# Breast Cancer: a disease of subtypes

## Guest Editor: Nicholas Wilcken

NOVEMBER 2016 | VOL 40 ISSUE NO 3

# *Cancer Forum* November 2016
# Breast cancer: a disease of subtypes

**Guest Editor: Nicholas Wilcken**

## Reports

# Breast cancer: a disease of subtypes

Nicholas Wilcken

Crown Princess Mary Cancer Centre, Westmead Hospital, University of Sydney, New South Wales, Australia.

Email: nicholas.wilcken@sydney.edu.au

As cancer medicine moved into the 21st century, the long relationship between molecular biology and clinical care was finally consummated with the aid of biomathematics, and the era of the cancer subtype was born.[1] The intuitive understanding that clinicians had – that not all breast cancers behaved the same – was given a molecular basis, and has subsequently informed our care and produced new tools with which to contain this disease.

In this edition of *Cancer Forum*, we aim to give a broad view of how our understanding of breast cancer as a disease of subtypes has changed the day to day management of our patients and shaped the new questions to be asked of future researchers.

## ER positive disease

We start by revisiting old favourites with new knowledge. Clara Lee and Howard Gurney take us through what has been a confusing journey in understanding tamoxifen metabolism.[2] It was found quite late that tamoxifen is in fact a prodrug, with most of its activity due to the metabolite endoxifen, produced in part by an enzyme called CYP2D6. The efficiency with which individuals metabolise tamoxifen was subsequently shown to vary, partly due to genetic factors.

This variation initially led to calls in the US for genotyping to be carried out for those patients treated with tamoxifen, although this advice has since been withdrawn. Lee and Gurney show why CYP2D6 genotyping only partially explains variations in endoxifen level, the likely reason being that studies examining whether CYP2D6 genotypes have prognostic implications for women on tamoxifen have produced such divergent conclusions.

Next, Clara Lee assesses the clinical implications of aromatase inhibitor use as adjuvant treatment, focussing on the important issue of bone health.[3] As our treatments improve, women with breast cancer are living longer and longer. In addition, accumulating evidence suggests that at least for some women with ER positive early breast cancer, being on endocrine therapy for as long as 10 or 15 years may be beneficial. Thus a focus on long term side-effects is appropriate and increasingly important. Although aromatase inhibitors can have an adverse effect on bone density, we now have the knowledge and technology to monitor and treat this problem, as outlined in this article.

Finally, I review what I have labelled ‘the enablers’ – new classes of drug that can impede the development of resistance to endocrine therapies.[4] Again, as our knowledge of the molecular basis of pathological events increases, so too do the opportunities to intervene in these processes for the benefit of our patients. It has long been clear in the laboratory and in our clinics that ER positive cancers eventually become resistant to endocrine therapy. We now have drugs – mTOR inhibitors, PI3 kinase inhibitors and cyclin dependent kinase inhibitors – that have proven clinical benefits.

## Triple negative disease

Bergin et al provide a comprehensive review of this most challenging of breast cancer subtypes.[5] Drawing on knowledge from the laboratories of the Walter and Eliza Hall Institute and extending this to the results of recent clinical trials, the authors explain the heterogeneity of this subtype and the limitations as well as the successes in our attempts to understand and treat this disease.

The rationale behind the potential benefits of platin therapy is explained, as well as the benefits and limitations of the PARP inhibitors and the possibility that immunotherapies may become clinically relevant treatments for a subgroup of ‘triple negative’ cancers. This last suggestion is expanded upon in our final chapter.

## HER2 positive disease

Great strides have been made in our management of HER2 positive disease. Our understanding of the disease and the development of new drugs have meant that it has become almost a separate disease identity. Most of what we

have learnt about treating breast cancer in the past has been done without knowledge of HER2 biology or the HER2 status of our patients.

Luckily trastuzumab, our first exemplar of targeted therapy after tamoxifen, has proved to be a spectacular success both in the adjuvant and metastatic setting. Clearly much more has to be learned, but already we have moved beyond trastuzumab as being the only drug that is effective for this breast cancer subtype.

First we discuss early HER2 positive breast cancer and ask whether adding new anti-HER2 drugs may improve outcomes. We then contemplate the question of whether in fact for some women with HER2 positive early breast cancer, we may be able to scale back some of the therapy to avoid toxicity while maintaining efficacy.[6]

Finally, Arlene Chan reviews the data from clinical trials that help us treat the women with metastatic disease for whom trastuzumab is no longer effective.[7] While we do have new and exciting drugs and have managed to extend survival for this group of women, Chan explains that we now need to explore ways of combating resistance to anti-HER2 therapies by targeting different molecules.

## Brain metastases

Brain metastases have always been a feared outcome for any cancer. However, as Claire Phillips explains, much has changed in the breast cancer world and the approach to the treatment of brain metastases needs to be adapted to disease subtype.[8] The standard approach of treating everyone the same way is now inappropriate, and improvements in technology have seen great improvements in management.

Phillips argues that women with brain metastases are best managed with the help of a multidisciplinary approach, involving imaging, radiation oncology and neurosurgery input in order to individualise treatment.

## Immunotherapy

And so perhaps to the least understood horizon. New immune checkpoint inhibitors have revolutionised the treatment of melanoma, and promising results are being obtained in non-small cell lung cancer, kidney cancer and other cancers. Will the same principles apply in breast cancer? Stephen Luen and Sherene Loi give us a comprehensive overview of the relevant data, much of it generated by Loi herself.[9]

Again, breast cancer subtype is important, although as Luen and Loi explain, responses to immunotherapies may be seen in all subtypes. The most promising data so far have been in triple negative disease and HER2 positive disease. While this is a very exciting development, early results are clearly not as dramatic as those seen in melanoma, and much is to be learned about the relationship between the immune system and breast cancer.

## Conclusion

This issue of *Cancer Forum* aims to put into clinical context the understanding that breast cancer is in effect a collection of diseases requiring different approaches. Much has been learned in the first 15 years of this millennium and patient outcomes have improved, but our appetite for further knowledge and better treatments remains.

## References

1. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001;98:10869-10874.

2. Lee CI, Gurney H. Tamoxifen, CYP2D6 and endoxifen in the treatment of hormone sensitive breast cancer: demystifying the connections. Cancer Forum [Internet]. 2016 Nov; 40(3):[about 4 p.]

3. Lee CI. Bone health in the treatment of postmenopausal women with Aromatase Inhibitors and premenopausal women treated with ovarian suppression and Aromatase inhibitors: a hands-on guide. Cancer Forum [Internet]. 2016 Nov; 40(3):[about 4 p.]

4. Wilcken N. The ‘enablers’: inhibitors of mTOR, PI3K and CDK that prolong endocrine sensitivity. Cancer Forum [Internet]. 2016 Nov; 40(3):[about 4 p.]

5. Bergin A, Oakman C, Lindemann GJ. Triple negative breast cancer: proven and promising systemic therapies. Cancer Forum [Internet]. 2016 Nov; 40(3):[about 4 p.]

6. Wilcken N. Adjuvant therapy: can we do better, or are we already giving too much treatment? Cancer Forum [Internet]. 2016 Nov; 40(3):[about 4 p.]

7. Chan A. HER2 positive metastatic breast cancer: what happens after first line failure? Cancer Forum [Internet]. 2016 Nov; 40(3):[about 4 p.]

8. Phillips C. Brain metastases: a subtype-specific approach. Cancer Forum [Internet]. 2016 Nov; 40(3):[about 4 p.]

9. Luen SJ, Loi S. Immunotherapy in breast cancer: the subtype story. Cancer Forum [Internet]. 2016 Nov; 40(3):[about 4 p.]

# Tamoxifen, CYP2D6 and endoxifen in the treatment of hormone sensitive breast cancer: demystifying the connections

Clara Inkyung Lee[1,3,4] and Howard Gurney[1,2,5,6]

1. The University of Sydney
2. Westmead Hospital
3. Bankstown Hospital
4. The University of New South Wales
5. Macquarie University Hospital
6. Macquarie University

Email: clara.lee@sydney.edu.au

**Abstract**

The role of the selective oestrogen receptor modulator, tamoxifen, is well established in the treatment of hormone sensitive breast cancer. The metabolism of tamoxifen to its active metabolites is however complex. Despite much research, a conclusive stance on the clinical implications of CYP2D6, active metabolites including endoxifen in efficacy and toxicity, is yet to be reached. Herein we examine the literature to clarify the connections between tamoxifen, CYP2D6 and endoxifen with resultant clinical recommendations.

As the first targeted systemic therapy in the history of solid tumour oncology, tamoxifen has a prominent place as an effective anti-cancer treatment (endocrine therapy) for hormone-sensitive breast cancer.[1] Although somewhat superseded by aromatase inhibitors in the treatment of disease in postmenopausal women, tamoxifen still has an important role. This is particularly the case in the treatment of pre and peri menopausal women, as well as in cases where toxicities and pre-existent comorbidities do not permit use of an aromatase inhibitor.

Tamoxifen set the early benchmark for endocrine therapies in breast cancer. A multitude of studies and subsequently the Oxford Overview clearly established that when used in the adjuvant setting, this selective oestrogen receptor modulator will reduce breast cancer recurrence by a half and breast cancer specific mortality by a third.[2] However, despite being in use for over three decades, there is no conclusive, unified stance regarding the therapeutic implications of its metabolism and its impact on efficacy.

In brief, tamoxifen itself is only weakly anti-oestrogenic and is biologically not effective until it is metabolised to produce active metabolites. Therefore, tamoxifen is a prodrug which is extensively metabolised by hydroxylation, demethylation and conjugation, giving rise to several metabolites. Endoxifen (4-OH-N-desmethyltamoxifen) and 4OH tamoxifen are the most active, and endoxifen is the most abundant.[3,4] It has been known for some time that genetic variability of the *CYP2D6* gene has an impact on the levels of active metabolites. However, CYP3A4, CYP2C9/19, UDP-glucuronosyltransferases and sulfotransferases as well as compliance, absorption and concomitant medications that inhibit the CYP2D6 enzyme also have an impact on tamoxifen metabolism.[5,6,7] Thus simply looking at *CYP2D6* genotype is unlikely to describe tamoxifen metabolism accurately. A simplified representation of tamoxifen metabolism is depicted in figure 1.

## Endoxifen

Endoxifen, as the most abundant and active anti-oestrogenic metabolite of tamoxifen, has been recognised as mediating the vast majority of both tamoxifen effects and anti-cancer benefits in the treatment of hormone-sensitive breast cancer.[8-12] It is therefore possible that it is the level of endoxifen that is important for clinical benefit rather than the dose of tamoxifen, yet this is not a parameter we routinely measure.

In the pre-clinical setting, endoxifen dose certainly matters. Cell culture studies indicate that the tamoxifen effect on breast cancer cells is not only endoxifen-dependent but also concentration-dependant, with data suggesting that endoxifen levels above 40nM are required for optimal oestrogen receptor blockade.[13] Mouse MCF7 breast cancer cell xenograft models have demonstrated that 97% of growth inhibition is attainable at 40nM, as compared to 83% at 15nM.[14]

In women treated with tamoxifen, endoxifen levels vary widely, and are loosely correlated with genotype. There are clear trends in level according to whether patients are “poor”, “intermediate” or “extensive” metabolisers. However, there is significant heterogeneity of endoxifen level despite genotype.[15]

Despite the wide acknowledgement of the importance of endoxifen, due to a lack of studies examining this question, there are no prospectively collected data correlating absolute endoxifen levels with survival or recurrence free survival. However, there are two retrospective studies of adjuvant tamoxifen examining the effect of endoxifen level: the first, the WHEL (Womens’ Healthy Eating and Living) group, examined 1370 women and showed a 26% worse disease-free survival in women in the lowest quintile of endoxifen (<15nM) compared to those in the upper four quintiles.[10] Similarly, Saladores et al demonstrated in 306 women that those in the lowest quintile (endoxifen <15nM) had worse disease free survival than those who had levels >35nM.[11]

## CYP2D6

As discussed above, *CYP2D6* is an important factor in the conversion of tamoxifen to endoxifen, and polymorphisms result in variable levels. However, the literature pertaining to *CYP2D6* is somewhat discordant and requires careful examination of the details.

Selected publications report *CYP2D6* genotype derived from analyses of tumour DNA rather than germline DNA.[16-19] This has been a cause of debate as to whether it is valid to assess patients’ inherent metabolism of tamoxifen via tumour DNA, as metabolism of tamoxifen by CYP2D6 occurs in the liver and therefore germline rather than tumour DNA is more relevant. This practice is also problematic in view of the Hardy Weinberg Equilibrium, which predicts the stability of allelic and genotypic frequencies through the generations in the absence of outside factors.[20]

The method by which *CYP2D6* genotype is determined also requires careful consideration. Commercial availability of *CYP2D6* genotyping does not guarantee that a comprehensive panel of assessment is offered. We have found varying degrees of comprehensiveness for *CYP2D6* single nucleotide polymporphisms tested amongst commercially available panels for genotyping *CYP2D6,* which renders standard evaluation of these problematic. As such, the panel below lists alleles and haplotypes that are required to be measured to classify phenotype according to the current categorisation recommended by the International Clinical Pharmacogenetics Implementation Consortium (figure 2).

The current phenotype categorisation of CYP2D6 was devised according to the metabolism of the drug codeine, so it is uncertain whether it can equally be applied to tamoxifen metabolism.[18] Historically, CYP2D6 had been phenotyped by categorisation systems derived from debrisoquine, sparteine and other drugs.[21,22] The recent categorisation system for CYP2D6 using codeine shifted several haplotypes from one phenotype to the other without evidence for this in regards to tamoxifen. This raises the question whether it is valid to use a system derived from codeine metabolism and apply it to tamoxifen metabolism.

Direct measurement of CYP2D6 enzyme activity, however, can be inferred by the N-desmethyl-tamoxifen/endoxifen ratio, as N-desmethyl-tamoxifen is converted to endoxifen by CYP2D6. We devised a categorisation system utilising this measure of protein activity by calculating the ratio and dichotomising patients to wild-type or variant metabolisers, which we found was superior to the current codeine devised classification system in predicting CYP2D6 protein activity.[23] Though our categorisation was demonstrated in our cohort of 106 patients to be superior to the pre-existent codeine classification system, we still propose that the most accurate measure of tamoxifen effect by endoxifen is to directly assess the endoxifen level rather than infer tamoxifen activity from genotype or phenotype.

As we have previously acknowledged, there is a trend for *CYP2D6* poor metabolisers to have lower endoxifen, and extensive metabolisers to have higher endoxifen.[24-26] However a high degree of overlap in endoxifen levels with *CYP2D6* genotype and phenotype has been replicated in other groups. Therefore *CYP2D6* genotype alone does not accurately estimate endoxifen level and whether potential therapeutic levels have been achieved.

There are also conflicting data linking *CYP2D6* genotype and disease free and overall survival in tamoxifen-treated women,[16,27-29] presumably in part because of the overlap mentioned above. Therefore, it is not possible to predict survival or response to tamoxifen based only on *CYP2D6* genotype.

We therefore support the use of direct endoxifen measurement rather than measuring genotype to guide therapeutic efficacy of tamoxifen effect.

## Dosing of tamoxifen

The current standard dose of tamoxifen is 20mg per day as established from clinical trials. This remains despite the known variability in *CYP2D6* and more importantly, endoxifen levels. We and others have examined the role of dose escalation in the face of low levels and found that with dose escalation of tamoxifen, endoxifen levels will always increase, though the rate of increment varies according to phenotype.[15]

We also conducted a study in a small cohort of tamoxifen-treated women who were experiencing intolerable toxicity that threatened compliance, to determine whether dose reduction improved hot flushes.[29] Firstly, we found that the distribution of *CYP2D6* genotype was similar to that in our original 122 patient cohort, suggesting that *CYP2D6* is not the cause of intolerable hot flushes, supporting our findings in the original cohort. Furthermore, we found that upon dose reduction from 20mg to 10mg, endoxifen levels halved and that a larger proportion of women were below the purported therapeutic level of 15nM. Although some patients reported subjective improvements in hot flushes upon dose reduction, when tested by the validated Loprinzi instrument,[30] there were no statistically significant differences in hot flushes between dose levels. Therefore, we recommend that dose should not be changed according to *CYP2D6* genotype or phenotype nor to hot flush toxicity of tamoxifen. Endoxifen levels however will change according to dose alteration, albeit to differing degrees and impacted to varying degrees to patients' CYP2D6 phenotype as well as environmental and other factors.[31,32]

Therefore, to summarise:

### 1) *Anti-oestrogenic activity*

- Tamoxifen itself is a weakly active prodrug that is converted by cytochrome p450 enzymes to produce active metabolites, of which endoxifen is the most potent and abundant.

