and it may be that this conclusion was premature. This is particularly relevant for premenopausal patients where extended AI treatment is not an option.

**3. TACT**

These are the first results of the UK adjuvant Taxotere study. There were 4,162 EBC (both node positive and negative, I believe although I have not documented this in my notes) patients enrolled, and they were randomized to all receive 8 cycles of chemo, including or not including Taxotere. The control arm was either (as chosen by centre) FEC x 8 (600/60/600 q 3 weeks) or Epirubicin x 4 (100mg/m2 q 3 wks) followed by CMF x 4 (100mg/m2 orally d 1-14 OR 600mg/

m2 iv d1 and 8/40/600 q 4 wks). The experimental arm was FEC x 4 followed by Taxotere x 4 (100mg/m2, q 3wks). Median follow up is 50 months, and 954 DFS events have occurred. 76% have achieved a dose intensity of over 85%. FN rate in the Taxotere arm was 8.3%, in the other arms 3.5%.

No DFS benefit has been demonstrated. 5 year DFS and OS are:

Control	74.7%	82%
Taxotere	73.9%	81.8%

However, for the subset HER2 +, ER -, the HR was 0.78 with confidence intervals 0.49 – 1.01. As with targeted treatment this again lends some evidence to the fact that chemotherapy regimens may also require “targeting” to subpopulations of breast cancer patients. Other reports at the meeting also questioned the need for anthracyclines in some patients.

**4. US Oncology trial 9735: TCyclo vs AC**

Updated results (median follow up 6.9.years) were presented, now showing an OS benefit for the TC arm. There was also an analysis of the 16% of patients over the age of 65 (median age 72, range 65-77), also demonstrating DFS benefit with acceptable toxicity.

1016 pts were assigned to either AC x 4 (60,600) or TC x 4 (75/600).

	TC	AC	P value	HR
DFS	85%	79%	0.018	0.69
OS	88%	84%	0.045	0.73
DFS < 65	88%	82%		0.64
DFS > 65	82%	85%		0.69
FN rate < 65	4.4%	2.3%		
FN rate > 65	7.7%	3.7%	NS (vs age)	

17% of patients had HER2 confirmed by FISH; DFS benefit of TC was seen for both HER2 positive and negative patients:

Her2 +ve	HR: 0.73 in favour of TC
Her2 -ve	HR: 0.56 in favour of TC

It is suggested there may be a synergy between Taxotere and Cyclophosphamide, and also that the dose of 75mg/m2 may be important, as a previous trial of AC vs AT with 60mg/m2 of Taxotere does not show a benefit.

This regimen is certainly an appealing one for patients with a contraindication to

anthracyclines, and potentially for some patients requiring Herceptin, in order to reduce cardiac toxicity.

### 5. BIG 1-98: value of centrally assessed Ki-67

Ki-67 is an established prognostic marker; it is less clear whether it has a role as a predictive marker for response to endocrine treatment. This study includes 2,685 (of the 4,922) pts in the monotherapy arms of the trial. Ki-67 labelling index was measured and divided at the median point.

Ki-67	N	4yr DFS	Treatment	4 yr DFS	HR	95%CI
Overall	2,685	89.1%	Let	91.8%	0.64	0.51-0.80
			Tam	86.5%		
0-11%	1,433	92.2%	Let	93.4%	0.82	0.58-1.16
			Tam	90.9%		
>11%	1,252	85.6%	Let	89.6%	0.54	0.40-0.72
			Tam	81.5%		

The STEPP analysis of these results clearly shows there is no benefit of letrozole over tamoxifen if the Ki-67 is below 11%. This holds true regardless of other tumour features such as HER2 status, T size, grade and nodal status. There is however an inverse relationship between Ki-67 and PR. These results are hypothesis generating, and will be further explored; however this may be a useful marker to determine which patients will benefit from upfront AI and which patients may be adequately treated on Tamoxifen alone.

### Bone Density and AI's

Results were presented for both Zometa and Denosumab indicating an abrogation of the bone loss caused by AI use. I have included summaries of the Z-Fast and ZO-FAST studies involving postmenopausal women treated with Letrozole, but also note that the same benefit was seen for the use of Zometa in the ABCSG 12 trial, a four arm study where premenopausal patients received goserelin plus tamoxifen or anastrozole with or without Zometa. An algorithm for management was also proposed in one of the posters.

### 1. Z-FAST

This is a North American study of 602 EBC patients treated with adjuvant Letrozole, randomized to receive either upfront Zometa (4mg iv q 6 months) or delayed Zometa (given when T score dropped below -2.0, or a clinical

fracture occurred). All patients were treated with vitamin D and calcium supplements. 36 months follow up is reported.

	Upfront (n=189)	Delayed (n=187)
Change in L spine BMD	+3.72%	-2.95%
absolute difference	+6.7%, p<0.001	
Change in hip BMD	+1.66%	-3.51%
absolute difference	5.2%, p<0.001	
Fractures	5.6%	6.3%
Disease recurrence	3%	4.7% p=0.24

15% of the delayed group required initiation of Zometa. There were no cases of ONJ and no issues with renal function in the patients receiving Zometa in either group.

### 2. ZO-FAST

This study was reported by Rick deBoer in a poster discussion session. The study included 1065 patients from UK, Europe and Australia. The design was as for the Z-FAST study, with pts who were receiving adjuvant letrozole randomized to receive upfront Zometa (4mg iv q 6 months) or delayed (if t score falls below -2.0 or a non-trauma fracture occurs). 24 month update was presented.