### *2) CYP2D6*

- CYP2D6 is the cytochrome p450 enzyme that has wide pharmacogenetic variability and impacts on conversion of tamoxifen to endoxifen.
- *CYP2D6* genotyping assessment should be performed on germline DNA and not tumour DNA.
- The current systems for phenotyping CYP2D6 are based on codeine metabolism.
- There are trends for patients with poor CYP2D6 metaboliser phenotype to have lower levels of endoxifen and for patients with extensive CYP2D6 metaboliser phenotype to have higher levels, however there is a great deal of overlap.
- *CYP2D6* genotype and recurrence-free survival have not been consistently correlated.
- *CYP2D6* genotype and hot flush toxicity have not been consistently correlated.

### *3) Endoxifen level*

- In two retrospective cohorts of tamoxifen-treated women with early breast cancer, worse recurrence-free survival was seen with levels lower than 15nM.
- Endoxifen therapeutic monitoring may be of value though currently this is not available in Australia in commercial laboratories outside of the research setting.

### *4) Dose of Tamoxifen*

- Changing tamoxifen dose impacts endoxifen level, with dose escalation causing increase and dose reduction a decrease in level. The degree of endoxifen level change is influenced by *CYP2D6* genotype.

### *5) Hot flushes*

- Neither endoxifen level nor *CYP2D6* genotype is associated with the severity of hot flush and this toxicity should not be used as a surrogate for tamoxifen efficacy or to estimate genotype or endoxifen level.

Ultimately, further research is required to ascertain the robustness of the therapeutic endoxifen level and the utility of this in a clinical setting. We recommend overall however, that CYP2D6 testing should not be used to determine whether a woman should be treated with tamoxifen or at what dose. If a threshold endoxifen level is demonstrated more clearly, then endoxifen level testing may become important.

***Figure 1:*** *Simplified representation of tamoxifen metabolism to endoxifen depicting key cytochrome P450 enzymes* [28,29]

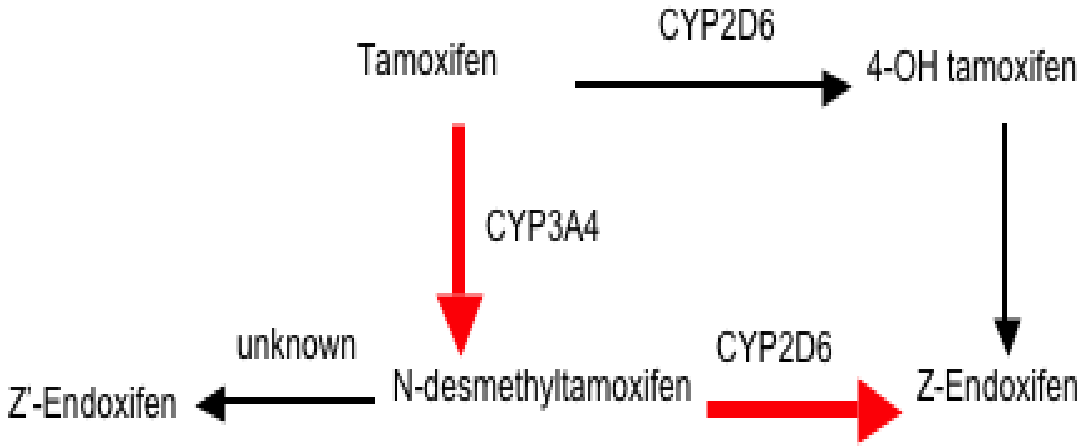


***Figure 2:*** *The current CYP2D6 phenotypic categorisation according to Crews et al for codeine, as recommended by the International Clinical Pharmacogenetics Implementation Consortium.*[18]

**Supplemental Table S5. Predicted metabolizer phenotypes based on *CYP2D6* diplotypes (allele combinations).**

| | | Predicted Metabolizer Phenotype (Range Multi-Ethnic Frequency[a]) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Allele** | ***1*** | ***2*** | ***1xN or *2xN*** | ***3*** | ***4 or *4xN*** | ***5*** | ***6*** | ***10*** | ***17*** | ***41*** |
| ***1*** | **EM** | **EM** | **UM** | **EM** | **EM** | **EM** | **EM** | **EM** | **EM** | **EM** |
| ***2*** | | **EM** | **UM** | **EM** | **EM** | **EM** | **EM** | **EM** | **EM** | **EM** |
| ***1xN or *2xN*** | | | **UM** | **EM or UM** | **EM or UM** | **EM or UM** | **EM or UM** | **UM** | **UM** | **UM** |
| ***3*** | | | | **PM** | **PM** | **PM** | **PM** | **IM** | **IM** | **IM** |
| ***4*** | | | | | **PM** | **PM** | **PM** | **IM** | **IM** | **IM** |
| ***5*** | | | | | | **PM** | **PM** | **IM** | **IM** | **IM** |
| ***6*** | | | | | | | **PM** | **IM** | **IM** | **IM** |
| ***10*** | | | | | | | | **EM[b]** | **EM[b]** | **EM[b]** |
| ***17*** | | | | | | | | | **EM[b]** | **EM[b]** |
| ***41*** | | | | | | | | | | **EM[b]** |

EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer

## References


1. Cole MP, Jones CT, Todd ID. A new anti-oestrogenic agent in late breast cancer. An early clinical appraisal of ICI46474. Br J Cancer. 1971;25:270-5.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15 year survival: an overview of the randomised trials. The Lancet. 2005;365(9472):1687-1717.
3. Crewe HK, Ellis SW, Lennard MS, et al. Variable contribution of cytochromes P450 2D6, 2C9 and 3A4 to the 4-hydroxylation of tamoxifen by human liver microsomes. Biochem Pharmacol. 1997;53:171-8.
4. Johnson MD, Zuo H, Lee KH, et al. Pharmacological characterization of 4-hydroxy-N-desmethyl tamoxifen, a novel active metabolite of tamoxifen. Breast Cancer Res Treat. 2004;85:151-9.
5. Crewe HK, Notley LM, Wunsch RM, et al. Metabolism of tamoxifen by recombinant human cytochrome P450 enzymes: formation of the 4-hydroxy, 4'-hydroxy and N-desmethyl metabolites and isomerization of trans-4-hydroxytamoxifen. Drug Metab Dispos. 2002;30:869-74.
6. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst. 2005;97:30-9.
7. Binkhorst L, Mathijssen RH, Jager A, et al. Individualization of tamoxifen therapy: much more than just CYP2D6 genotyping. Cancer Treat Rev. 2015;41:289-99.
8. Wu X, Hawse JR, Subramaniam M, et al. The tamoxifen metabolite, endoxifen, is a potent antiestrogen that targets estrogen receptor alpha for degradation in breast cancer cells. Cancer Res. 2009;69:1722-7.
9. Gong IY, Teft WA, Ly J, et al. Determination of clinically therapeutic endoxifen concentrations based on efficacy from human MCF7 breast cancer xenografts. Breast Cancer Res Treat. 2013;139:61-9.
10. Madlensky L, Natarajan L, Tchu S, et al. Tamoxifen metabolite concentrations, CYP2D6 genotype, and breast cancer outcomes. Clin Pharmacol Ther. 2011;89:718-25.
11. Saladores P, Murdter T, Eccles D, et al. Tamoxifen metabolism predicts drug concentrations and outcome in premenopausal patients with early breast cancer. Pharmacogenomics J. 2015;15:84-94.
12. Hawse JR, Subramaniam M, Cicek M, et al. Endoxifen's molecular mechanisms of action are concentration dependent and different than that of other anti-estrogens. PLoS One. 2013 8:e54613.
13. Wu X, Hawse JR, Subramaniam M, et al. The tamoxifen metabolite, endoxifen, is a potent antiestrogen that targets estrogen receptor alpha for degradation in breast cancer cells. Cancer Res. 2009;69:1722-7.
14. Gong IY, Teft WA, Ly J, et al. Determination of clinically therapeutic endoxifen concentrations based on efficacy from human MCF7 breast cancer xenografts. Breast Cancer Res Treat. 2013;139:61-9.
15. Fox P, Balleine RL, Lee C, et al. TADE study paper Dose Escalation of Tamoxifen in Patients with Low Endoxifen Level: Evidence for Therapeutic Drug Monitoring—The TADE Study, Clinical Cancer Research, 2016.
16. Brauch H, Schroth W, Goetz MP, et al. Tamoxifen use in postmenopausal breast cancer: CYP2D6 matters. J Clin Oncol. 2013;31:176-80.
17. Province MA, Goetz MP, Brauch H, et al. CYP2D6 genotype and adjuvant tamoxifen: meta-analysis of heterogeneous study populations. Clin Pharmacol Ther. 2014;95:216-27.
18. Johnson JA, Hamadeh IS, Langaee TY. Loss of heterozygosity at the CYP2D6 locus in breast cancer: implications for tamoxifen pharmacogenetic studies. J Natl Cancer Inst. 2015;107.
19. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95:376-82.
20. Salanti G, Amountza G, Ntzani EE. Hardy–Weinberg equilibrium in genetic association studies: an empirical evaluation of reporting, deviations, and power. Eur J Hum Genet. 2005;13;840–848. doi:10.1038.
21. Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultrarapid metabolism of debrisoquine (geneamplificatlon/ sparteilne/ bufuralol/ pharmacogenetlcs/ drugtherapy)

22. Evans DAP, Harmer D, Downhan. The genetic control of sparteine and debrisoquine metabolism in man with new methods of analysing bimodal. J Med Genet. 1983;20:321-32.
23. Lee CI, Low ASK, Fox P. Simplified CYP2D6 metabolizer phenotype categorization of patients treated with tamoxifen: Role for endoxifen level monitoring. J Clin Oncol. 2016;34 (suppl; abstr 536)
24. Nowell SA, Ahn J, Rae JM, et al. Association of genetic variation in tamoxifen-metabolizing enzymes with overall survival and recurrence of disease in breast cancer patients. Breast Cancer Res Treat. 2005;91:249-58.
25. Murdter TE, Schroth W, Bacchus-Gerybadze L, et al. Activity levels of tamoxifen metabolites at the estrogen receptor and the impact of genetic polymorphisms of phase I and II enzymes on their concentration levels in plasma. Clin Pharmacol Ther. 2011;89:708-17.
26. Wu AH, Lorizio W, Tchu S, et al. Estimation of tamoxifen metabolite concentrations in the blood of breast cancer patients through CYP2D6 genotype activity score. Breast Cancer Res Treat. 2012;133:677-83.
27. Regan MM, Leyland-Jones B, Bouzyk M, et al. CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the breast international group 1-98 trial. J Natl Cancer Inst. 2012;104:441-51.
28. Brauch H, Schroth W, Goetz MP, et al. Tamoxifen use in postmenopausal breast cancer: CYP2D6 matters. J Clin Oncol. 2013;31:176-80.
29. Lee CI, Fox P, Balakrishnar B. Tamoxifen (TAM)-induced severe hot flashes (HF): Is dose reduction (DR) a safe and effective strategy? J Clin Onc. 2015;33(15)557.
30. Sloan J, Loprinzi C, Novotny P. Methodologic Lessons Learned From Hot Flash Studies. J Clin Oncol. 2001;19(23):4280-4290.
31. Stearns V, Johnson MD, Rae JM, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin inhibitor paroxetine. J Natl Cancer Inst. 2003;95(23):1758-64.
32. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst. 2005;97(1):30-9.

# Bone health in the treatment of postmenopausal women with Aromatase Inhibitors and premenopausal women treated with ovarian suppression and Aromatase inhibitors: a hands-on guide

Clara I Lee

The University of Sydney Sydney, New South Wales, Australia.
The University of New South Wales, Sydney, New South Wales, Australia.
Bankstown Hospital, Sydney, New South Wales, Australia.

Email: clara.lee@sydney.edu.au

**Abstract**
In postmenopausal women, and premenopausal women treated concomitantly with ovarian suppression, aromatase inhibitors are a standard of care in the adjuvant treatment of hormone sensitive breast cancer. Dosed daily for up to ten years, these drugs are not without significant toxicity. Given such protracted duration of treatment and that the majority of women treated in this setting have very favourable disease free and overall survival from their early stage breast cancer, long-term toxicity is a particular concern. The most concerning long-term toxicity is the deleterious effect of aromatase inhibitors on bone density. Accelerated bone loss due to aromatase inhibitors confers increased fracture risk and thereby significant morbidity. Therefore it is important to investigate and monitor bone health prior to commencement of and during aromatase inihibitor treatment, and ensure appropriate measures to optimize bone health are instituted. Recommendations from the summary of the literature to date, relevant to the Australian setting are outlined in this paper.

Approximately 70% of early breast cancers are hormone sensitive (in that they express either or both oestrogen and progesterone receptors) and adjuvant endocrine therapies, with or without chemotherapy, reduce the risk of cancer recurrence, improve survival and are therefore regarded as standard treatment.[1] Evidence to date has demonstrated that to derive maximal adjuvant benefit, at least five years of daily dosing of endocrine therapy is required. While tamoxifen is active in both pre and postmenopausal women, aromatase inhibitors are only active in postmenopausal women.

When compared with tamoxifen, adjuvant treatment with aromatase inhibitors leads to improved breast cancer specific disease free survival and overall survival and differences in toxicity profiles.[2] Accelerated loss of bone mineral density is a well-recognised toxicity of the aromatase inhibitors,[3-6] whereas tamoxifen does not detrimentally affect bone mineral density in postmenopausal women. However tamoxifen confers a small but established increased risk of endometrial cancer and venous thromboembolism and therefore aromatase inhibitors are often used instead.[7,8] Bone health thus becomes not only an immediate, but also a long-term issue,[9-12] as the five year survival for all women with early breast cancer is now 90%, and a majority of these women will survive for decades beyond their initial diagnosis.[13]

## Aromatase Inhibitors and bone loss

Large trials testing aromatase inhibitor treatment have examined bone outcomes. While women with normal bone density (T-score > -1.5) did not develop osteoporosis (T-score < -2.5) after five years of treatment,[14,15] there was an increase in fractures in the cohorts as a whole. Women commenced on an adjuvant aromatase inhibitor may develop significant bone loss (>10%) over the initial 12 months with further development of osteopenia or osteoporosis during the years of their adjuvant treatment.

Such an increased fracture risk may require additional treatment or a change to tamoxifen depending on clinical appropriateness. While early studies did not suggest that such effects on bone from aromatase inhibitors were a significant problem,[16-17] subsequent reports that have been more focused on bone-related outcomes and suggest otherwise. [6,13-15] Gnant and colleagues published the results of their randomised trial in 2015, examining the use of the RANK-ligand inhibitor, denosumab, to combat bone mineral density-related adverse events. In this study, the fracture rate in patients in the placebo arm was alarmingly high.[18] These new data further support the utility of adjuvant antiresorptive agents in the prevention of bone loss, and serve to augment their importance in this role more so than once thought.[19] In fact, there is emerging evidence and some recent published data suggesting that antiresorptive agents may improve disease free survival in addition to preventing bone loss.[20] It is quite reassuring, however, that once aromatase inhibitor treatment is completed, the accelerated bone demineralisation and increased fracture risk does not progress nor continue.[21]

Thus in these generally fit women in whom we induce pharmacologic acceleration of bone demineralisation due to their adjuvant breast cancer treatment,[22] it is important to identify those who require additional treatment to preserve bone mass.[3]

## General measures to minimise bone loss

### *Weight bearing exercise and smoking cessation*

Both of these lifestyle measures are important in maintaining both health.

### *Ensuring adequate calcium intake*

All women treated with adjuvant aromatase inhibitor should ingest 1g (equivalent to 4 serves of dairy) per day of calcium in dietary intake.[23] Should dietary intake fall short of this, supplemental calcium is recommended at 600mg depending on dietary intake. Previous concerns regarding the potential for calcium supplementation to increase coronary artery calcification have been largely allayed with reference to postmenopausal women.[24]

### *Ensuring adequate vitamin D levels*

Vitamin D levels fluctuate, largely depending on season, sun-exposure and individual genetics. Vitamin D insufficiency has been found in a significant proportion of women commencing aromatase inhibitors.[25,26] Australian guidelines define levels of 50 nmol/L and above at the end of winter as acceptable though low normal, and levels of 75 nmol/L and above as normal. All patients should have their vitamin D levels checked at baseline, prior to commencing adjuvant aromatase inhibitor endocrine therapy. In the case of subnormal vitamin D levels, replacement is recommended as specified in the Australian vitamin D position statement paper.[27]

## Assessment of bone mineral density

Recent evidence confirms that improving bone mineral density (BMD) with anti-resorptive agents can reduce fracture risk, so it is prudent to check baseline BMD with a dual energy x-ray absorptiometry (DEXA) scan at the time of commencement of an aromatase inhibitor in all patients.[18]

If T-score of either femoral neck or lumbar spine is > -1.5 then the DEXA should be repeated in a year's time, as the most precipitous reduction in BMD is expected to occur in the first year.[28,29] A 10% or more loss of BMD suggests there may be additional processes other than aromatase inhibitor toxicity accounting for loss of BMD. Therefore, should there be 10% of BMD loss or more compared with the baseline DEXA and T-score < -1.5, a referral to an endocrinologist for further investigation should be made.

If at any stage the T score is < -1.5, then treatment should be considered. For T scores -1.5 to -2.5 (osteopenic), a lateral thoracic plain x-ray should be performed, as there is a reported high incidence of pre-existent vertebral fractures in such women commencing aromatase inhibitor.[25] In these patients, should there be evidence of vertebral fractures (or >20% loss of anterior compared with posterior vertebral height) this will qualify for Pharmaceutical Benefits Scheme supported bisphosphonate therapy or rank-ligand inhibitor. A DEXA scan should then be repeated every two years.

For those with T score <-2.5 (osteoporotic), those who are also over 70 years of age qualify for denosumab, as do those under 70 but with a history of fracture or evidence of vertebral body fracture on x-ray. For those who do not qualify, oral bisphosphonates may now be prescribed off Pharmaceutical Benefits Scheme quite inexpensively.

## Bone-active agents

### *Bisphosphonates*

The role of bisphosphonates is clear in the treatment of osteoporosis in the presence of minimal trauma fracture or in the elderly, and is reimbursed by the PBS. In the treatment of aromatase inhibitor accelerated bone density loss however, there is a clear role also, though the indication without advanced age or fracture is not reimbursable.

In a recently reported clinical study, patients have volunteered that oral bisphosphonate regimens are not only equivalent in efficacy to intravenous administration, but preferred over intravenous regimens.[30] These drugs however are not without toxicity. Given in the oral form, upper gastrointestinal side effects include dyspepsia, gastro-oesophageal reflux and peptic ulceration, and both intravenous and oral preparations can very rarely induce the potentially serious complication of osteonecrosis of the jaw.[11,31] There may be a role for use of oral bisphosphonate on private prescription to prevent further bone loss in the absence of minimal trauma fracture, as the cost is similar to PBS subsidised risedronate and alendronate.

Baseline calcium levels also need to be monitored pre-treatment with bisphosphonates, with hypocalcaemia being an occasional but potentially serious toxicity of these drugs in clinic. Additionally, renal function needs to be monitored.[32] Despite this, though effective in maintaining BMD, it seems there is still a persistent fracture risk with this treatment.[33-35]

### *RANK-ligand inhibitors*

Denosumab, a rank-ligand inhibitor, is an effective alternative to the bisphosphonate, zoledronic acid in the treatment of osteoporosis. This is a well-tolerated drug given as a six monthly subcutaneous injection, and has been shown to be effective in the management of aromatase inhibitor induced bone loss.[18,36] Although osteonecrosis of the jaw can occur with RANK ligand inhibitors, it may occur less frequently than that which is seen with bisphosphonates and reassuringly in a recently reported large trial, no cases were reported with denosumab.[18] Hypocalcaemia occurs more frequently with rank-ligand inhibitors than with bisphosphonates and vitamin D should be >50nmol/L before administration of RANK ligand inhibitors. Renal failure is not a limiting factor with this drug.

## Conclusion

It is clear that the management of bone health in postmenopausal women treated with adjuvant aromatase inhibitor endocrine therapy is multifaceted, requires coordination and close follow-up to ensure optimal well-being with improved survival rates. With the aforementioned strategies outlined, bone health can be optimised and the deleterious impact of aromatase inhibitors on bone can be countered if appropriately managed. Ultimately, the steps described here can be utilised within a multidisciplinary context and should assist in the processes to ensure optimal bone health in our patients.

## References

1. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011;378:771-84.
2. Dowsett M, Forbes JF, Bradley R, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386:1341-52.
3. Hadji P, Body JJ, Aapro MS, et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. Ann Oncol. 2008;19:1407-16.
4. Body JJ. Prevention and treatment of side-effects of systemic treatment: bone loss. Ann Oncol. 2010;21 Suppl 7:vii180-5.

5. Nuzzo F, Gallo C, Lastoria S, et al. Bone effect of adjuvant tamoxifen, letrozole or letrozole plus zoledronic acid in early-stage breast cancer: the randomized phase 3 HOBOE study. Ann Oncol. 2012;23:2027-33.
6. McCloskey E. Effects of third-generation aromatase inhibitors on bone. Eur J Cancer. 2006;42:1044-51.
7. Coleman RE, Body JJ, Gralow JR, et al. Bone loss in patients with breast cancer receiving aromatase inhibitors and associated treatment strategies. Cancer Treat Rev. 2008;34 Suppl 1:S31-42.
8. Cauley JA. Bone loss associated with prevention of breast cancer. Lancet Oncol. 2012;13:221-2.
9. Gralow JR. Bone density in breast cancer: when to intervene? J Clin Oncol. 2007;25:3194-7.
10. Gnant M, Blaha P, Dubsky P, et al. Adjuvant bisphosphonates in endocrine-responsive breast cancer: what is their place in therapy? Ther Adv Med Oncol. 2009;1:123-36.
11. Perez EA, Weilbaecher K. Aromatase inhibitors and bone loss. Oncology (Williston Park) 2006;20:1029-39; discussion 1039-40, 1042, 1048.
12. Rugo HS. Strategies for the prevention of treatment-related bone loss in women receiving adjuvant hormonal therapy. Clin Breast Cancer. 2007;7 Suppl 1:S21-8.
13. Cancer in Australia 2014: actual incidence data from 1982 to 2011 and mortality data from 1982 to 2012 with projections to 2014. Asia Pac J Clin Oncol. 2015;11:208-20.
14. Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol. 2008;26:1051-7.
15. Markopoulos C. Managing bone health in women with breast cancer under adjuvant treatment with aromatase inhibitors: pretreatment bone mineral density is important. Breast Cancer Res. 2010;12:403.
16. Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. Lancet Oncol. 2011;12:1101-8.
17. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. 2010;11:1135-41.
18. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2015;386:433-43.
19. Dhesy-Thind SK. Screening for osteoporosis in postmenopausal women with breast cancer receiving aromatase inhibitors: less is more. J Clin Oncol. 2012;30:1408-10.
20. Coleman R, Powles T, Paterson A, et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet. 2015;386:1353-61.
21. Eastell R, Adams J, Clack G, et al. Long-term effects of anastrozole on bone mineral density: 7-year results from the ATAC trial. Ann Oncol. 2011;22:857-62.
22. Decensi A, Sun Z, Guerrieri-Gonzaga A, et al. Bone mineral density and circulating biomarkers in the BIG 1-98 trial comparing adjuvant letrozole, tamoxifen and their sequences. Breast Cancer Res Treat. 2014;144:321-9.
23. Holmes-Walker J, Prelevic GM, Jacobs HS. Effects of calcium and exercise on bone mineral density in premenopausal women with osteoporosis. Curr Opin Obstet Gynecol. 1995;7:323-6.
24. Manson JE, Allison MA, Carr JJ, et al. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. Menopause. 2010;17:683-91.
25. Bouvard B, Hoppe E, Soulie P, et al. High prevalence of vertebral fractures in women with breast cancer starting aromatase inhibitor therapy. Ann Oncol. 2012;23:1151-6.
26. Servitja S, Nogues X, Prieto-Alhambra D, et al. Bone health in a prospective cohort of postmenopausal women receiving aromatase inhibitors for early breast cancer. Breast. 2012;21:95-101.
27. Nowson CA, McGrath JJ, Ebeling PR, et al. Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Aust. 2012;196:686-7.
28. Hadji P, Ziller M, Kieback DG, et al. Effects of exemestane and tamoxifen on bone health within the Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial: results of a German, 12-month, prospective, randomised substudy. Ann Oncol. 2009;20:1203-9.

29. Jones S, Stokoe C, Sborov M, et al. The effect of tamoxifen or exemestane on bone mineral density during the first 2 years of adjuvant treatment of postmenopausal women with early breast cancer. Clin Breast Cancer. 2008;8:527-32.
30. Gralow J. Phase III trial of bisphosphonates as adjuvant therapy in primary breast cancer: SWOG/Alliance/ECOG-ACRIN/NCIC Clinical Trials Group/NRG Oncology study S0307. J Clin Oncol. 2016;33 (suppl; abstr 503)
31. Chowdhury S, Pickering LM, Ellis PA. Adjuvant aromatase inhibitors and bone health. J Br Menopause Soc. 2006;12:97-103.
32. Brufsky AM. Managing bone loss in women with early-stage breast cancer receiving aromatase inhibitors. Clin Breast Cancer. 2007;8 Suppl 1:S22-34.
33. Bundred NJ, Campbell ID, Davidson N, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. Cancer. 2008;112:1001-10.
34. Saad F, Adachi JD, Brown JP, et al. Cancer treatment-induced bone loss in breast and prostate cancer. J Clin Oncol. 2008;26:5465-76.
35. Bouvard B, Soulie P, Hoppe E, et al. Fracture incidence after 3 years of aromatase inhibitor therapy. Ann Oncol. 2014;25:843-7.
36. Ellis GK, Bone HG, Chlebowski R, et al. Effect of denosumab on bone mineral density in women receiving adjuvant aromatase inhibitors for non-metastatic breast cancer: subgroup analyses of a phase 3 study. Breast Cancer Res Treat. 2009;118:81-7.

# The ‘enablers’: inhibitors of mTOR, PI3K and CDK that prolong endocrine sensitivity

Nicholas Wilcken

Crown Princess Mary Cancer Centre, Westmead Hospital, University of Sydney, Sydney, New South Wales, Australia.

Email: nicholas.wilcken@sydney.edu.au

**Abstract**

For many years, tamoxifen and the aromatase inhibitors have been the mainstay of treatment for ER positive breast cancer, although it has been apparent that resistance to these drugs is a limiting factor. We are now at the beginning of a new era, as drugs that block the development of endocrine resistance are becoming available. Pre-clinical research has given us an understanding of some of the molecular mechanisms of endocrine resistance, identifying new targets for drug development. Chief among these are the PI3 kinase/AKT pathway and the cell cycle control mechanism governed by cyclins and cyclin dependent kinases (CDKs). We are now in the process of integrating mTOR inhibitors, PI3kinas inhibitors and CDK 4/6 inhibitors into clinical practice on the back of clinical trial results that show they can prolong the effects of endocrine agents.

Endocrine therapy for breast cancer dates back to 1896, when the Scottish surgeon Beatson demonstrated the effectiveness of oophorectomy.[1] He was testing a hypothesis derived from observations on cows in his farm, and was right but for the wrong reasons.

However we have continued to make clinical progress without always understanding why. Older readers will remember stilboestrol (an estradiol analogue) being effective in metastatic breast cancer, and even now estradiol can induce responses after progression on aromatase inhibitors.[2] One should always be a little sceptical therefore, when offered detailed diagrams and explanations of mechanisms of action. Even in the modern era, as Luen and Loi show in the last contribution to this Forum, we initially were mistaken when considering the mechanism of action of trastuzumab.

That said, the model of drug interaction with the estrogen receptor (ER) has served well as an explanation for the mechanisms of action of the selective estrogen receptor modifiers (SERMs) and the aromatase inhibitors (AIs), and the difference in their toxicities. What has been less clear is why the agents become ineffective over time.

More recently, an increased understanding of intra-cellular signalling pathways and confirmatory preclinical work has led to clinical trials of relevance to clinical practice. Benefits have been seen with drugs that manipulate two relatively separate pathways: the PI3K/AKT/mTOR survival pathway and the cell cycle regulating pathway.

## Manipulating the PI3K survival pathway – mTOR inhibition

It is simplistic but useful to conceptualise two complementary pathways that link the outside environment to the inner workings of the cell. Thus we have our transmembrane receptors (like HER2 and EGFR) becoming activated as a response to external triggers and initiating activation of intracellular molecules along different (although cross-talking) pathways: the ‘proliferative’ pathway (ras, raf, MAP kinase) and the ‘survival’ or anti-apoptosis pathway (PI3 kinase, AKT, mTOR).

These signal transduction pathways allow the cell to characterise with great sensitivity the nature of the external environment and fine tune what the growth (or quiescence) state of the cell is optimal. Clearly in the malignant state, these processes malfunction and the challenge for scientists and healthcare professionals is to try and interrupt overactive signals.

A large amount of preclinical data exist to show that the PI3 kinase, AKT, mTOR pathway is frequently up-regulated in cancers, and mutations (especially of PI3K genes) can be identified.[3] This is true of breast cancer generally, although the incidence of mutations varies between subtypes. PI3K mutations are more frequently seen in ER positive disease (about 35%) and HER2 positive disease (about 25%) than in triple negative disease (<10%). In ER positive disease there are preclinical (and now clinical) data to show that resistance to endocrine therapies is at least in part mediated by abnormalities in the PI3K pathway. A logical development therefore is to examine the action of drugs that can inhibit this pathway. (Companion studies are examining resistance to anti-HER2 therapies.)

The first agents to be tested in ER positive breast cancer were mTOR inhibitors, and the clinical proof of principle was demonstrated in the BOLERO 2 trial.[4] This was a phase III study comparing everolimus (Afinitor) plus exemestane with exemestane alone in women with metastatic disease after progression on a standard aromatase inhibitor. The results were compelling. Median progression free survival was 6.9 v 2.8 months (investigator assessment) or 10.6 v 4.1 months (central assessment) with HRs of 0.43 and 0.36 respectively, p<0.001, demonstrating that there was a 60% improvement in the time the disease remained under control.

There was however a complication, namely toxicity. Although the toxicity reported was modest (serious toxicity occurred in less than 10% of cases: grade 3 stomatitis 8%, fatigue 4%, pneumonitis 3%), two things are worthy of note. The first is that these were the usual fitter-than-average clinical trial patients, and the second is that grade 3 toxicity is actually quite significant for the patient receiving treatment. On the other hand, grade 1 toxicity may be too easily recorded (56% had some degree of stomatitis), and we often need to learn about toxicity from our own clinical practices. Anecdotally, clinician enthusiasm for using this drug has lessened somewhat since it first became available on the PBS in Australia because of concerns about toxicity.

On balance however, this is an important proof of principle – clearly inhibiting the PI3K pathway does have an impact on endocrine resistance and this mTOR inhibitor confers a meaningful clinical benefit. It is likely that careful patient selection will lead to the greatest good and the least harm.

## Manipulating the PI3K survival pathway – PI3K inhibition

The ability to identify clinically effective, low toxicity PI3K inhibitors continues, with no such drugs yet approved in Australia. It should be noted that PI3K biology is complex, and it may be some time before the right balance between efficacy and toxicity is found. PI3K is actually a family of kinases. They are heterodimers, with a regulatory (p85) and a catalytic (p110) domain with p110 existing as four isoforms (alpha to delta), all with potentially slightly different biological functions. In breast cancer, most mutations occur in PI3K alpha (PI3KCA), although it is still uncertain whether having a PI3K mutation is actually predictive of response to PI3K inhibitors. Additionally different drugs affect different PI3K isoforms and the clinical relevance of this is not yet clear.

Buparlisib (BKM120) for example, is a pan PI3K inhibitor, inhibiting all isoforms of p110. It clearly has activity in metastatic ER positive breast cancer, and neoadjuvant studies are ongoing. The most definitive study to date is the BELLE 2 study, the results of which were first presented in December 2015 at the San Antonio Breast Cancer Symposium.[5]

This phase III trial randomised over 1000 women with metastatic ER positive breast cancer and progression after aromatase inhibitors to fulvestrant (at the appropriate 500mg dose) plus or minus buparlisib. The statistical analysis of this trial is complicated to a degree because the investigators had stipulated a number of co-primary endpoints, based on well justified biological criteria. In short, when the whole cohort was examined there was a modest benefit in progression free survival (PFS) (median 6.9 v 5 months, HR 0.78, p=0.001).