	Upfront (n=730)	Delayed (n=718)
Change in L spine BMD	+3.7%	-4.5%
absolute difference	+8.2%, p<0.0001	
Change in hip BMD	+1.7%	-3%
absolute difference	+4.7%, p<0.0001	
Fractures	13pts	17pts
Disease recurrence	21 pts	32pts

100 patients in the delayed group required initiation of Zometa. There were two cases of suspected ONJ in patients on Zometa, and 2 cases of renal failure (both in patients not receiving Zometa).

### 3. Denosumab

Bone loss is mediated by osteoclasts which depend on activation of RANK ligand. Denosumab, a monoclonal antibody to RANK ligand, is therefore potentially a useful agent for prevention or reduction of bone loss in patients receiving AIs. The study reported was a phase three, randomized double blind placebo controlled trial of Denosumab in patients receiving adjuvant AI's. 60mg Denosumab was given subcutaneously every 6 months for 4 doses. All patients were also given vitamin D and calcium supplements. All patients were already taking an AI and had evidence of bone loss (L spine BMD), but no patients had

osteoporosis at baseline.

	Denosumab (n=127)	Placebo (n=125)
Completed 24 months treatment	99	106
Increase in L spine BMD at 12 months	5.5%	
Increase in L spine BMD at 24 months	7.6%	
Preservation of baseline BMD at 24 months	95%	34% (p<0.0001)
Adverse events	91%	90%

None of the adverse events were considered to be treatment related. No effect on renal function has been demonstrated. Long term effects of denosumab are as yet unknown. The changes in BMD after the cessation of denosumab are also not yet known. These results do suggest that Denosumab is an effective agent in preserving bone density on AI's, and has the potential to improve it.

**4. Management algorithm**

ASCO guidelines state that patients with breast cancer with BMD <-2.5 (ie those who are osteoporotic) should receive bisphosphonate treatment. Those with osteopaenia (T score -1 to -2.5) should receive individualized treatment. BMD is clearly not the only indicator of fracture risk as the majority of fractures occur in patients with BMD better than -2.5. Poster number 504 (Hadj, Aapro et al) presented a systematic literature review to provide further evidence based information to use in constructing management guidelines.

The following risk factors for fracture were identified in breast cancer patients:

- AI treatment
- T score <-1.5
- Age >65
- Family history of hip fracture
- Personal history of fragility fracture after age 50
- Oral corticosteroid use, > 6 months
- Low BMI <20

Other risk factors, including the use of chemotherapy and smoking had insufficient data to be included.

The recommendations of the group, for patients on AI's were as follows:

- For patients with T score < -2.0
- For patients with any two of the following risk factors:

- T score <-1.5
- Age >65
- Family history of hip fracture
- Personal history of fragility fracture after age 50
- Oral corticosteroid use for greater than 6 months

Patients falling into these groups should all receive:

- Vitamin D and Calcium supplements
- Zometa 4 mg twice yearly

Concepts and ideas as presented by some world leaders

There are a number of topics that I will include, as I think they represent changing and new concepts:

- Richard Peto on the Overview
- Are Anthracyclines as useful as we have all thought?
- Insulin and IGF I receptors in breast cancer
- HER network targeting
- Breast Cancer Stem Cells and treatment

**1. The Overview**

Richard Peto presented data on the 15 yr local recurrence and overall survival benefit for postmastectomy radiotherapy for 1-3 node and 4 or more node positive patients:

	Node negative	1-3 nodes	4 or more nodes
LR	Rth	2.4%	5.3%
	No Rth	5.8%	24.7%
BC mortality	Rth		43.3%
	No Rth		50.9% p=0.002
Total mortality	Rth	41.3%	50.1%
	No Rth	37.4%	56.1%

For node negative patients at 15 years there is a reduced OS of 3.9% if they received radiotherapy. However, the absolute benefit for 1-3N+ is 5.3% and for N4+ is 6.2% in all cause mortality. These results are robust involving 30,000 randomised patients.

Further analysis of the benefit of 5 years of adjuvant Tamoxifen according to PR status was also presented. DFS at 10 years:

	5 yrs Tam	Control
ER/PR neg	No benefit	
ER -ve/PR +ve	32.4% (ie. no benefit)	33%
ER +ve/PR -ve	29%	44.6%
ER +ve/PR +ve	25%	38.4%

These results indicate that no additional information in relation to treatment benefit is

provided by the measurement of PR status. ( $p=0.74$ ). It also indicates that ER negative PR positive patients do not gain benefit from Tamoxifen, although previously it was considered that these patients did benefit.

Review of chemotherapy benefits indicate that ER does not influence the proportional benefit from chemotherapy. In addition, using the overview results of Taxane vs Anthracycline vs non-anthracycline chemo vs control, an estimate of Taxane benefit vs. nil is made, underscoring the value of many incremental **small** gains from adjuvant treatment:

Taxane vs Non-Taxane	RR		0.83
			$p=0.00001$
Taxane vs control	HR	Recurrence:	0.38
		Mortality:	0.46
			$p<0.00001$
(no difference noted for ER+ and ER-)			

## 2. Anthracyclines

Denis Slamon's presentation on the benefit of adjuvant anthracyclines suggests that it is likely only of value in those patients with over-expression of Topo IIA. This appears to be linked to HER 2 status, but occurs only in 35% of HER2 positive patients. Therefore, potentially only about 8% of all patients may benefit from Anthracyclines (versus non anthracycline chemotherapy); the exquisite sensitivity of these cancers has been sufficient to drive the overall benefit seen in adjuvant anthracycline trials to date. This conclusion is based on the meta-analysis of 6 trials showing that HER 2 positive patients only, benefit from the addition of Anthracycline; HER 2 positivity itself, however, is not responsible for this sensitivity, as shown by the addition of HER2 overexpression in MCF 7 cells. This analysis therefore suggests that there may be no benefit of anthracycline versus non-anthracycline chemotherapy in a surprisingly large proportion of patients – at least 75%, if not more.

## 3. Stem Cells

Several presentations and posters addressed the concept of stem cells, including as a target of treatment. The difference between normal stem cells and cancer stem cells remains unclear. However, it is clear that cancer stem cells are relatively resistant to chemotherapy and radiotherapy. This has been demonstrated in studies examining the proportion of stem cells in biopsies before and after treatment – one

study of 35 patients treated with chemotherapy pre-operatively demonstrated a 5 to 15% increase in stem cells, as assessed by the "mammosphere" assay, a measure of self renewal. A study using Lapatanib followed by Trastuzumab as neo-adjuvant treatment demonstrated a 50% reduction in size following 6 weeks of Lapatanib; after a subsequent 12 weeks of Trastuzumab size reduction was 82%. The tumorigenic population reduced in this time from 18.4% to 5.5%. It is likely therefore that the targeted treatments may be appropriate candidates as stem cell inhibitors.

## 4. Trastuzumab Resistance

Kent Osborne presented a fascinating talk on Trastuzumab resistance mechanisms, and went on to suggest methods to overcome this that may provide a leap forward in treatment efficacy for HER 2 positive breast cancer.

The HER network provides proliferation and survival signals to a subset of breast cancer. It is a multilayered system, with the input layer of 4 receptors (HER 1 to 4); there are 11 ligands, signaling pathways from membrane to nucleus and the output layer of transcription factors and the genes they regulate; there are also feedback circuits that control these functions. Both ER and IGFR can activate the HER receptors and pathways.

Trastuzumab resistance, either de novo or acquired occurs in the majority of HER 2 positive breast cancers, probably due to a variety of mechanisms. In particular, other HER receptors and dimmers may circumvent the HER2 blockade. Combination targeted treatments show promise in treating these cancers: an MCF 7, HER 2 positive cell line was permanently suppressed by the combination of Tamoxifen, Pertuzumab (blocks any dimerisation of HER2), Trastuzumab and Gefitinib. The interaction of ER in this system is of interest also; oestrogen deprivation may be more effective in preventing upregulation of the ER than tamoxifen; there is also the question as to whether ER blockade may be needed in initially ER negative cancers.

### Posters

#### 1. Neulasta: posters 1090 and 2063

How should we be using Neulasta in breast cancer patients? Cost is an important factor, and if we can identify the patients most likely to benefit, as well as minimize the cost per dose, we can certainly do a lot better than at present –

and perhaps PBS listing may be able to be more appropriate. Here are two interesting small studies that may begin to help in this regard.

Jenkins et al, from Birmingham UK, have demonstrated that pretreatment neutrophil and lymphocyte counts are predictive of subsequent dose reductions and risk of receiving suboptimal dose intensity. They studied 360 patients who received adjuvant FE(60mg/m<sup>2</sup>)C. 21% of patients received dose intensity <85%. The rate of FN was 9%, and dose reductions 29%. No growth factors were used. 4 risk groups were identified using the cutoffs of ANC 4.1, and ALC 2.0; those with both below these cutoffs had a 36% chance of suboptimal dose intensity. Baseline counts therefore may be useful in identifying patients who will benefit from upfront Neulasta.

Bartelt et al from Cincinnati, Ohio demonstrated that a dose of 3mg Neulasta provided similar efficacy to the 6mg dose, with reduced toxicity. They studied 34 patients receiving adjuvant TAC. There were no episodes of FN in either group; infection rate was 5.1% vs 6% (6 vs 3mg dose). There was less bone pain ( $p=0.02$ ) and no hypergranulocytosis in the 3 mg treated patients.

## **2. Gene signatures in 1-3 node positive patients: poster 1064**

We know from statistics and personal experience that there are clearly very good prognosis patients included in the node positive subset of patients as well as the node negative group. Gene signatures may well be an appropriate way to identify these patients in addition.

Mook et al have shown that the Amsterdam 70-gene signature also predicts outcome for the 1-3 positive node patients. 106 patients were included in the study. The 70-gene signature outperforms other prognostic factors in identifying a subgroup with a 10yr survival of >90%. This is to be further studies in the MINDACT trial (once validated) and may lead to determination of those patients who do not require adjuvant chemotherapy in this group.

## **3. ONJ: poster 2056**

Ripamonti et al, from Milan, Italy, report on their experience of preventive measures to reduce the incidence of ONJ. Preventive measures included a dental assessment, by a dentist,

together with OPG XRay. Dental checks were continued. Prior to institution of this policy, amongst 813 patients receiving bisphosphonates for bone metastases between 1999 and 2007, 3.3% developed ONJ. Of the 153 patients followed since 2005 who have undergone these "preventive measures", 1 case has occurred, a rate of 0.6%. Most patients have received either Pamidronate, Zometa or a sequence of the two. 73% of the patients were breast cancer patients. Unfortunately the details of the dental interventions were not documented, however the results are certainly encouraging, and I think also reflect my own subjective experience in recent years.