Toxicity was significant, with transaminitis, hyperglycaemia and psychiatric problems of concern. As with everolimus, the actual risk of grade 3 events was not high, but this is probably not going to be an easy drug to use, with patient selection (for example not diabetic, no history of depression) critical.

However the most interesting aspect of this study was the translational subset of patients with identifiable PI3K mutations detected in circulating tumour DNA (ctDNA). In this group of 200 patients, there appeared to be a more pronounced benefit for those with a ctDNA-detected mutation, and no

benefit in those with detectable ctDNA but no mutation. It is therefore possible that with improvements in technology we may be able to accurately and cheaply identify those who stand to gain a lot and may accept some toxicity, as well as those who can avoid toxicity and be offered a different drug.

There thus remains substantial interest in developing drugs that interact with this pathway in ER positive (and HER2 positive) disease. It may be for example that a more specific p110alpha inhibiting PI3K inhibitor such as alpesilib could avoid some toxicity, but maintain efficacy. Additionally, drugs that target both AKT and mTOR are in development. The biology of these approaches seems sound and initial efficacy signals are positive, but the drugs we have to date might be regarded as our own era's stilboestrol, and we are waiting for a tamoxifen.

## The CDK inhibitors

Meanwhile the science of cell cycle control has been evolving. Nobel prize-winning work in the 1980s demonstrated that in all cells from yeast to mammals, a system of "checkpoint" activators mediates progression through the cell cycle, ensuring orderly activity in the cell and appropriate, accurate DNA copying and mitosis. Thus cyclin dependent kinases (CDKs), periodically activated by specific cyclin proteins, determine for example if a cell will enter the G1 phase of the cell cycle or remain quiescent in $G_0$. Ultimately all the pathways mentioned above impinge upon this central process, and to the extent that cancer is a disease of abnormal proliferation, the cyclin/CDK system is critical.

Since those early findings aberrant CDK activity in cancer cells has been described, and in particular in ER positive breast cancer cells, the cyclin D1/CDK4 partnership has been implicated. In the test tube, artificially increasing the amount of cyclin D1 (thus over-activating CDK4) leads to endocrine resistance,[6] raising the possibility that impeding CDK4 activity might usefully overcome endocrine resistance in the clinical setting.

This knowledge has given rise to the era of CDK inhibitors which are now being tested in various clinical scenarios.[7] The flagship studies so far have been the PALOMA 1 and PALOMA 3 trials of palbociclib, a CDK4 and CDK6 inhibitor.[8,9] In the first phase II study women with untreated metastatic disease were treated with letrozole alone versus with palbociclib and in the phase III study, women treated and progressing on previous aromatase inhibitors were randomised to fulvestrant plus or minus palbociclib.

In both instances, results were quite remarkable, with PFS in the first line cohorts 20 v 10 months (HR 0.49, p=0.0004) and in the second line 9.2 v 3.8 months (HR 0.42, p<0.001). This suggests first that this drug is very active and second, that it may be equally active whether given before or after resistance has developed. This may have an impact on the sequence in which all of these 'enablers' might best be used, but clearly much has yet to be learned, including identifying predictors of sensitivity and resistance. Early data suggest that PI3KCA mutations do not affect the efficacy of palbociclib, but that cyclin D status may have this effect.

Finally, unlike the mTOR and PI3K inhibitors tested so far, toxicity seems to be a lot more manageable with this and other CDKIs. Neutropaenia is common but infection rare, and there is some fatigue. This may then be a drug that could be used in well women in the adjuvant setting, and an international adjuvant trial is being activated (the PALLAS study, coordinated in Australia by the ANZ Breast Cancer Trials Group).

## Conclusion

After many decades over which progress was limited, the ER positive space is now one of very active scientific enquiry and there are already some arrivals from the bench to the bedside – in fact make that 'side', as most of our patients with metastatic breast cancer now are well and active and not in bed.

Clearly there is still a lot to learn about endocrine resistance and how best to target treatment, but the first steps have been taken and we are moving into the adjuvant space. It is not unrealistic to expect that some of these drugs and many of their descendants will have a significant role in improving surgical outcomes in the neoadjuvant setting, reducing the incidence of metastatic disease by

successful adjuvant use and helping to turn metastatic disease more and more into a long term chronic condition rather than a fatal one.

Lastly, we should also always be ready to challenge orthodoxy, bearing in mind that perhaps like Beatson, we could be right for the wrong reasons.

## References

1. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancet. 1896 Jul 18; 148(3803):162-165.

2. Munster PN, Carpenter JT. Estradiol in Breast Cancer Treatment: Reviving the Past. JAMA. 2009 Aug 19;302(7):797-8.

3. LoRusso PM. Inhibition of the PI3K/AKT/mTOR Pathway in Solid Tumors. J Clin Oncol. 2016 Sep 12 ePUB. Available from: http://jco.ascopubs.org/content/early/2016/09/07/JCO.2014.59.0018.abstract

4. Baselga J, Campone M, Piccart M, et al. Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med. 2012;366:520-9.

5. Baselga J, Im SA, Iwata H, et al. PIK3CA status in circulating tumor DNA (ctDNA) predicts efficacy of buparlisib (BUP) plus fulvestrant (FULV) in postmenopausal women with endocrine-resistant HR+/HER2– advanced breast cancer (BC): first results from the randomized, phase III BELLE-2 trial. San Antonio Breast Cancer Symposium; San Antonio, TX, USA; Dec 6–10, 2015. Abstract S6–01.

6. Wilcken NRC, Prall O, Musgrove EA, et al. Inducible overexpression of cyclin D1 in breast cancer cells reverses the growth-inhibitory effects of antiestrogens. Clinical Cancer Research. 1997;3:849-854.

7. O'Leary B, Finn RS, Turner NC. Treating cancer with selective CDK4/6 inhibitors. Nature Reviews Clinical Oncology. 2016;13:417–430.

8. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015;16:25-35.

9. Turner NC, Ro J, Andre F, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med. 2015;373:209-19.

# Triple negative breast cancer: proven and promising systemic therapies

Alice Bergin[1,2] Catherine Oakman[1,3] Geoffrey J Lindeman[1,2,4,5]

1. Department of Medical Oncology, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, Parkville, Victoria, Australia.
2. Stem Cells and Cancer Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia.
3. Department of Medical Oncology, Western Health, St Albans, Victoria, Australia.
4. Department of Medicine, The University of Melbourne, Parkville, Victoria, Australia.
5. Parkville Integrated Familial Cancer Centre, Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Parkville, Victoria, Australia.

Email: lindeman@wehi.edu.au

**Abstract**

Triple-negative breast cancer (TNBC) is a heterogeneous disease. While simply defined by immunohistochemical parameters, TNBC actually encompasses a raft of tumour subtypes with variable prognoses and treatment sensitivities. Systemic treatment decisions for patients with TNBC are becoming increasingly complex. In many cases, decision-making remains hampered by the current lack of predictive and prognostic biomarkers, and as such, chemotherapy remains the mainstay of systemic treatment options. Sequential anthracycline and taxane regimens, delivered as either neoadjuvant or adjuvant therapy, are widely accepted as the 'standard of care' in early stage disease. TNBC in *BRCA1* and *BRCA2* mutation carriers are more likely to be sensitive to platinum-based chemotherapy and PARP inhibition. The role for these approaches is currently under investigation in large clinical trials for this population. As with certain other solid tumours, harnessing the immune system to tackle this challenging breast cancer subtype is showing some promise and the role of immunotherapy in TNBC is currently being investigated in large clinical trials. Data on safety and efficacy are eagerly awaited but will need to take into account the heterogeneous nature of this disease.

Systemic therapy options for triple-negative breast cancer (TNBC) are increasingly seen as a complex clinical conundrum. Although historical approaches have focused on chemotherapy, promising novel therapies are emerging as a result of new insights into TNBC biology and growing recognition of the heterogeneous nature of this breast cancer subtype.

## Classification and clinical behaviour of TNBC

'Triple-negative' encompasses a diverse breast cancer subtype. TNBC is defined by immunohistochemistry as <1% immunostaining for oestrogen and progesterone receptors,[1] and no HER2 protein overexpression (0 or 1+ on immunohistochemistry (IHC)) or *HER2* gene amplification.[2] TNBC accounts for approximately 12-17% of all breast cancers.[3]

When evaluated by gene expression profiling, most TNBCs exhibit a basal-like phenotype. Similarly, most (but not all) of the basal-like group are triple-negative.[4,5] Six molecular subtypes of TNBC (eponymously named Lehmann subtypes) have been defined from pooled gene-expression studies: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL) and luminal androgen receptor (LAR).[5] These molecularly defined subtypes highlight the marked biological diversity within TNBC and this stratification may enable the development of targeted therapies but are not yet translatable for day-to-day management of patients with TNBC.

Although most TNBC occur in young women and are high grade, invasive ductal carcinomas with aggressive disease behaviour, TNBC can also include better prognostic subtypes of medullary, apocrine and squamous cell.[6] A study published in 2006 demonstrated the significant clinical

heterogeneity in this group. The study by Haffty and colleagues found that in the absence of systemic chemotherapy after surgery, a subgroup of women with TNBC remained disease free five years following surgery.[6] Further work is required to discover prognostic biomarkers that identify individuals with an excellent prognosis who do not require intensive adjuvant therapy as well as predictive biomarkers that help guide specific systemic therapy.

## Systemic therapy options for TNBC and markers of response

Chemotherapy is currently the only recommended systemic therapy for early stage TNBC. Chemotherapy can be administered before (neoadjuvant) or after (adjuvant) surgery with no reported difference in disease free and overall survival.[7] Neoadjuvant chemotherapy may render operable an inoperable locally advanced cancer and may allow breast conservation surgery rather than mastectomy.

The neoadjuvant approach also allows assessment of the chemo-responsiveness of the cancer in the breast and nodal tissue. A pathological complete response (pCR) can be defined as no residual invasive disease in the breast or nodal tissues. In patients with TNBC pCR correlates with favourable outcome.[8] An important finding by Liedtke et al was that patients with TNBC have increased rates of pCR when compared to those with non-triple negative disease and pCR correlated with excellent overall survival at three years compared to those with residual disease (RD).[9] The higher rate of pCR in TNBC likely reflects their highly proliferative nature.[10]

More recently, Symmans et al have described the residual cancer burden (RCB) to illustrate the spectrum of residual disease.[10] RCB can be calculated using four parameters from the post-treatment surgical specimen; the dimension of the tumour bed in the resection specimen, the proportion containing invasive carcinoma, the number of axillary nodes containing metastatic carcinoma and the largest metastasis in an axillary node. The parameters of the RCB index were found to be individually associated with significantly higher risk of distant relapse in a cohort of 241 women (and validated in a further 141) who had neoadjuvant anthracycline and taxane chemotherapy.

There is currently no clearly preferred regimen of chemotherapy for patients with TNBC compared with non-TNBC. Evidence to date is largely derived from retrospective, sub-group analyses with relatively small patient numbers and suboptimal power to enable definitive treatment recommendations. Most large adjuvant chemotherapy studies were undertaken prior to our current understanding of biological subtypes and the results therefore derived from biologically heterogeneous breast cancer populations. Given the aggressive nature of the TNBC phenotype as a whole, the current recommendations for TNBC are polychemotherapy with sequential anthracycline (such as doxorubicin or epirubin) and taxane (paclitaxel or docetaxel) in various well-described regimens.[11]

## Platinum-based systemic therapy

The role of DNA-damaging platinums (such as carboplatin and cisplatin) in treatment of early TNBC is still undefined. There are pre-clinical and clinical reports of exquisite platinum sensitivity in tumours with defective double strand DNA repair, such as that mediated by *BRCA1* or *BRCA2* mutations.[12] A hallmark feature of *BRCA1* and *BRCA2*-associated tumours is defective homologous recombination DNA repair and over 75% of invasive breast cancers arising in *BRCA1* mutation carriers are TNBC.[13] The overlap between *BRCA1*-associated cancers and TNBC has created much interest in whether platinums may also improve outcomes in non-BRCA mutated sporadic TNBC.

In a single arm, phase II trial of 28 women with TNBC, Silver et al reported that single agent neoadjuvant cisplatin (75 mg/m2 q21 x four cycles) resulted in pCR in 6 (21%) women.[14] The two *BRCA1* mutation carriers enrolled on trial achieved pCR and lower *BRCA1* mRNA expression was significantly associated with a larger percentage of patients achieving a good response.

In the randomised open-label, phase II neoadjuvant trial, GEICAM 2006-03 in basal-like TNBC (defined by the presence of CK5/6- or EGFR-positive cells by immunochemistry), Alba et al reported on neoadjuvant epirubicin and cyclophosphamide, followed by docetaxel with or without carboplatin (AUC6 q21). Both treatment arms (94 patients) had a pCR rate of 30%.[15] Carboplatin was associated with more anaemia and thrombocytopenia. Unfortunately the statistical design did not allow

comparison between the arms and response was not stratified in terms of *BRCA1*/*BRCA2* mutation carrier status or tumour '*BRCA*-like' features.

In the randomised phase II trial, GeparSixto, patients received weekly pegylated anthracycline, taxane and bevacizumab. Within the TNBC group, patients (n=315) were further randomly assigned to receive weekly carboplatin (AUC 2, dropped to AUC 1.5 after interim safety analysis) or placebo. The addition of carboplatin led to a statistically significant higher pCR of 53% versus 37% in the placebo arm.[16] Treatment discontinuation was high in both arms (48% in the carboplatin arm and 39% in the placebo arm), largely due to therapy-related toxicities. This improvement in pCR correlated with improved disease free survival.[17] However a criticism of this study is that the platinum was added to non-standard chemotherapy; omission of an alkylating agent (cyclophosphamide) in the control arm raises the question of whether the platinum improved outcomes only because the alkylating agent was absent.

The phase II open label 2x2 factorial design CALGB 40603 trial did assess the addition of carboplatin to a standard neoadjuvant backbone of sequential anthracycline and taxane chemotherapy.[18] Patients were randomised to receive weekly paclitaxel followed by dose-dense doxorubicin and cyclophosphamide versus the addition of carboplatin (AUC6 q21 concurrent with paclitaxel) and/or bevacizumab. Patients in the carboplatin-containing arms experienced a statistically significantly increase in pCR compared to the non-carboplatin-containing arms (54% versus 41%, p=0.003) but this improvement in pCR did not correlate with improved long-term outcome.[19] In the absence of improved long-term outcome, the addition of carboplatin is not yet supported as a standard of care.

In advanced TNBC, the TNT study was designed to test the hypothesis that impaired DNA repair mechanisms confer greater sensitivity to platinum agents than to taxanes.[20] This randomised, phase III trial compared single agent carboplatin (AUC 6) versus docetaxel (100 mg/m$^2$) every 21 days for six-eight cycles (or until progression) in patients with recurrent locally advanced TNBC, metastatic breast cancer or known *BRCA1* and *BRCA2* mutation carriers (with any hormone- and HER2-receptor status). The study found no evidence for benefit with carboplatin over docetaxel in unselected populations of patients with advanced TNBC. However, patients with germline *BRCA1* and *BRCA2* mutation had improved disease-free survival with carboplatin.

The findings in the TNT study appear consistent with those of Silver et al and are both indicative of the need to prospectively identify patients with tumours that harbour DNA repair defects to select them for appropriate therapy. Up to 25% of sporadic breast cancer may show a 'BRCA-ness' phenotype, through epigenetic inactivation of *BRCA1* (through hyper-methylation) and *FANCF* (via methylation) and *BRCA2* inactivation via *EMSY* amplification.[21] There are considerable efforts underway to identify mechanisms and biomarkers for sporadic tumours that exhibit BRCA-ness and to utilise this vulnerability to target therapy.

## The management of residual disease

A challenging clinical scenario is a TNBC patient with residual disease following neoadjuvant chemotherapy. It is known that non-pCR is associated with poor outcome with high chance of relapse and death within three years.[11] It is not currently known how to improve outcomes. This scenario will become more prevalent as more patients receive neoadjuvant chemotherapy.