## **4. Benefit from adjuvant tamoxifen: posters 2004 and 2069**

Recently, we have all become aware that individual variation in metabolism of Tamoxifen (to the active metabolite endotamoxifen) influences possible benefit from it, as does the use of certain drugs, in particular SSRI's that also influence this. Here are two other interesting individual variations that also appear to be linked to the benefit of Tamoxifen, and even AI's too.

Jansen et al from Sweden have studied the ratio of 17 $\beta$ -hydroxysteroid dehydrogenase 1 and 2 and its relationship to breast cancer outcome in Tamoxifen treated patients. These enzymes affect the production of oestrogen in postmenopausal women. 17HSD1 converts oestrone to oestradiol, and 17HSD2 converts oestradiol to oestrone. A high D1 and low D2 is associated with a decreased BC survival. In 1780 patients treated with Tam or nil, they have shown that a low 17HSD1 is associated with an increased benefit from Tamoxifen and if D1>D2 there is no benefit from Tamoxifen.

An analysis of hot flushes and adjuvant benefit from Anastrozole and Tamoxifen in the ATAC study, indicates that there is a link between effectiveness and the incidence of hot flushes. Those reporting hot flushes had a 3.6% absolute lower recurrence rate than those who did not. Further work is looking at SSRI influence. (Cuzick et al).

## **5. Herceptin beyond progression: posters 4056, 4057, 4059**

Three posters have looked at available data on use and possible benefit of Herceptin beyond progression. In summary there is some

evidence that indicates that the continuation of Herceptin in combination with chemotherapy in this scenario prolongs survival and provides improved response rates. This is in the pre-Lapatinib era however. The question as to whether to continue Herceptin or switch to Lapatinib remains.

Von Minckwitz (Germany) reports that a study randomizing patients to receive Herceptin plus Capecitabine vs Capecitabine alone, following progression on first line Herceptin treatment, only accrued 156 of the planned 482 patients, over a period of 3.5 years. The trial was therefore closed early. There was a trend to benefit of the continued Herceptin - hazard ratio for progression was 0.82 (CI 0.53 to 1.26). The RR was 24.6% for Capecitabine alone, and 48.9% for the combination; the PFS was 5.6 months vs 8.5 months. No p values were presented; final results expected Q1 2008.

Montemurro et al presented a retrospective review of 407 patients. 245 patients progressing patients were able to receive further treatment. 112 patients continued Trastuzumab, and 133 did not. TTP, RR and OS were similar in both groups. Details of treatment received were not presented.

Finally, national statistics from Germany were detailed by Jackisch et al. Based on 910 patients, median OS was shown to be 28 months for patients treated with chemo and Trastuzumab and 44 months for those with endocrine treatment and Trastuzumab. For patients treated with Trastuzumab (112) vs not (81) beyond progression there was an overall survival benefit (13.4 to 20.1 months,  $p=0.0014$ ).

## 6. EBC prognosis prediction: poster 5026

A web based calculator for estimating risk of breast cancer death was presented. I have yet to take a look at it, but the address is: <http://www.cancer-math.net/> and it looks interesting. SEER data on breast cancer survival together with the outcome of 25,000 patients treated in the past 40 years at the Harvard Hospitals are used together with US census data for non breast cancer death; treatment benefits are derived from the metaanalyses and are the same as Adjuvantonline. The factors taken into account include ER, PR, HER2, histology, grade, size, number of nodes status and patient age. Information is provided on risk of death and cancer death in the next 15 years, and benefit

of adjuvant therapy, also expressed as years of life saved. It seems time that HER2 status and herceptin treatment are included in the calculators are available – this has now become a major detraction from the use of Adjuvantonline.

## 7. Sequence of Tam and AI in MBC: poster 2083

Kyritsis et al have undertaken a population based retrospective review of patients treated with Tamoxifen and AI's for ER positive metastatic breast cancer (MBC) in BC, Canada. All patients from Jan 1998 to Sept. 2004 were included. The information has come from the BC Cancer Agency Information System. An OS benefit was shown for patients receiving the sequence Tamoxifen to AI versus AI to Tamoxifen:

Tam Followed by AI:	221 patients	OS:	37 months
AI Followed by Tam:	63 patients	OS:	21 months

This is a small study, and other explanations may exist, including that the patients who have been treated more recently, presumably with upfront AI, may have had more effective adjuvant endocrine treatment (including possibly both AI and Tamoxifen), meaning their disease has relapsed later in its course, therefore experiencing shorter survival from time of diagnosis of MBC. However, there may be a biological explanation and it will be interesting to see if the sequence treatments arms in the BIG 1-98 trial will have the same result.

As usual there were many and varied posters, which provided much food for thought ..... This of course can only hope to be a tiny titbit!

On this note, I will complete this marathon report, and congratulate (and thank) those of you who have made it through to the end. It would be in everybody's interests if I could have some volunteers for the next conference reports! I am planning to be more organised again this year and ask some of our advanced trainees to provide the reports as these are a great chance to reflect on what you have heard, and I think make it an even more worthwhile learning opportunity. I would be keen to receive nominations of advanced trainees for this job.. Thanks!

## HER2 testing in early breast cancer *Stephen Fox*

As from the 1<sup>st</sup> October 2006 evidence of HER2 amplification by an in situ hybridization (ISH) test is the mandated methodology for patient eligibility for treatment with Herceptin as set down by the Pharmaceutical Benefits Advisory Committee (PBAC). Roche is supporting chromogenic (CISH) and silver ISH (SISH) testing (other methodologies of ISH will also be supported with appropriate validation) of all early breast cancer tumours from resection specimens and from biopsy material where clinically indicated e.g. patients receiving neoadjuvant therapy.

ISH has been mandated in light of PBAC's concern about HER2 immunohistochemistry (IHC) from quality assurance schemes that show significant errors in both positive and negative from IHC testing. For example only 80% of IHC 3+ are actually amplified when tested by ISH whereas 5.8% of 1+ IHC have subsequently shown to be amplified. The discrepancy has been shown partly to be due to technical and partly due to pathologist interpretation. Thus **ALL early breast cancers should be tested by ISH including 0 and 1+ by IHC, since a not insignificant proportion of these IHC negative tumours will be amplified.** Testing of ALL breast cancers is currently not being widely performed and the patients who are not currently being recognised will be adversely affected. It is patients with amplified tumours rather than those tumours overexpressing HER2 protein that derive most benefit from the drug. ISH testing of multiple tumours with different phenotypes should also be performed, as it should not be assumed that such tumours are derived from the same clone.

Amplification results depend on the assay used. ISH currently uses a single probe and thus the score is an average number of signals derived from counting 30 tumour nuclei. Results are expressed as negative for amplification (comprising diploid <2.5 and polysomic 2.5-4.0 tumours) or positive for amplification (>6) as per the ASCO/CAP guidelines<sup>1</sup>. Amplified cases have also been arbitrarily stratified into low [6-10 signals] or high [>10 signals] level but patients with tumours showing either high or low level amplification are eligible for Herceptin treatment (the classification into high and low is an attempt to give an indication of the likelihood of treatment response). In equivocal tumours [score 4.0-6], currently the sample is sent for FISH to confirm polysomy and exclude low level amplification. However, from February 2008, all CISH (or SISH) reference laboratories will use a second ISH probe to chromosome 17 (Chr17) on a parallel section to determine amplification in these cases (5-10% of all breast cancers). In these equivocal cases, a ratio of HER2: chr17 will be given with tumours >2.2 being amplified and tumours <1.8 being non-amplified<sup>1</sup>. Tumours with an equivocal ratio (1.8- 2.2) will be sent for FISH to resolve amplification status.

Cases that are non-diagnostic using CISH or SISH (usually due to technical issues including fixatives that denature DNA) in the ISH reference laboratory will also be sent for fluorescent ISH (FISH) at the Reference Laboratory at St Vincent's Hospital Sydney, as this technique is more sensitive and may resolve some of these issues.

Reference: <http://jop.ascopubs.org/cgi/content/full/3/1/48>].

## An overview of initiatives undertaken by the Victorian Integrated Cancer Services

Elise Davies

The Integrated Cancer Services (ICS) are funded to support the development of integrated care and defined referral pathways for the populations they serve. The ICS are the platform through which improvements in cancer service delivery and patient care is being implemented.

The identification, development, implementation and evaluation of initiatives is guided by the Patient Management Frameworks (which describe optimal care for a range of tumour streams), the model for safety and quality in cancer care (*Clinical Excellence in cancer care: a model for safety and quality in Victorian cancer services*) and two documents that provide policy direction for cancer care coordination and multidisciplinary care (*Linking cancer care: a guide for implementing coordinated cancer care*, *Achieving best practice cancer care: a guide for implementing multidisciplinary care*).

Clinicians and consumers are involved in ICS initiatives in variety of ways from providing data to support the need for a particular initiative to steering or undertaking the development, implementation and evaluation of initiatives.

Outlined below is a range of initiatives that are being carried out in specific tumour streams within individual ICS. This is not an exhaustive list but an indication of the range of initiatives as reported by the ICS in August 2007.

### Breast cancer initiatives

- Development of a service model for women with advanced breast cancer
- Development of tools and templates to strengthen the multidisciplinary team process and facilitate communication with General Practice
- Development of guidelines for consistent follow up care
- Development of a multidisciplinary psychosocial model of care for an integrated breast services (between two health services

- Scoping current access to mammography for specimen analysis during hook wire localisations and removal of impalpable lesions

### Genitourinary cancer initiatives

- Improving management and support for treatment morbidity (incontinence and impotence) associated with treatment for prostate cancer
- Development and implementation of a shared model of care for patient follow up between genitourinary clinicians and General Practitioners
- Process mapping of urology clinics to improve flow of cancer patients through clinics and improve primary care co-management of initial referrals and discharges

### Skin cancer initiatives

- Improving patient information for patients with melanoma in the region by gaining an understanding of the consumer experience and consumer needs related to information and support
- Development of consistent follow-up guidelines for melanoma and non-melanoma skin cancers
- Investigation of requirements for synoptic pathology reporting to improve diagnosis and treatment

### Gynaecological cancer initiatives

- Streamlining of referral processes for patients presenting with ovarian cancer in the ICS region
- Improving patient information
- Identification of psychosocial care needs of women with ovarian cancer three months post chemotherapy treatment
- Development of mechanisms to ensure access to multidisciplinary care meetings for all patients across the ICS region

- Improving the transition from acute care to community based palliative care for women with gynaecological cancers

### Lung cancer initiatives

- Improving access to home oxygen for patients in the ICS region
- Mapping the patient journey to identify and analyse the cause and duration of delays for presentation to initial treatment
- Mapping of lung cancer services within region against ideal pathway as described in the NHMRC guidelines and Patient Management Framework
- Development of a cancer informatics program for the multidisciplinary lung cancer clinic in a specific health service
- Exploring patient expectations and preferences for follow-up after lung cancer treatment