A trial specifically examining adjuvant chemotherapy in HER2 negative breast cancer patients with residual disease post neoadjuvant chemotherapy is the collaborative Japanese and Korean breast cancer trials group trial, CREATE-X.[22] This phase III, double-blind, randomised trial compared capecitabine (2,500 mg/m$^2$/d for 14 days, q21 for eight cycles) versus placebo. Approximately one third of patients in the study had TNBC. Patients with hormone positive breast cancer also received adjuvant endocrine therapy. Capecitabine improved disease-free survival (74.1% vs 67.7% HR 0.70) and overall survival (94% vs 89.2% HR 0.60). This benefit from capecitabine is in contrast to other studies that have shown no benefit from the addition of capecitabine to neo or adjuvant chemotherapy,[23] however this study is unique in design as it is assessing a sub-selected population of patients with residual disease following standard therapy.

Promising data have also emerged from the International Breast Cancer Study Group (IBCSG) Trial 22-00, which compared low-dose oral cyclophosphamide (50 mg/d continuously) and oral

methotrexate (2.5 mg/d day 1, 2 every week) for one year as maintenance adjuvant therapy versus no treatment in hormone-receptor negative breast cancer. This treatment commenced after surgery and standard adjuvant chemotherapy. The trial found that the subgroup of women with node positive TNBC had the greatest benefit (albeit not statistically significant) in terms of five-year disease-free survival, with 71.9% in the treatment group versus 64.2 % in the control.[24] This trial was not in patients with residual disease after neoadjuvant chemotherapy but it did identify a promising metronomic combination that warrants further investigation in high-risk patients.

While both the CREATE-X and IBCSG 22-00 trial hold promise, the inclusion of adjuvant therapy in patients with residual disease following neoadjuvant therapy as a standard of care requires further follow up and publication of mature data from theses trials.

## PARP inhibition

An intriguing clinical target in TNBC is the enzyme, poly adenosine diphosphate ribose polymerase, (PARP). The role of PARP inhibitors is currently being evaluated by a number of rigorous, well-designed clinical trials.

Cells with compromised DNA damage repair are vulnerable. As previously described, *BRCA1* and *BRCA2* deficient cells have impaired homologous recombination. Exposure of these deficient cells to a PARP inhibitor can result in catastrophic mutations and cell death.[25] This is an example of synthetic lethality, when mutation (or inhibition) of two (or more) repair pathways provokes cell death.

A phase I trial established that the PARP inhibitor, olaparib, was well tolerated, and had anti-tumour efficacy in *BRCA1* and *BRCA2* mutation carriers.[26] *BRCA1/2* mutation carriers with advanced, recurrent breast cancer were treated with olaparib.[27] Of the patients with TNBC, response rates were 25% and 54% in lower and higher dosing cohorts respectively. The study provided positive proof-of-concept that olaparib has clinically relevant activity in BRCA-associated TNBC.

The SOLACE phase I trial is currently underway to determine the maximum tolerated dose of olaparib in combination with low dose cyclophosphamide in advanced *BRCA*-associated breast cancer and TNBC (ACTRN12613000924752). This is a study conducted by the Australia New Zealand Breast Cancer Trials Group (ANZBCTG) and is due to report soon.

OlympiA (NCT02032823), is a randomised, double blind, placebo-controlled phase III study evaluating adjuvant olaparib in *BRCA1/2* mutation carriers who have completed neoadjuvant chemotherapy, but did not achieve a pCR or had high-risk disease and have completed adjuvant therapy. Olaparib (300 mg BD) versus placebo is administered for 12 months. The primary outcome is invasive disease-free survival and recruitment is ongoing, including in Australia via the Australia New Zealand Breast Cancer Trials Group.

Another PARP inhibitor, veliparib, has also been shown to have activity in *BRCA1/2* mutation carriers with metastatic breast cancer when combined with temozolamide.[28] BROCADE3, a phase III randomised, placebo-controlled trial of carboplatin and paclitaxel with or without veliparib in metastatic HER2 negative or locally advanced unresectable *BRCA*-associated breast cancer is currently recruiting patients. The trial is designed to determine clinical benefit in terms of progression-free survival and will provide important insights into treatment of *BRCA*-associated breast cancers.

The roles of carboplatin and PARP inhibition in addition to standard chemotherapy are currently being studied in the neoadjuvant BRIGHTNESS trial (NCT02032277). This three-arm, randomised, placebo-controlled, double blind phase III study is evaluating pCR following neoadjuvant paclitaxel +/- carboplatin +/- PARP inhibitor veliparib followed by doxorubicin and cyclophosphamide. Patients are stratified by *BRCA1/2* status. The results of BRIGHTNESS are eagerly awaited. BRIGHTNESS follows on from I-SPY 2, which showed promise when carboplatin and PARP inhibition were added to standard chemotherapy.[29]

## TNBC and the immunotherapy age

Harnessing the immune system for the treatment of TNBC, like other solid-organ malignancies, is compelling. In node positive TNBC increased lymphocyte infiltration of the tumour and adjacent stroma are significantly associated with a good prognosis, regardless of chemotherapy type.[30] In addition, tumour-infiltrating lymphocytes can predict improved pCR.[31,32]

Tumours can utilise the PD-1/PD-L1 pathway to avoid immune surveillance and promote neoplastic growth. Keynote 012 was a single arm trial of anti PD1 (pembrolizumab) in heavily pre-treated TNBC.[33] Overall response rate was 18.5% and toxicities were generally mild. The Lehmann IM subtype of TNBC contains gene sets rich in immune signaling pathways and this subtype may represent a responding cohort.[6] Ongoing trials are evaluating the role of immunotherapy as a single agent and in combination with chemotherapy in TNBC.

## Conclusion

We are in an exciting era where insights into the biology and heterogeneity of TNBC are providing new biomarkers and therapeutic targets that are likely to be increasingly exploited to treat this clinically challenging subtype of breast cancer. It is becoming increasingly clear that determining the *BRCA1/2* mutation status of patients could inform their clinical management. Current studies will elucidate the role of platinums, PARP inhibitors and immunotherapy.

## References


1. Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer. J Clin Oncol. 2010;28(16):2784-2795.
2. Wolff AC, Hammond MEH, Hicks DG. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol. 2013;31(31):3997-4013.
3. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010 Nov 11;363(20):1938-48.
4. Purrington KS, Visscher DW, Wang C, et al. Genes associated with histopathologic features of triple negative breast tumours predict molecular subtypes. Breast Cancer Res Treat. 2016;157:117-131.
5. Lehmann BD1, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(7):2750-67.
6. Haffty BG, Yang Q, Reiss M, et al. Locoregional Relapse and Distant Metastasis in Conservatively Managed Triple Negative Early-Stage Breast Cancer. J Clin Oncol. 2006;24:5652-5657.
7. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol. 2008;26:778-785.
8. von Minckwitz G, Untch M, Blohmer J-U, et al. Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes. J Clin Oncol. 2012;30:1796-1804.
9. Liedtke C, Mazouni C, Hess KR, et al. Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer. J Clin Oncol. 2008;26:1275-1281.
10. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of Residual Breast Cancer Burden to Predict Survival After Neoadjuvant Chemotherapy. J Clin Oncol. 2007;25:4414-4422.
11. Oakman C, Moretti E, Galardi F, et al. Adjuvant systemic treatment for individual patients with triple negative breast cancer. The Breast. 2011;20(S3):S135-S141.
12. Farmer H, McCabe N, Lord C, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(917).
13. Hartmann LC, Lindor NM. Risk reducing surgery in breast and ovarian cancer NEJM. 2016;374:454-68.

14. Silver DP, Richardson AL, Eklund AC. Efficacy of neo-adjuant cisplatin in triple-negative breast cancer. J Clin Oncol. 2010;28(7):1145-1153.
15. Alba E, Chacon JL, Lluch A, et al. A randomized phase II trial of platinum salts in basal like breast cancer patients in the neo-adjuvant setting. Results from the GEICAM/2006-03, multi-centre study. Breast Cancer Res Treat. 2012;136:487-493.
16. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol. 2014;15:747–56.
17. von Minckwitz G, Loibl S, Schneeweiss A, et al. Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto). [abstract]. In: Proceedings of the Thirty-Eighth Annual CTRC-AACR San Antonio Breast Cancer Symposium: 2015 Dec 8-12; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res;76(4 Suppl):Abstract nr S2-04
18. Sikov WM, Berry DA, Perou CM, et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol. 2014;33:13-21.
19. Sikov WM, Berry DA, Perou CM, et al. Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/- carboplatin and/or bevacizumab in triple-negative breast cancer: Outcomes from CALGB 40603 (Alliance). [abstract]. In: Proceedings of the Thirty-Eighth Annual CTRC-AACR San Antonio Breast Cancer Symposium: 2015 Dec 8-12; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res;76(4 Suppl):Abstract nr S2-05.
20. Tutt A, Ellis P, Kilburn L, et al. Abstract S3-01: The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or *BRCA1/2* breast cancer (CRUK/07/012) Cancer Res. 2015;75:S3-01.
21. Turner N, Tutt A, Ashworth A. Hallmarks of “BRCAness” in sporadic cancers. Nat Rev Cancer. 2004;4:814-19.
22. Lee S-J, Toi M, Lee ES, et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X, JBCRG-04. Cancer Res. 2015;76:S1-07.
23. Joensuu H, Gligorov J. Adjuvant treatments for triple-negative breast cancers. Ann Oncol. 2012 Aug;23 Suppl 6:vi40-5.
24. Colleoni M, Gray KP, Gelber SI, et al. Low-dose cytotoxics as “anti-angiogenesis treatment” following adjuvant induction chemotherapy for patients with ER-negative and PgR-negative breast cancer. J Clin Oncol. 2015;33 (suppl; abstr 1002)
25. Chionh F, Mitchell G, Lindeman G, et al. The role of poly adenosine diphosphate ribose polymerase inhibitors in breast and ovarian cancer: Current status and future directions. Asia Pac J Clin Onc. 2011;7:197–211.
26. Fong PC, Boss DS, Yap TA. Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from BRCA Mutation Carriers. N Engl J Med. 2009;361:123-34.
27. Tutt A, Robson M, Garber JE. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010;376:235–44.
28. Isakoff SJ, Overmoyer B, Tung NM. A phase II trial of the PARP inhibitor veliparib (ABT888) and temozolomide for metastatic breast cancer. J Clin Oncol. 2010;28(15):1019.
29. Barker AD, Sigman CC, Kelloff GJ, et al. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther. 2009;86(1):97-100.
30. Loi S, Sirtaine N, Piette F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol. 2013;31(3):860–67.
31. Denkert C, Loibl S, Noske A, et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol. 2010;28:105–3.
32. Ono M, Tsuda H, Shimizu C, et al. Tumor-infiltrating lymphocytes are correlated with response to neoadjuvant chemotherapy in triple-negative breast cancer. Breast Cancer Res Treat. 2012;132:793–805.
33. Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. Cancer Res. 2015;75:S1-09

# Adjuvant therapy of HER2 positive disease: can we do better, or are we already giving too much treatment?

Nicholas Wilcken

Crown Princess Mary Cancer Centre, Westmead Hospital, University of Sydney, Sydney, New South Wales, Australia.

Email: nicholas.wilcken@sydney.edu.au

**Abstract**
Thanks to careful persistent research, the outlook for women diagnosed with early HER2 positive breast cancer has improved markedly over the last two decades. The evolution of HER2-targeted treatments has been a game changer, and the pathology report that reads “HER2 amplified” is not as dreaded as it once was. Clinical trials have proven the safety and effectiveness of adjuvant trastuzumab, and longer term follow-up has been reassuring. However, now is a good time to reflect on these achievements and ask ourselves two questions: how can we do better, and can some patients get by with less treatment?

The development of trastuzumab as treatment for HER2 positive early breast cancer has been a triumph of post-enlightenment rationalism.[1] From the demonstration that HER2 amplification conferred a poor prognosis, to developing an antibody to this receptor, to showing the effectiveness of this antibody in cell culture and mouse models, we came to testing trastuzumab in humans with metastatic breast cancer.

There we learnt useful lessons. There was unexpected cardiac toxicity, and the drug wasn’t very active in the absence of chemotherapy, but was very active in combination with a number of different chemotherapy types. Thus armed with useful knowledge and experience, we tested in the adjuvant setting with spectacular results.

Long term follow-up has been reassuring – this is a drug with low toxicity and sustained efficacy, even though it is combined with anthracycline and taxane chemotherapy.[2] An 85% 10 year overall survival for a disease that was previously of poor prognosis is quite remarkable, and the outlook of many of our patients with lower risk than those in the trials must be even better. All the adjuvant trials were restricted to node positive or high risk early breast cancer, whereas we frequently see women with node negative disease and small tumours. This begs two clinically relevant questions: is there much room for improvement? And can we de-escalate?

Of course, we would always like to improve and we will soon see if the addition of adjuvant pertuzumab (as tested in the APHINITY trial – clinicaltrials.gov identifier NCT01358877) improves disease free survival. It would be surprising if it didn’t, but then we had a similar perspective about the addition of lapatinib, and the combination of lapatinib and trastuzumab did not materially improve outcomes.[3] If pertuzumab does improve disease free survival, then the question will be by how much, because this is a very expensive drug, and very modest benefits may not be cost-effective.

In addition, we have a number of anti-HER2 drugs that are active in the metastatic setting, and because of cost each such drug cannot be tested in multi-thousand patient adjuvant trials. In the recent past, new drugs or combinations have been tested in the neoadjuvant setting to save time and money. However we have the unresolved problem of whether success there necessarily predicts for long term outcomes. This is a complex issue, but it remains unclear whether, just because a drug shrinks a primary tumour better than another drug it necessary follows that long term survival is better.[4]

The answer may be two fold. First in understanding HER2 biology better, we should be able to predict those who will do especially well with additional anti-HER2 therapies (or to paraphrase, will do badly if given chemotherapy and trastuzumab alone). Second, in the absence of persuasive biological reasoning, we may need to test these drugs in smaller cohorts of higher risk patients, and restrict use to such subgroups.

Which raises the issue of de-escalation. Many of the patients we now treat with six months of chemotherapy and a year of trastuzumab would not have even been eligible for the adjuvant trials, as they often have small node negative tumours. It's therefore likely that we are over-treating some of them. However proving that is probably not possible, and it's a brave oncologist who 'under-treats' in today's environment. But progress can and needs to be made.

Duration doesn't seem to be the answer, at least with current biological understanding taken into account. With reference to all HER2 positive patients, two years of trastuzumab is not better than one,[5] and it seems that six months is not quite as good as one year. However it appears extremely unlikely that the entirely empirical one year of treatment just happens to coincide with the biologically correct duration. The more reasonable explanation is that increased biological understanding is required as to which patients do not require therapy, which patients can be treated for only three months and which patients need longer treatment and more drugs.

Very helpful additional knowledge came from the study reported by Tolaney et al.[6] Recognising that a randomised trial of trastuzumab versus not in women with small tumours would not be achievable, they devised a 'shortcut' treatment to test in a single arm trial. Women with node negative, small tumours (about half were less than 10mm) could elect to be treated with weekly paclitaxel and one year of trastuzumab, thus avoiding the toxicity and inconvenience of three months of anthracycline chemotherapy.

Over 400 women were accrued, and at an average four years' follow-up there were only 12 events, and only two of these were distant recurrences. Obviously longer term follow-up would be reassuring, but it is not possible to immediately improve on present knowledge. Thus, although these patients may not have needed any treatment at all, they have at least avoided anthracyclines and had a shorter time on chemotherapy.

We therefore have a reasonably evidence-based de-escalation strategy to use, and indeed this regimen could always serve as a comparator arm in a randomised trial (perhaps compared to six months of trastuzumab), although the low event rate will always be a challenge.

Taking all relevant findings into account, much has been achieved in the adjuvant treatment of early breast cancer, although there is the natural desire to improve. As long as we deal with HER2 positive disease as a mono-identity however, logistics will make it difficult to test new agents in the adjuvant setting. There is an urgent need to understand HER2 biology more comprehensively so that we can more accurately identify those patients who would most benefit from the new drugs being tested and used in metastatic disease (as outlined in the next chapter), and those who need very little if any treatment.

## References

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235:177-82.

2. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831 J Clin Oncol. 2014;32:3744-3752.

3. Martine Piccart-Gebhart, Eileen Holmes, Jos´e Baselga, et al. Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial. J Clin Oncol. 2015; 34:1034-1042.

4. Rose BS, Winer EP, Mamon HJ. Perils of the Pathologic Complete Response. Published Ahead of Print on August 22, 2016 as 10.1200/JCO.2016.68.1718.

5. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 Years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomized controlled trial. Lancet. 2013;382:1021-8.

6. Tolaney SM, Barry WT, Dang CT. Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer. N Engl J Med. 2015;372:134-41.

# HER2 positive metastatic breast cancer: what happens after first line failure?

Arlene Chan

School of Medicine, Curtin University, Western Australia, Australia.
Breast Clinical Trials Unit, Hollywood Private Hospital, Western Australia, Australia.
Breast Cancer Research Centre, Western Australia, Australia.

Email: arlenechan@me.com

**Abstract**
For women with metastatic HER2 positive breast cancer, the introduction of trastuzumab into routine practice was transformative. More recently, the addition of pertuzumab has further improved the outlook. However in almost all cases, the disease unfortunately progresses. Much research has gone into what to do next. Fortunately we now have evidence to support a number of strategies, with the underlying understanding that HER2 blockade should be continued for as long as possible. Historically, lapatinib was the first anti-HER2 agent to show activity after relapse on trastuzumab. Subsequently the effectiveness of T-DM1 (Kadcyla) has been demonstrated, as has the use of alternating chemotherapy agents with trastuzumab. Research is now focussed on understanding and combating the mechanisms of resistance to anti-HER2 agents that inevitably develop. Promising data suggest that mTOR inhibitors, PI3 kinase inhibitors and immune-activating therapies may be helpful.

It is universally accepted that the ideal first line treatment of HER2 positive metastatic breast cancer is a taxane combined with both trastuzumab and pertuzumab. This combination is approved and funded in Australia. What is less clear is the best sequence of treatment choices to make after first line failure.

Preclinical and clinical evidence suggests that in patients with HER2 positive metastatic breast cancer who have progressed beyond first-line anti-HER2 treatment, it remains important to provide ongoing HER2 suppression if tumour control is to be achieved. To date, the published studies have largely included patients who had received trastuzumab and chemotherapy in the first-line setting.

In this setting, the first trial to demonstrate an improvement in time to progression was the EGF100151 trial, which randomised HER2 positive metastatic breast cancer patients to lapatinib and capecitabine versus capecitabine alone.[1] The primary endpoint was achieved with a hazard ratio of 0.57 (95%CI 0.43-0.77, p<0.001), demonstrating that maintaining HER2 blockade halved the risk of cancer progression.

A particular subset of patients with HER2 positive disease who appeared to benefit from lapatinib were those with progressive cerebral metastases. The EGF105084 trial evaluated lapatinib as monotherapy and in combination with capecitabine, and was able to demonstrate a reduction in volume of cerebral disease by MRI assessment. Monotherapy led to a ≥ 20% central nervous system (CNS) volumetric reduction in 21.4% of patients, whilst lapatinib and capecitabine led to ≥ 20% CNS volumetric reduction in 40% of patients. In both treatment groups, there was a significant improvement in progression-free survival (PFS) in those patients who showed reduction in CNS disease.[2] However, to date these gains in PFS have not translated into an overall survival (OS) benefit.

The development of T-DM1 and its evaluation in the pivotal trial, EMILIA, establishes this agent as the most effective anti-HER2 agent after patients have progressed on trastuzumab-based treatment, anthracycline and taxanes. The development of this monoclonal antibody- emtansine conjugate was evaluated in this phase III trial, where 991 patients were randomised to T-DM1 monotherapy versus lapatinib and capecitabine in the second-line setting. The dual primary endpoints of PFS and overall survival were significantly in favour of T-DM1 with a hazard ratio of 0.65 (95% CI 0.55-0.77; p<0.001) and 0.68 (95%CI 0.55-0.85; P<0.001), respectively.[3]

An exploratory assessment for CNS progression in the two treatment arms showed a similar PFS in those patients with baseline CNS disease or who developed CNS disease on treatment, while overall survival continued to favour the patients receiving T-DM1. Of particular interest was that the PFS and OS findings occurred in the setting of higher rates of CNS progression on treatment in the T-DM1 compared to lapatinib and capecitabine arm (22.2% vs. 16%, respectively); and new CNS disease (2% vs. 0.7%, respectively).[4]

Other therapies that have shown efficacy in the second-line setting after trastuzumab and taxane chemotherapy in the first-line setting include the combination of lapatinib and trastuzumab (EGF104900), where PFS and OS favoured the dual anti-HER2 therapy as compared to lapatinib alone; hazard ratio 0.74 for both endpoints.[5]

In addition, in the era prior to T-DM1, a number of retrospective studies showed efficacy for continuation of trastuzumab with a change in chemotherapy partner. GBG26 was the first prospective study to demonstrate an improvement in PFS with continuation of trastuzumab in combination with capecitabine versus capecitabine alone. Despite early cessation of the study due to a slowing of recruitment, the 5.5 months improvement in PFS was significant with a p value of 0.02.[6] Following a median follow-up of 20.7 months, patients who continued or resumed trastuzumab or lapatinib after second progression had superior post-progression survival of 18.8 months versus 13.3 mths (p=0.02).[7] Further, a pooled analysis of 29 studies that compared continuation of trastuzumab and chemotherapy against the chemotherapy agent alone, favoured the combination regimen with an overall time to progression of seven months and OS of 23 months.[8]

In the era of pertuzumab and T-DM1, a new challenge for management of patients with HER2-positive metastatic breast cancer in the second-line setting arises. There are no published studies which evaluated the efficacy of T-DM1 in patients previously treated with dual HER2 blockade with trastuzumab and pertuzumab. Given the oncogenic addiction to the HER2 pathway as supported by preclinical and clinical studies, it is likely that the efficacy of the antibody-cytotoxic drug conjugate will persist. However it remains to be determined how effective T-DM1 will be in patients who have already received trastuzumab and pertuzumab. As T-DM1 is considered an effective option in the first-line setting in patients who have a short disease-free interval following adjuvant trastuzumab-chemotherapy treatment, the second-line setting treatment for these patients may be another circumstance where other therapeutic approaches are needed.

A number of studies have demonstrated that the PI3K/Akt/mTOR pathway is a predominant pathway by which trastuzumab resistance may develop. Bolero 3 randomised 569 patients with HER2 positive metastatic breast cancer who had received trastuzumab, a taxane and up to three lines of chemotherapy to trastuzumab and vinorelbine versus trastuzumab, vinorelbine and everolimus. The primary endpoint of PFS was significantly better in the triplet combination arm with a hazard ratio 0.78 (95%CI 0.65-0.96, p=0.0067), although overall survival results are still awaited.[9] A number of pan-PI3K inhibitors and alpha-specific PI3K inhibitors are in clinical trial evaluation in HER2-negative, hormone receptor positive breast cancer, paving the way for a smaller number of trials now accruing in which agents such as buparlisib, BEZ235, coPANlisib are being given with trastuzumab in HER2-positive metastatic breast cancer.

Other investigators are evaluating the efficacy of CDK4/6 inhibitors (palbociclib, abemaciclib) with trastuzumab with or without endocrine treatment. Preclinical and clinical data support the importance of the immune environment – both innate and adaptive – in the mechanism of tumour cell evasion of immune-surveillance. The two breast cancer subtypes in which the immune environment appears to have the greatest role, are HER2 positive and triple negative disease. Immune mechanisms that have been postulated to be in play include: heightened antibody-dependent cell-mediated or complement-dependent cytotoxicity, triggering of Fc receptor positive cells, activated CD8-positive lymphocytes and NK cells. As such the development of checkpoint inhibitors which has shown efficacy in other solid tumours such as melanoma, are now under active clinical trial evaluation.[10] This matter is further discussed in the final article in this Forum.

## References


1. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses Breast Can Res Treat. 2008:112(3):533-43.
2. Lin N, Dieras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer Clin Cancer Res. 2009:15(4):1452-9.
3. Verma S, Miles D, Gianni L, et al Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer N Engl J Med. 2012:367:1783-91.
4. Krop I, Lin Nu, Blackwell K, et al Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann Oncol. 2015:1:113-9.
5. Blackwell K, Burstein H, Storniolo A, et al. Overall Survival Benefit With Lapatinib in Combination With Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer: Final Results From the EGF104900 Study J Clin Oncol. 2012:30:2585-2592.
6. Von Minckwitz G, Du Bois A, Schmidt M, et al. Trastuzumab Beyond Progression in Human Epidermal Growth Factor Receptor 2–Positive Advanced Breast Cancer: A German Breast Group 26/Breast International Group 03-05 Study. J Clin Oncol. 2009:1999-2006.
7. Von Minckwitz G, Schwedler K, Schmidt M, et al. GBG 26/BIG 03-05 Study Group And Participating Investigators. et al Trastuzumab beyond progression: Overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer Eur J Cancer. 2011:47:2273-81.
8. Petrelli F, Barni S, et al. A Pooled Analysis of 2618 Patients Treated With Trastuzumab Beyond Progression for Advanced Breast Cancer. Clin Breast Cancer. 2013:13:81-87.
9. Andre F, O'regan R, Ozguroglu M, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial Lancet Oncology. 2014:15:580-91.
10. Bianchini G, Gianni L, et al. The immune system and response to HER2-targeted treatment in breast cancer. Lancet Oncology. 2014:15:e58-e68.

# Brain metastases: a subtype-specific medical approach

Claire Phillips

Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia.
University of Melbourne, Victoria, Australia

Email: Claire.Phillips@petermac.org

**Abstract**
In the past, brain metastases were essentially all treated in the same way, and heralded a poor prognosis. Improvements in ways of delivering radiotherapy as well as in anaesthetic and neurosurgical techniques and in imaging mean that much more can be achieved. A knowledge of what subtype of breast cancer is being treated is now critical to take into account, especially in HER2 positive disease, where an expanding array of anti-HER2 drugs means that extra-cranial disease may be controlled for many years. Ideally, brain metastases should be managed in a multidisciplinary setting, so that imaging, radiation oncology and neurosurgery input can be combined.

Brain metastases (BM) are a common, and frequently challenging, clinical problem in the contemporary management of metastatic breast cancer. While the management of extracranial metastatic breast cancer is now strongly defined by tumour phenotype, this approach is not so well defined for BM. This review considers brain metastases in HER2 breast cancer and triple negative breast cancer (TNBC) cancer populations as BM are common in these phenotypes; estimated to occur in 30-55% of patients with metastatic HER2 positive breast cancer (HER2BC) and 25-46% of patients with metastatic hormone negative HER2 receptor negative, or 'Triple negative', breast cancer.[1] BM from these phenotypes present contrasting clinical scenarios and management must be tailored accordingly.

## Prognostic factors

The Radiation Therapy Oncology Group (RTOG) conducted many of the most significant BM trials, especially through the 1980s and 90s. Its large database of BM patients from these studies has provided critical information regarding prognostic factors for breast cancer BM, presented as the Breast Cancer Graded Prognostic Analysis (BrGPA), Table 1a.[2] The BrGPA shows clearly that phenotype and performance status are the most important prognostic factors for breast cancer BM, whereas patient age has minor significance Table 1b. The total number of brain metastases was not found to an independent prognostic factor in the BrGPA but others have questioned this, finding lesion number to be of similar prognostic significance to age.[3]

## Typical patterns of disease behaviour

### *HER2-positive disease (HER2BC)*

HER2BC has a well-described propensity to metastasise to the central nervous system (CNS).[1] This is thought to be due to several factors; tropism of HER2BC cells for the CNS, the striking success of targeted-HER2 therapies in treating extracranial metastatic disease (ECD) and the relatively poor efficacy of these systemic agents against disease within the brain (and neuraxis more generally). The natural history of HER2BC has been changed by the targeted-HER2 agents, which prevent early death from visceral metastases and so 'allow time' for more patients to develop BM while living with metastatic breast cancer.

There has been a dramatic shift in the median survival of patients with HER2BC BM. The population in the RTOG database was mostly treated before the availability of HER2-targeted therapies (and newer agents for hormone positive breast cancer). For this population the median survival of the best prognosis patients with ER negative HER2BC was 17.9 months and ER positive HER2BC 22.9 months.[2] In a recent unselected series from Memorial Sloan Kettering Cancer Centre the median survival for ER negative HER2BC was 41 months and for ER positive HER2BC 63 months.[4]

Although BM develop as the first site of metastatic disease in about 2% of patients with metastatic HER2BC,[5] it is more common for BM to arise while a patient is receiving HER2-targeted therapy for ECD. BM may arise (or progress) while ECD is well controlled. If ECD progression occurs with new or progressive BM, the ECD may well be controlled with another line of HER2-targeted whereas the BM cannot be expected to respond with such confidence. Therefore, the challenge in HER2BC is to maintain control of BM over many months to several years, and not simply to offer palliation of symptomatic BM in a dying patient.

### *Triple-negative breast cancer (TNBC)*

TNBC also has a particular propensity to metastasize to the brain and the interval from early-stage disease to BM diagnosis is the shortest of all breast cancer phenotypes.[6,7] In the RTOG database, this was 27.5 months (compared 35.8 months for ER negative HER2BC and 47.4 months for ER positive HER2BC and 54.4 months for ER/PR positive HER2 negative BC).[8] BM as a first site of metastatic disease is more common in TNBC than the other phenotypes.[9-10] BM from TNBC typically occur in the setting of chemoresistance; that is, the response of intra and extracranial disease to chemotherapy is often poor or of short duration. Because of this there is a substantial competing risk of death from progressive extracranial disease. New agents such as the poly ADP ribose polymerase inhibitors and the immune therapy agents have not altered this devastating pattern in a meaningful way.[11-12]

The median survival of all patients with TNBC BM is approximately six months, 3-4 months for poor performance status and 6-9 months for good performance status patients.[2] In some recent series median survival is as high as 12 months for the best performance status patients.[10] TNBC BM often respond well to radiotherapy (of any type) but the duration of response is shorter than for other phenotypes. Similarly, local failure after surgical excision can be rapid. It is common for patients to succumb quickly to progressive extracranial disease, early recurrence of BM after therapy, or both. For the majority of patients, the development of TNBC BM represents an immediate threat to quality and duration of life and management is truly palliative in nature.

## Treatment

The mainstays of first-line therapy for BM are whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) and neurosurgery. SRS and neurosurgery are local therapies that only treat the known BM (gross disease). They have complimentary but overlapping clinical roles. WBRT is regional, treating known BM and any subclinical disease (occult disease). Systemic agents have much less predictable efficacy and are reserved for progressive disease, usually when there is no local therapy option.

### *Whole brain radiotherapy*

WBRT delivers a moderate dose of radiotherapy to all of the brain tissue. It is palliative in nature and does not deliver enough radiation dose to effect ‘cure’ of gross disease. WBRT can reduce recurrence in the brain at sites other than the known BM (distant brain failure) by treating occult disease present in the brain at time of WBRT, however the risk of occult breast cancer BM relative to number of known BM and by phenotype is unknown. In prior phase III BM studies of local therapy with or without WBRT, a 50% reduction in distant brain BM was observed after WBRT and this persisted for up to 12 months.[13-15] Thereafter the rate of distant BM was the same, whether WBRT was given or not.[15] These studies included tumours from any disease site but most commonly non-small cell lung cancer (60%). A retrospective review of breast cancer cases treated with radiosurgery but no WBRT found that the 12-month rate of distant brain failure was highest in TNBC (79%), intermediate for HR+breast cancer (~47%) and least for HER2BC (36%). The rate of failure by lesion number, extracranial disease status and use of systemic therapies was not reported.[16]

Short-term side effects of WBRT include fatigue, total alopecia, headache, nausea, vomiting and transient memory impairment (especially in the elderly). The main long-term side effect is reduced short-term memory. While this can be detected if measured carefully, global cognitive impairment that affects social function is uncommon,[17] particularly in the breast cancer population that does not smoke or have other risk factors for cerebrovascular disease to the same extent as the lung cancer population. WBRT can be given for a second time (ideally at least 12 months after the first course) but is not given repeatedly because with each repeat course the risk of serious neuro-cognitive impairment and frank brain parenchyma necrosis goes up substantially.