### Upper gastro-intestinal cancer initiatives

- Development of patient information
- Audit of multidisciplinary process within two health services to investigate its use and effectiveness in providing care to complex patients
- Mapping of the patient journey within the ICS region to identify key points in the journey , particularly when care coordination is required
- Development of guidelines for consistent follow-up

Spiri Galetakis  
Acting Manager, Integrated Cancer Services  
Cancer and Palliative Care, Programs Branch  
Metropolitan Health and Aged Care Services  
Department of Human Services  
50 Lonsdale Street  
Melbourne 3000, Victoria

Phone: (03) 9096 2131/ Mobile: 0432 133 004  
Fax: (03) 9096 9204  
Email: [spiridoula.galetakis@dhs.vic.gov.au](mailto:spiridoula.galetakis@dhs.vic.gov.au)  
<http://www.health.vic.gov.au/cancer>

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## Australian New Zealand Breast Cancer Trials Group Trial Activation Status and Accrual Report

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### Trials Pending Activation

#### IBCSG 35-07 / BIG 1-07 (SOLE)

**A phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4-6 years of prior adjuvant endocrine therapy for postmenopausal women with hormone receptor positive, node positive, early breast cancer.**

Total international accrual – 7  
International target accrual - 4800

**Expressions of Interest:** The Operations Office has now received expression of interest from 22 investigators who wish to participate in the SOLE study. To register EOI, please access our website ([www.anzbctg.org](http://www.anzbctg.org)), log in, select “Clinical Trials” from

**Estimated date of first ANZ BCTG site activation:** April 2

### Trials Open for Patient Entry

#### ANZ 0701 (Co-SOFT)

**IBCSG Trial 24-02 (SOFT) Cognitive Function Substudy – designed to evaluate and compare changes in cognitive function over 1 year in premenopausal breast cancer patients who receive adjuvant tamoxifen (T) with or without ovarian function suppression (OFS).**

ANZ BCTG accrual - 1  
Total international accrual – 1  
International target accrual - 357

Investigators currently participating in the SOFT study are encouraged to consider activating this cognitive function substudy. An ethics submission template is available. Should you have any questions please do not hesitate to contact us: [cosoft@anzbctg.org](mailto:cosoft@anzbctg.org)

**ANZ 0702 / BIG 2-06 (ALTTO)**

**A randomised, multi-centre, open-label, phase III study of adjuvant lapatinib, trastuzumab, their sequence and their combination in patients with HER2ErbB2 positive primary breast cancer**

ANZ BCTG Institutions activated in January 2008: Monash Medical Centre, Lismore Base Hospital, Royal Hobart Hospital.

ANZ BCTG accrual - 0

Total international accrual – 333

International target accrual – 8000

**Activation status:** Staff at all institutions are requested to continue the submission of regulatory documentation to the ANZ BCTG Operations Office in conjunction with their ethics review, thereby enabling activation as soon as possible following ethics approval. A maximum of 43 sites may participate in the ANZ BCTG. Queries may be directed to: [ALTTO@anzbctg.newcastle.edu.au](mailto:ALTTO@anzbctg.newcastle.edu.au)

**ANZ 0601 / CIRG / TORI 010**

**A Randomized Phase 2 Trial of Double-Blind, Placebo Controlled AMG 706 in Combination with Paclitaxel, or Open-Label Bevacizumab in Combination with Paclitaxel, as First Line Therapy in Women with HER2 Negative Locally Recurrent or Metastatic Breast Cancer**

ANZ BCTG accrual – 10

Total international accrual – 174

International target accrual – 273

At the current accrual rate, CIRG have projected that international recruitment to this study will be completed by the end of June 2008. Should you have any queries regarding this study, please contact us: [cirg010@anzbctg.newcastle.edu.au](mailto:cirg010@anzbctg.newcastle.edu.au)

**ANZ 0502 (NeoGem)**

**A phase II trial evaluating the efficacy and safety of epirubicin and cyclophosphamide (EC) followed by docetaxel with gemcitabine**

**(DG) (+ trastuzumab if HER2 positive) as neoadjuvant chemotherapy for women with large operable or locally advanced breast carcinoma.**

***Treatment Arms: EC x 4 followed by DG x 4 (HER2 negative) or DGT x 4 (HER2 positive) + T to for a total of one year of treatment.***

ANZ BCTG accrual – 34

ANZ BCTG target accrual - 147

Activated sites: To meet the accrual target for this study, participating sites need to accrue at least one patient each month. Please assist us to meet study timelines by continuing to screen and enter patients to this important ANZ BCTG trial.

A maximum of 20 sites may participate in this study. If you are interested in participating, or have queries please contact us: [neogem@anzbctg.newcastle.edu.au](mailto:neogem@anzbctg.newcastle.edu.au)

**ANZ 0501 (LATER)**

**A randomised double blind trial in postmenopausal women who have completed 5 years of adjuvant endocrine therapy for early, hormone sensitive breast cancer more than one (1) year previous, and who are disease-free at study entry.**

ANZ BCTG accrual – 15

ANZ BCTG target accrual - 2500

Should you wish to participate and have not obtained an expression of interest package, please contact us: [later@anzbctg.newcastle.edu.au](mailto:later@anzbctg.newcastle.edu.au)

**ANZ 02P2 / IBIS II (Prevention, DCIS, Bone Sub-Study)**

**An international multi-centre trial of anastrozole vs placebo in postmenopausal women at increased risk of breast cancer, and tamoxifen vs anastrozole in postmenopausal women with hormone sensitive DCIS, and a bone sub-study to assess the effects on bone mineral density and bone biomarkers of anastrozole when**

### **used to prevent breast cancer in postmenopausal women.**

ANZ BCTG Accrual: Prevention – 162, DCIS – 49, Bone Sub-Study – 48: Total - 211

Total international accrual: Prevention – 1834, DCIS – 1324, Bone Sub Study – 720: Total-3158

International target accrual - 6000, DCIS - 4000, Bone Sub Study - 1000

Should you wish to participate and have not obtained an expression of interest package, please contact us: [ibisii@anzbctg.newcastle.edu.au](mailto:ibisii@anzbctg.newcastle.edu.au). A recruitment feature on this website is an IBIS-II Participants page which is accessible to the public.