Hippocampal-avoidance WBRT (HA-WBRT) is a complex, resource-intensive, intensity-modulated form of WBRT in which the total dose to the bilateral hippocampi is kept as low as possible, ideally less than 10 Gy. The intention of this therapy is to reduce the cognitive toxicity of WBRT, in particular effects on memory. An RTOG phase II study was designed to assess cognition for up to two years after WBRT, but the median survival of the study population was only 6.8 months.[18] The investigators reported cognitive outcomes at four months after WBRT. Cognitive outcomes were better after HA-WBRT compared to an historic control population. Disease response in the brain was not reported. BM recurrence in the hippocampus was 4.5%. This is weak evidence for the proof of principle that a reduced dose to the hippocampus may protect patients from the transient memory impairment that is known to occur 2–4 months after WBRT. Cognitive outcomes 12 or 24 months after HA-WBRT are not yet known. A cost-benefit analysis, using standardised United States Medicare costs adjusted for Chicago found that HA- WBRT became cost-effective for patients with a median survival of at least 12 months.[19] This model assumed that hippocampal-avoidance WBRT removes all risk of cognitive impairment.

WBRT plays an important palliative role in treatment of multiple symptomatic brain metastases which are not amenable to SRS and/or neurosurgery or when extensive leptomeningeal disease is present.

### *Stereotactic radiosurgery*

SRS is a specialised radiation technique in which sophisticated technology is used to deliver 1-5 large radiation doses to small targets, typically up to 3.0cm but potentially up to 4.0cm in size. The high radiation dose delivered with SRS achieves better local control of the treated BM than WBRT but in trials to date, survival is only improved for patients with a solitary BM (compared with use of WBRT alone).[20]

SRS has typically been reserved for treatment of 1 to 3 or maybe four BM, but in recent years there has been a shift towards use of SRS for treatment of multiple lesions, as many as 10 lesions or more.[21] This shift has been facilitated by improvements in SRS technology, however there are no clinical trial data to guide practice with regard to which patients benefit from this approach. Consequently practice varies widely depending on access to SRS technology and the philosophy of the treating medical team. Patient choice can also be a driving factor.

Early toxicities of SRS are headache, nausea and transient worsening of any neurologic deficit due to post-treatment oedema (days to weeks). These are uncommon. There is no hair loss. The main long-term toxicity is radiation necrosis (months to years). This is asymptomatic in 20-30% of cases and symptomatic in 5-10%.

### *Neurosurgery*

Neurosurgery is generally reserved for solitary or larger and symptomatic lesions. Modern neurosurgery typically involves a short hospital stay and has low morbidity but not all lesions are amenable to safe resection. Removal of a BM usually leads to prompt resolution of any associated oedema and achieves rapid palliation of headache and any neurologic deficits.

Side effects include neurologic deficit, infection, wound problems and anaesthetic misadventure. The risk of these primarily depends on tumour location, patient age and medical comorbidities.

### *Systemic agents*

Historically, clinical trials of systemic therapies have excluded patients with BM. Consequently prospective data on the use of systemic agents for BM that might guide treatment are limited. A few small phase II studies and post hoc analyses of large phase III trials have demonstrated that many systemic agents have activity in the brain. These agents include cytotoxic agents such as capecitabine, platinum agents, microtubule inhibitors, temozolomide, and methotrexate. Targeted therapies with potential CNS activity include lapatinib in combination with capecitabine, TDM-1 in HER2BC, and anecdotally, some novel immune checkpoint inhibitors. There is considerable interest in systemic agents for breast cancer BM but no specific systemic agent is yet approved specifically for this indication.[22,23] Radiosensitising agents have been combined with WBRT and SRS in an attempt to optimise CNS control but results have been disappointing.

## Management

For HER2BC, the need to integrate available therapies over several years is complex. Ideally a multidisciplinary team made up of breast medical and radiation oncologists, neuro-radiation oncologist, neurosurgeon and neuroradiologist would consider any new case of oligometastatic BM and any case of progressive BM. Apart form large BM that need an urgent neurosurgical opinion, there is always time to refer such cases to a larger centre for a multidisciplinary opinion where such a service is not available in the treating centre. Radiology picture archiving and communication systems and email have made this especially feasible.

For poor performance status and TNBC patients, the early input of a palliative care multidisciplinary team is important.

### *Poor performance status patients*

When performance status is poor (Karnofsky < 70), the influence of tumour phenotype on prognosis is less marked and the emphasis of management is to palliate. In this setting asymptomatic BM should be observed. Where performance status is poor because of a large ECD disease burden survival will likely be determined by response of that ECD to any systemic therapy. In this case consideration of best supportive care over any treatment for symptomatic BM is important. Where it is deemed appropriate to offer palliative treatment, available evidence supports the use of WBRT over SRS (whatever the lesion number) as WBRT is quick and simple to instigate at any radiotherapy department, addresses the likely higher rate of occult BM with uncontrolled extracranial disease, and is cost effective.[19,24] Chemotherapy is not usually recommended in this setting, given the low chance of disease response and high chance of acute toxicity.

If poor performance status is of short duration and very likely due to a large BM, neurosurgery should be considered as excision is very likely to restore pre-morbid function. Most neurosurgeons would not operate if the predicted survival is in the order of three months or less.

### *Good performance status HER2BC*

Given the long median survival with HER2BM, avoidance of early WBRT is ideal however the ‘correct’ number of BM for which WBRT is best withheld is not known. It is important to acknowledge that WBRT plays an important role treating multiple small lesions (‘miliary’ disease) and when leptomeningeal disease is present. When WBRT is truly indicated, the wish is to give ’full dose’ WBRT rather than the ‘gentle’ version that is typically used for repeat WBRT, reinforcing the importance of not giving WBRT unless it is truly necessary.

In many cases SRS and/or neurosurgery can be used to treat gross BM over years. These therapies should always be considered before WBRT is given to a well patient. Similarly, it is not always necessary to treat small asymptomatic BM immediately. Surveillance MRI (usually every three months) will demonstrate if the lesions are growing or stable, the former requiring consideration for treatment whereas continued observation is appropriate for the latter. It must be emphasised that this approach pertains to patients who are receiving a targeted HER2 agent or for whom another line of HER2 therapy is available. Good control of ECD is correlated with better CNS disease control (either because of reduced CNS seeding or due to activity of the systemic agent in the CNS or both – the former seems to be the dominant reason for most patients). The best integration of neurosurgery, radiation and systemic therapy for management of de novo BM is unknown and is an important area for future clinical study.

Multiple progressive HER2BM after WBRT can pose a substantial risk to the patient’s life and/or cognition, which can justify use of repeat WBRT. However, a change of HER2-targeted systemic therapy may offer an effective alternative in HER2BC and should be considered prior to repeat WBRT.

### *Good performance status TNBC*

The poor overall prognosis and high probability of early failure in the brain and at distant sites mean that WBRT should provide the basis of treatment. Neurosurgery should be used as necessary for large symptomatic lesions. SRS may be used to try to improve local control of individual lesions but in at least one series, local control of TNBC with SRS was disappointing.[25] SRS alone with delay of WBRT is not recommended for this phenotype because of high rates of distant brain failure. The exception may be in the case of one or two de novo BM, absence of any ECD and a long interval

since diagnosis and treatment of the primary breast cancer (a rare scenario in TNBC). Systemic therapy is rarely effective and is not recommended as an alternative to radiation and neurosurgery.

## Conclusion

Performance status and breast cancer phenotype strongly influence the outcome after the diagnosis of BM and this must be taken into account when making management decisions. A multidisciplinary approach to BM management is encouraged, such that radiological, radiation oncology and neurosurgical input can be combined. There is a pressing need for prospective clinical trials that are breast cancer phenotype-specific. The goal is to better understand how the various treatment modalities may be best sequenced and integrated in order to improve the outcomes of BCBM therapy.

**Table 1a*** *Prognosis scores indicated by the Radiation Therapy Oncology Group (RTOG) Breast Cancer Graded Prognostic Analysis and the MD Anderson Cancer Centre (MDACC) modification*

| | Score | | | | |
|---|---|---|---|---|---|
| | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| **RTOG Breast Graded Prognostic Assessment** | | | | | |
| KPS | ≤50 | 60 | 70–80 | 90–100 | – |
| Phenotype | TNBC | – | HR+BC | HER2HN | HER2HP |
| Age (years) | ≥60 | <60 | – | – | – |
| **MDACC revalidation of RTOG Graded Prognostic Analysis** | | | | | |
| KPS | ≤50 | 60 | 70–80 | 90–100 | |
| Phenotype | TNBC | HR+BC | HER2HN | HER2HP | – |
| Age (years) | >50 | ≤50 | – | – | – |
| Number | >3 | 1–3 | – | – | – |

RTOG = Radiation Therapy Oncology Group; KPS = Karnofsky performance status; MDACC = MD Anderson Cancer Centre, HER2HN = HER2-positive, hormone-negative; HER2HP = HER2-positive, hormone-positive

**Table 1b*** *Radiation Therapy Oncology Group (RTOG) Breast Cancer Graded Prognostic Analysis and MD Anderson Cancer Centre (MDACC) modification scores and overall survival*

| RTOG score | Overall survival (months) | MDACC score | Overall survival (months) |
|---|---|---|---|
| 0–1.0 | 3.4 | 0 –1.0 | 2.6 |
| 1.5–2.0 | 7.7 | 1.5–2.0 | 9.2 |
| 2.5–3.0 | 15.1 | 2.5–3.0 | 29.9 |
| 3.5–4.0 | 25.3 | 3.5–4.0 | 28.8 |

* Adapted from references 3 and 13

## References


1. Lim NU, Amiri-Kordestani L, Palmieri D, et al. CNS metastases in breast cancer: Old challenge, new frontiers. Clin Cancer Res. 2013;19(23):6404-18. doi: 10.1158/1078-0432.CCR-13-079.

2. Sperduto P, Kased N, Roberge D et al. Effect of tumour subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases. Int J Radiat Biol Oncol Phys. 2012;82(5):2111-2117.doi:10.1016/j.jrobp.2011.02.027.

3. Subbiah IM, Lei X Weinberg et al. Validation and development of a modified breast graded prognostic assessment as a tool for survival in patients with breast cancer and brain metastases. J Clin Oncol. 2015;33(20):2239-2245. doi: 10.1200/JCO.2014.58.8517.

4. Morikawa A, Diab A, Patil S, et al, Radiation therapy for central nervous system brain metastases: A contemporary experience at Memorial Sloan Kettering Cancer Centre (MSKCC). ASCO. 2013 Poster Abstract 144.

5. Petalozzi BC, Holmes E, de Azambuja E, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). Lancet Oncol. 2013;14:244-248 doi: 10.1016/S1470-2045(13)70017-2.

6. Yonemori K, Tsuta K, Ono M, et al, Disruption of the blood brain barrier by brain metastases of triple negative and basal-type breast cancer but not HER2/neu-positive breast cancer. Cancer. 2010;116:302-308. doi:10.1002/cncr.24735.

7. Bos PD, Zhang Xiang-H-F, Nadal C, et al, Genes that mediate breast cancer metastasis to the brain. Nature. 2009;459:1005-1009. doi:10.1038/nature08021.

8. Sperduto P, Kneed N, Roberge D, et al, The effect of tumour subtype on the time from primary diagnosis to development of brain metastases and survival in patients with breast cancer. J Neurooncol. 2013;112:467-472. doi:10.1007/s11060-013-1083-9.

9. Niwinska A, Murawska M, Pogoda K. Breast cancer subtypes and response to systemic treatment after whole-brain radiotherapy in patients with brain metastases. Cancer. 2010:4238-4247.doi 10.1002/cncr.25391.

10. Xu Z, Schlesinger D, Toulmin S, et al. Impact of triple-negative phenotype on prognosis with breast cancer brain metastases. Int J Radiat Biol Phys. 2012;84(3):612-618. doi: 10.1016/j.ijrobp.2011.12.054.

11. Karginova O, Siegel M, van Swearingen A, et al. Efficacy of carboplatin alone and in combination with ABT888 in intracranial murine models of BRCA-mutated and BRCA-wild type triple negative breast cancer. Molecular Cancer Therapeutics. 2015; doi:10.1158/1535-7163.MCT-14-0474.

12. Anders C, Deal AM, Abramson V, et al. TBCRC 018: phase II study of iniparib in combination with irinotecan to treat progressive triple negative breast cancer brain metastases. Breast cancer research and treatment.2014;146(3):557-566.

13. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol. 2011;29(2):134-141. doi: 10.1200/JCO.2010.30.1655.

14. Patchell RA, Tibbs PA, Regine WF, et al. Post-operative radiotherapy in the treatment of single metastases to the brain: a randomised trial. JAMA. 1998;280:1485-1489. doi:10.102001/jama.280.17.1485.

15. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole brain radiotherapy versus stereotactic radiosurgery alone for the treatment of brain metastases: a randomised clinical trial. JAMA. 2006;295:2483-2491. doi:10.1001/jama.295.21.2483.

16. Vern-Gross TZ, Lawrence JA, Case LD, et al. Breast cancer subtype affects patterns of failure of brain metastases after treatment with stereotactic radiosurgery. J Neurooncol. 2012;110(3):391-8. doi:1007/s11060-012-0976-3.

17. Sun A, Bae K, Gore E, et al. Phase III trial of prophylactic cranial irradiation with observation in patients with locally advanced non-small cell lung cancer: neurocognitive and quality of life analysis. J Clin Oncol. 2010;29:279-286. DOI: 10.1200/JCO.2010.29.6053.

18. Gondi V, Pugh S, Tome W, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole brain radiotherapy for brain metastases (RTOG 0933): A Phase III multi-institutional trial. J Clinc Oncol. 2014;32:3810-3816.

19. Savitz S, Chen R, Sher D. Cost-effectiveness analysis of neurocognitive-sparing treatment for brain metastases. Cancer. 2015;121:4231-9. doi:10.1002/cncr.29642.

20. Andrews D, Scott C, Sperduto P, et al. Whole brain radiotherapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet. 2004;363:1665-72.doi:10.1016/S0140-6736(04)16250-8.

21. Yamamoto M, Serizawa T, Shuto T, et al, Stereotactic radiosurgery for patients with multiple brain metastases ( JLGK0901): a multi-institutional prospective observational study. Lancet Oncol. 2014;15(4):387-95. doi: 10.1016/S1470-2045(14)70061-0.

22. Bartsch R, Berghoff AS, Preusser M, Optimal management of brain metastases from breast cancer. Issues and considerations. CNS Drugs. 2013;27(2):121-34. Doi:10.1007/s40263-012-0024-z.

23. Sim HW, Morris PG, Patil S, et al. Brain metastases in breast cancer. Exper Rev Anticancer Ther. 2014;14(2):173-83. doi 10.1586/14737140.

24. Tsao MN, Rades D, Wirth A. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. Practical Radiation Oncology. 2012;2:210-225. doi: 10.1016/j.prro.2011.12.004.

25. Cho E, Rubinstein L, Stevenson P, et al. The use of stereotactic radiosurgery for brain metastases from breast cancer: Who benefits most? Breast Cancer Res Treat. 2015; 149(3):743-749. doi:10.1997/s10549-014-3242-x

# Immunotherapy in breast cancer: the subtype story

Stephen J Luen and Sherene Loi

Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Victoria, Australia.

Email: sherene.loi@petermac.org

**Abstract**

Great hopes have been accorded to the potential of immunotherapy to exploit host anti-tumour immunity and deliver improved survival outcomes. Impressive results in cancers known to be immunogenic have led to a plethora of immunotherapy trials in several cancer types, including breast cancer. Descriptions of tumour-infiltrating lymphocytes in early breast cancer have unravelled the landscape of immunogenicity across the breast cancer subtypes, and provide rationale for investigation into immunotherapeutic approaches. Subsequently, numerous clinical trials have been launched, predominantly with checkpoint blockade. While triple negative and HER2-positive breast cancers appear to be more immunogenic than ER-positive/HER-2 negative breast cancers, responses to checkpoint blockade are still seen in this subtype, suggesting that subtype alone may not be a sufficient predictor of response to immunotherapies. Moreover, tumour-intrinsic contributors towards immunogenicity and immune-evasion are increasingly being explored, as is the ability of conventional therapies to modulate the immune microenvironment. Reports from early phase trials in breast cancer show that while immunotherapeutic approaches may not be suitable for all breast cancer patients, there are promising signs for a potential role of immunotherapy in the treatment of selected breast cancers.

The presence of lymphocytic infiltrates in breast cancer were noted as early as 1922,[1] demonstrating that host immune-surveillance has the potential to recognise cells that have undergone neoplastic transformation. More recently, retrospective analyses of prospectively collected tissue samples from clinical trials has served as a means to not only quantify the landscape of tumour-infiltrating lymphocytes in breast cancer, but also to examine its influence on response to treatment and disease outcomes. Together these results suggest anti-tumour immunity can be a key determinant of disease outcomes in breast cancer and provides justification for evaluation of immunotherapeutic approaches.

Compared with several other solid tumours, clinical trials of immunotherapy agents in breast cancer are in the developmental stage. Immune checkpoint blockade, in particular, has demonstrated clinical activity and reasonable safety profiles in early phase trials. Given the modest response rates observed in advanced disease, much consideration has been given to enhanced patient selection with the use of predictive biomarkers and an improved understanding of the relevance of pre-existing anti-tumour immunity. Furthermore, combinations of standard or targeted therapies with checkpoint blockade may have the potential to further improve therapeutic benefits through immune modulation.

This review aims to describe the immune landscape across breast cancer subtypes and summarise results from early phase immunotherapy trials in breast cancer. Finally, we will discuss some of the future directions and the emerging prospects of immunotherapy in breast cancer. While this review focuses predominantly on checkpoint blockade, it should be noted that other promising immune approaches are increasingly being tested in breast cancer, including vaccination.

## Immune infiltrates and patterns of pre-existing immunity

### *Immune infiltrates in breast cancer subtypes*

Adaptive T-cell mediated cytotoxic responses have been recognised as a dominant mechanism of host anti-tumour immune responses,[2,3] and are thought to arise from the recognition of tumour-specific epitopes (neoantigens), the by-product of expressed somatic cancer mutations.[4-6]

Investigation into the interaction between host immunity and breast tumours has predominantly been carried out through evaluation of tumour-infiltrating lymphocytes (TIL). Consistent with a key role of adaptive T-cell immunity, lymphocytic infiltrates are most commonly dominated by T cells, with variably lower levels of B cells, NK cells, macrophages, and dendritic cells.[7,8] Various methodologies have been employed to quantify and characterise TILs in breast cancer, most commonly using light microscopy of haematoxylin and eosin stained sections of tumour samples, but also by immunohistochemistry and gene expression. Each of these methodologies has its own strengths and weaknesses, however the results have been mostly consistent with each other.

While not generally considered a strongly immunogenic tumour, numerous retrospective studies evaluating TILs in prospectively collected tumour samples from early breast cancer have now revealed remarkable diversity in the degree of lymphocytic infiltrates,[9-17] implying that certain subsets of breast cancer are more immunogenic than others.[8,18] Among the clinically utilised subtypes, HER2-positive and triple negative breast cancers generally harbour higher TIL levels than ER-positive/HER2-negative breast cancers, suggesting that luminal breast tumours are generally less immunogenic. It should be noted, however, that substantial heterogeneity exists even among luminal tumours, suggesting a subgroup of luminal tumours may be more immunogenic than others.

### *Clinical implications of host immunity*

Beyond the mere presence of tumour-infiltrating lymphocytes, the clinical implications of host immunity have been demonstrated by significant associations with prognosis and response to therapies,[8] although this differs by breast cancer subtype. The prognostic significance of TILs has been most consistently shown in the TNBC subtype in the context of anthracycline chemotherapy,[19] but also independently in the HER2-positive subtype in patients undergoing a variety of treatments both with and without HER2-targeted agents.[14,20] This relationship is linear with increasing percentage of lymphocytic infiltrates associated with improved survival. By contrast, no prognostic significance of TILs has been found in the ER-positive/HER2-negative subtype, although this may be hindered by substantial heterogeneity.

Increasing TIL levels have also been demonstrated to be predictive of pathological complete response (pCR) to neoadjuvant therapy, predominantly in HER2-positive disease with HER2-targeted agents, but also in TNBC.[14,15,17,21,22] Using statistical interaction terms, some studies have also shown improved disease outcomes to treatment in those with higher levels of TILs. For example, in the FinHER study, those with higher TIL levels had a significantly improved distant disease-free survival benefit to trastuzumab.[12] Taken together, these studies suggest that immune infiltrates can play important roles in maximising the efficacy of specific therapeutic agents.

### *Rationale for immunotherapeutic approaches*

Evaluation of TILs in early breast cancer has established that host anti-tumour immunity can exert an influence in disease and treatment outcomes in selected breast tumours, most notably in TNBC and HER2-positive subtypes. Interestingly, the quantity of immune infiltrate appears to be most strongly associated with disease outcomes, implying the amplitude of pre-existing immunity is of key importance. Armed with this knowledge, and spurred on by impressive survival benefits to immunotherapy seen in melanoma,[23-25] non-small cell lung cancer,[26,27] and renal cell carcinoma,[28] multiple clinical trials of checkpoint blockade as monotherapy, as well as in combination with standard and targeted therapies, have been launched in specific breast cancer subtypes.

## Checkpoint blockade

While lymphocytic infiltrates appear to play an important biological role, the diagnosis of breast cancer ultimately represents escape from immune control.[29] Subsequent research into the full spectrum of immune-evasive mechanisms has intensified. In particular, immune checkpoints have emerged as key regulators of self-tolerance and regulation of established immune responses.[30] Checkpoint blockade efficacy is thought be mediated by re-engagement pre-existing immune responses. There have been relatively few studies of checkpoint blockade with reported outcomes in breast cancer compared with other cancer types - of these, most have focused on TNBC. At the time of this report, there had been no published phase III trials of checkpoint blockade in breast cancer.

### *Anti-CTLA4 checkpoint blockade*

Anti-CTLA4 immunotherapy has been utilised only in small exploratory studies in breast cancer, primarily to investigate changes in peripheral immune cell profiles. The first was a phase I trial of 26 patients with ER-positive advanced breast cancer with the use of tremelimumab in dose-escalation in combination with exemestane.[31] No objective responses were reported. However an increase in CD4+ and CD8+ T cells expressing inducible costimulatory was noted, as well as an increase in the ratio of CD4+ and CD8+ T cells to regulatory T cells. In a second study, 18 patients with early breast cancer were treated with either Ipilimumab alone, cryoablation plus ipilimumab, or cryoablation alone prior to mastectomy.[32] The combination approach with cryoablation plus ipilimumab was reported to lead to potentially favourable immunological changes in peripheral blood as well as in tumour. While these studies suggest a potential role for anti-CTLA4 checkpoint blockade, the lack of evidence of efficacy thus far has been disappointing. Moreover, toxicity observed with these agents is common, similar to toxicities profiles observed in other studies of anti-CTLA4 treatment. If it is to play a role in the treatment of breast cancer, it appears unlikely to be as a monotherapy.

### *Anti-PD1/PD-L1 checkpoint blockade*

Several early phase trials of anti-PD1 and anti-PD-L1 checkpoint blockade as monotherapy have been reported with response rates and toxicity profiles suggestive that anti-PD1/PD-L1 immunotherapies are worthy of further investigation (table 1).[33-36] There is significant heterogeneity among these trials with regard to investigational agent used, included breast cancer subtypes, PD-L1 evaluation methodology and eligibility, and prior treatment experience. Overall response rates in these trials varied from 5%-19%, with some responses exhibiting durability, even in patients who have experienced heavy treatment.

In order to improve patient selection, PD-L1 expression has been marked as having a potential role as a predictive biomarker and has been evaluated in all the described early phase trials. In other cancer types, PD-L1 expression has shown some promise as a predictive biomarker of PD-1/PDL-1 checkpoint blockade response, however this has been inconsistent.[26,27,37,38] Furthermore, PD-L1 evaluation has been hampered by heterogeneity in methodologies, the use of different cut-off values for positivity, and the use of different tissue types given the inducible nature of PD-L1 (archival tissue versus fresh metastatic biopsies).[39,40] Despite this, higher response rates have generally been observed in those with higher PD-L1 expression in early phase checkpoint blockade trials in breast cancer. For example, in the JAVELIN clinical trial,[33] using a PD-L1 cut-off value of ≥ 10%, the overall response rate was 33.3% in the whole cohort, and 44.4% in the TNBC cohort, implying that PD-L1 expression could improve patient selection, although this requires validation in larger studies. The ability of TILs to add to PD-L1 in helping to identify responders to PD-1/PD-L1 inhibition as immunotherapy is unknown and under active investigation.

Questions still remain as to whether there are significant differences in response rates and efficacy to checkpoint blockade between the breast cancer subtypes. As previously described, TIL levels are reported to be higher in TNBC and HER2-positive breast cancer compared with the ER-positive/HER-2 negative subtype. Interestingly, PD-L1 expression has shown a similar pattern among breast cancer subtypes.[33,41] Despite this, a response rate of 14% was seen in a phase I expansion cohort of single agent pembrolizumab in ER-positive/HER-2 negative metastatic breast cancer,[36] demonstrating that PD1/PD-L1 checkpoint blockade can have activity in this breast cancer subtype. It should be noted however, that patients were only eligible if they were PD-L1 positive (using a definition of ≥ 1% expression on tumour cells or any expression in the stroma) - 248 patients were screened with only 19.4% being PD-L1 positive. Taken together, PD1/PD-L1 checkpoint blockade has demonstrated efficacy in selected patients across all breast cancer subtypes. While PD-L1 expression is incompletely predictive of treatment response, it may better predict response than breast cancer subtype. Further studies will be required to confirm these findings.

## Combination therapy with checkpoint blockade

Given the modest response rates observed in early phase trials, strong consideration has been given to combining conventional and targeted therapies with immune checkpoint blockade to improve outcomes. The rationale behind this approach stems from observations across several studies that mechanisms of response to conventional agents including chemotherapy, radiotherapy and targeted therapies may be partly mediated by immune effects – via modulation of the tumour immune microenvironment, or by stimulation of immunogenicity.[42,43] This may occur via a process of enhanced apoptosis of immunogenic cell death, whereby release of tumour neoantigens on tumour cell death

results in enhanced uptake by antigen presenting cells and subsequent recruitment of effector T cells.[44,45] Several studies are currently underway investigating the approach of combination chemotherapy or radiotherapy with checkpoint blockade in breast cancer.[46,47] One early phase trial investigated the combination of taxane chemotherapy with atezolizumab (anti PD-L1 checkpoint blockade) in advanced TNBC,[48] demonstrating reasonable safety profiles, as well as encouraging response rates, with the highest response rates observed in patients receiving therapy in the first line metastatic setting. Subsequently, a phase III randomised, placebo-controlled trial is currently underway (clinicaltrails.gov identifier: NCT02425891).[46]

Specific genomic and transcriptomic alterations are increasingly recognised as contributors towards immune escape.[49] Some of these alterations may be targetable, suggesting a possible personalised approach to immunotherapy with the combination of checkpoint blockade with targeted therapies. In HER2-positive disease for example, trastuzumab and trastuzumab emtansine conjugate (T-DM1) treatment has been observed to be able to induce tumour lymphocytic infiltration.[50,51] Additionally, combination T-DM1 and checkpoint blockade has demonstrated enhanced efficacy in animal models with primary resistance to immunotherapy.[51] Subsequently, several studies of PD-1/PD-L1 inhibition in combination with HER2-targeted agents are underway.[52-54] Similarly in TNBC, MEK inhibition in mouse models with Ras-MAPK genomic alterations has demonstrated the potential to relieve immune suppression and upregulate interferon gamma-mediated antigen presentation and PD-L1 expression.[55] Therefore, a rational approach may be the combination of MEK inhibition with PD1/PD-L1 checkpoint blockade in patients with TNBC harbouring genomic alterations in the Ras/MAPK pathway. The role of MEK inhibition in TNBC is currently being explored in a clinical trial in combination with paclitaxel (clinicaltrails.gov identifier: NCT02322814).

## Future prospects of immunotherapy in breast cancer

Further research into the intersection between the unique genomic and transcriptomic profiles of breast cancer and anti-tumour immunity will provide a clearer picture of the tumour-intrinsic determinants of immunogenicity and immune-evasion.[56] This will provide further considerations for optimising combination immunotherapy approaches. Moreover, phenotyping of the constituents of immune responses will allow us to better understand the balance between an effective immune response and a suppressed immune response, including the establishment of multiple immune checkpoints. Several other checkpoint targeted therapies are in drug development and may also be rational combination partners with PD-1/PD-L1 checkpoint blockade.

The timing of immune based treatment warrants important consideration. Metastatic tumour biopsies have generally harboured lower TIL levels than primary disease,[57] perhaps through extensive immunoediting, or the establishment of immune-evasive mechanisms. Therefore, highly treatment experienced patients with extensive disease burden are expected to be less likely to respond to checkpoint blockade as a single agent than earlier disease with a lesser extent of disease. Finally, it appears unlikely that all unselected patients will benefit from an immunotherapeutic approach, exemplifying the need to stop of biomarkers that may indicate when a patient can be prescribed treatment that will be effective.

## Conclusion

Recent breakthroughs in immunotherapy, particularly checkpoint blockade, have led to a great deal of excitement regarding potential therapeutic benefits in all cancer types. Furthermore, detailed quantification and characterisation of the immune microenvironment of breast cancer and its subtypes have provided ample justification for evaluation of immunotherapy in breast cancer. Reports from several early phase trials show response rates that have maintained our enthusiasm. However it has become clear that checkpoint blockade as monotherapy will be insufficient in many patients with advanced breast cancer. To combat this, research efforts are now focusing on the key determinants of immunogenicity, and the factors that contribute towards immune-escape. If these are fully understood, a personalised approach to combination immunotherapy may have great potential to enhance breast cancer outcomes in the right patients.

# Table 1

† The study cohort was not selected for by PD-L1 status, however only participants with PD-L1 expression ≥ 5% have been reported. ‡ Confirmed overall response rate shown - the highest overall response rate was observed in those undergoing treatment in the first line advanced setting. Abbreviations: TNBC, triple negative breast cancer; PD-L1, programmed cell-death ligand 1; ORR, overall response rate.

**Table 1 - Summary of early phase anti-PD1/PD-L1 trials in advanced breast cancer**

| Trial | Phase | Study population | Number of participants | Study compound | PD-L1 status | ORR | Median duration of response | Median time to response |
|---|---|---|---|---|---|---|---|---|
| JAVELIN[33] | Phase Ib | All subtypes | 168 | Avelumab | Unselected | 4.8% | 28.7 weeks | 11.4 weeks |
| KEYNOTE-012[34] | Phase I | TNBC | 32 | Pembrolizumab | PD-L1 ≥ 1% of tumour cells or any staining in the stroma | 18.5% | Not reached | 17.9 weeks |
| NCT01375842[35] | Phase I | TNBC | 21 | Atezolizumab | PD-L1 ≥ 5% of infiltrating immune cells† | 19.0% | Not reached | Not reported |
| KEYNOTE-028[36] | Phase Ib | ER-positive/HER2-negative | 25 | Pembrolizumab | PD-L1 ≥ 1% of tumour cells or any staining in the stroma | 14.0% | Not reached | 8.0 weeks |
| NCT01633970[48] | Phase Ib | TNBC | 32 | Atezolizumab + nab-paclitaxel | Unselected | 42.0%‡ | Not reported | Not reported |

## References


1. Sistrunk WE, Maccarty WC. Life Expectancy Following Radical Amputation for Carcinoma of the Breast: A Clinical and Pathologic Study of 218 Cases. Ann Surg. 1922;75:61-9.
2. Matsushita H, Vesely MD, Koboldt DC, et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature. 2012;482:400-4.
3. Wick DA, Webb JR, Nielsen JS, et al. Surveillance of the tumor mutanome by T cells during progression from primary to recurrent ovarian cancer. Clin Cancer Res. 2014;20:1125-34.
4. Castle JC, Kreiter S, Diekmann J, et al. Exploiting the mutanome for tumor vaccination. Cancer Res. 2012;72:1081-91.
5. Robbins PF, Lu YC, El-Gamil M, et al. Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. Nat Med. 2013;19:747-52.
6. Dadmarz R, Sgagias MK, Rosenberg SA, et al. CD4+ T lymphocytes infiltrating human breast cancer recognise autologous tumor in an MHC-class-II restricted fashion. Cancer Immunol Immunother. 1995;40:1-9.
7. Ruffell B, Au A, Rugo HS, et al. Leukocyte composition of human breast cancer. Proc Natl Acad Sci USA. 2012;109:2796-801.
8. Savas P, Salgado R, Denkert C, et al. Clinical relevance of host immunity in breast cancer: from TILs to the clinic. Nat Rev Clin Oncol. 2016;13:228-41.
9. Loi S, Sirtaine N, Piette F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol. 2013;31:860-7.
10. Adams S, Gray RJ, Demaria S, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol. 2014;32:2959-66.
11. Ali HR, Provenzano E, Dawson SJ, et al. Association between CD8+