### **IBCSG 34-05 / SWOG 0230 (POEMS - Prevention of Early Menopause Study)**

**Phase III trial of LHRH analog administration during chemotherapy to reduce ovarian failure following chemotherapy in early stage, hormone receptor negative breast cancer.**

#### ***Treatment Arms: Chemotherapy Vs Chemotherapy plus Ovarian Function Suppression***

ANZ BCTG accrual - 14  
Total international accrual – 91  
International target accrual - 416

If you require assistance with your ethics submission, or if you are interested in activating this trial please contact us: [s0230@anzbctg.newcastle.edu.au](mailto:s0230@anzbctg.newcastle.edu.au). Alternatively, you may download an activation package from the member's section of ANZ BCTG website: [www.anzbctg.org](http://www.anzbctg.org)

### **IBCSG 27-02 (Loco-regional Relapse)**

**A randomised clinical trial of adjuvant chemotherapy for radically resected loco-regional relapse of breast cancer.**

#### ***Treatment Arms: Chemotherapy vs Observation***

ANZ BCTG accrual - 2  
Total international accrual – 116  
International target accrual - 977

Should you wish to participate in this study and have not obtained an expression of interest package, please contact us: [ibcsg27@anzbctg.newcastle.edu.au](mailto:ibcsg27@anzbctg.newcastle.edu.au)

### **IBCSG 24-02, IBCSG 25-02 (SOFT and TEXT)**

#### **SOFT**

**A Phase III Trial Evaluating the Role of Ovarian Function Suppression and the Role of Exemestane as Adjuvant Therapies for Premenopausal Women with Endocrine Responsive Breast Cancer.**

#### ***Treatment Arms: Tamoxifen Vs Ovarian Function Suppression + Tamoxifen Vs Ovarian Function Suppression + Exemestane***

ANZ BCTG accrual - 127  
Total international accrual – 1514  
International target accrual - 3000

If you are interested in activating the SOFT trial, or require assistance with an ethics submission please contact us: [stp@anzbctg.newcastle.edu.au](mailto:stp@anzbctg.newcastle.edu.au).

### **IBCSG 23-01 (Sentinel Node Biopsy (Micrometastases) Trial)**

**A randomised trial of axillary dissection versus no axillary dissection for patients with clinically node negative breast cancer and micrometastases in the sentinel node.**

#### ***Treatment Arms: Axillary Dissection vs No Axillary Dissection***

ANZ BCTG accrual - 15  
Total international accrual – 592 (681 including pilot)  
International target accrual - 1960

Should you wish to participate in this study and have not received an activation package, please contact us: [ibcsg23@anzbctg.newcastle.edu.au](mailto:ibcsg23@anzbctg.newcastle.edu.au).

Alternatively, you may download an activation package from the member's section of ANZ BCTG website: [www.anzbctg.org](http://www.anzbctg.org).

### **IBCSG 22-00 (Chemotherapy Maintenance)**

**Low-dose cytotoxics as “anti-angiogenesis treatment” following adjuvant induction chemotherapy for patients with ER-negative and PgR-negative breast cancer.**

***Treatment Arms: Induction Chemotherapy Only vs Induction Chemotherapy followed by 12 months continuous oral CM therapy***

ANZ BCTG accrual - 52

Total international accrual – 684

International target accrual - 900

Should you wish to participate in this study and have not obtained an expression of interest package, please contact us: [ibcsg22@anzbctg.newcastle.edu.au](mailto:ibcsg22@anzbctg.newcastle.edu.au)

### **BIG 1-98 Cognitive Function Substudy**

**Investigating cognitive function for patients participating in the BIG 1-98 study in selected centres**

ANZ BCTG accrual - 39

Total international accrual – 116

International target accrual - 296

For all trial related enquiries, please contact the ANZ BCTG Operations Office on: [big1-98@anzbctg.newcastle.edu.au](mailto:big1-98@anzbctg.newcastle.edu.au)

We would like to take this opportunity to thank all staff at all ANZ BCTG institutions for their recruitment efforts during the month of December. If there are any queries regarding the above studies, please do not hesitate to contact staff at the ANZ BCTG Operations Office via the trial specific email addresses noted above.

**Data Management Department  
ANZ BCTG Operations Office  
[www.anzbctg.org](http://www.anzbctg.org)**

### **TROG 06.02**

**A multicentre feasibility study of accelerated partial breast irradiation using three-dimensional conformal radiation therapy for early breast cancer**

Target accrual: 48

Target accrual: 20

### **TROG 07.01**

**A Randomised Phase iii study of Radiation Doses and Fractionation Schedules in Low-risk Ductal Carcinoma In-Situ (DCIS) of the Breast**

Target accrual: 610

Target accrual: 20



**Extract from WONGI YABBER**  
**VOLUME 14, ISSUE 4 NOVEMBER 2007**  
**Newsletter of the Australian Cancer Network**  
*Wongi Yabber is published in February, May, August and November as a service to all ACN supporters and interest groups*  
**Full copy available on website: [www.cancer.org.au/acn](http://www.cancer.org.au/acn)**

### Does positive thinking have power over Cancer?

People with cancer find considerable comfort in the notion that they can “do something” to influence their outcome. Researchers have been duly investigating the relationship between psychosocial factors and outcome in cancer for the past 30 years.

The findings of another well designed study by James Coyne and colleagues (as reported in the Australian, on Tuesday 23rd October 2007) which has found no relationship between positive thinking and cancer outcome, increases the body of evidence supporting the conclusion that mental states do not affect survival time in cancer. Recent reviews and metaanalyses have similarly reported that combined effect sizes are nonsignificant, and concluded that both mental states and psychotherapeutic interventions are unlikely to affect outcome. This is good news for those who feel that when patients have a poor outcome, they should not be burdened with guilt that they have not “been positive enough”.

However, there are two limitations to this conclusion. First, most reviewers have criticised the methodological rigor of the studies performed to date, and suggested that larger and more homogenous samples, and better measurement, design and control

of potentially confounding variables are needed. Second, a multiplicity of constructs have been discussed and measured under the term “mental state.” These have included depression, hopelessness, optimism, fighting spirit and minimization, to name but a few. Similarly, psychotherapeutic interventions have varied widely in their goals and method of delivery. Generally, these are lumped together in metaanalyses and reviews, without consideration of potential differences in their impact both theoretically and empirically. Thus

I feel that to conclude once and for all that mental states have no influence over cancer outcome is premature.

Reviewers have recently suggested that the cost of funding a definitive study on this topic would not be justified, given the burden of evidence against such a relationship. Perhaps this is reasonable. The likely influence of mental states is in any case likely to be small. Of much more concern is the quality of life of those living with cancer, and research effort needs to focus on optimising that.

**Prof Phyllis Butow**  
**Co-Director, Medical**  
**Psychology Research Unit,**  
**School of Psychology,**  
**University of Sydney**

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*All correspondence should be directed to:*  
 GPO Box 4708 SYDNEY NSW 2001  
 email: [acn@cancer.org.au](mailto:acn@cancer.org.au)

Australian Cancer Network Secretariat  
 Tel: +61 (2) 8063 4141 Fax: +61 (2) 8063 4101  
 Email: [acn@cancer.org.au](mailto:acn@cancer.org.au)  
 Website: [www.cancer.org.au/acn](http://www.cancer.org.au/acn)

**Medical Director**  
 Professor Bruce Barraclough AO FRACS

**Senior Medical Advisor**  
 Emeritus Professor Tom Reeve AC CBE FRACS

**Executive Assistant & Co-Editor**  
 Ms Christine Vuletich

**Office Assistant & Circulation**  
 Ms Alice Winter-Irving

## Key Published Articles Listing— Breast Cancer

Title	Author & Journal
<b>Adjuvant Chemotherapy with Sequential or Concurrent Anthracycline and Docetaxel: Breast International Group 02-98 Randomised Trial</b>	<b>Francis P, Crown J, Di Leo A, Buyse M, et al.</b> JNCI 2008; 100: 121-133
<b>Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: supplementary results from the BIG 1-98 randomised trial</b>	<b>Rasmussen B, Regan M, Lykkesfeldt AE, P Dell'Orto, et al.</b> Lancet Oncology 2008; 9: 23-28
<b>Quality of life and quality-adjusted survival (Q-TWiST) in patients receiving dose-intensive or standard dose chemotherapy for high-risk primary breast cancer</b>	<b>Berhard J, Zahrieh Z, Zhang JJ, Martinelli G, et al.</b> BJC 2008; 98: 25-33 <a href="http://www.bjcancer.com">www.bjcancer.com</a>
<b>A pilot study to evaluate the impact of involving breast cancer patients in the multidisciplinary discussion of their disease and treatment plan</b>	<b>Choy ET, Chiu A, Butow P, Young J, Spillane A Elsevier</b> The Breast 2007; 16: 178-189 <a href="http://www.elsevier.com/locate/breast">www.elsevier.com/locate/breast</a> <a href="http://www.sciencedirect.com">www.sciencedirect.com</a>

## Forthcoming Meetings

You can view the forthcoming committee meetings on our website via the weblink below:

[http://www.cancervic.org.au/downloads/cal\\_2008\\_2009\\_External\\_mtgs.pdf](http://www.cancervic.org.au/downloads/cal_2008_2009_External_mtgs.pdf)

## The Cancer Council Victoria

The Cancer Council Victoria was set up by an Act of Parliament in 1936. To find out more about the Cancer Council visit [www.cancervic.org.au/introduction](http://www.cancervic.org.au/introduction).

### Victorian Cooperative Oncology Group

The Victorian Cooperative Oncology Group (VCOG) established in 1976, provides advice to the Cancer Council, on all clinical aspects of cancer control, in particular clinical research, screening diagnosis, treatment, palliative medicine, cancer genetics and professional education. The strategic role of the VCOG is to have a 'parliament' of clinical cancer specialists with a view to promoting a range of cooperative measures to optimise cancer treatment in Victoria. The VCOG consists of a primary committee, 8 cancer-site and 5 task-specific advisory committees and 5 trial research sub-committees. These committees bring together in regular meetings approximately 400 key specialist health care professionals and scientists, representing the various treatment disciplines and Centres in Victoria. The VCOG has established valuable linkages between public and private health care professionals, institutions and governments.

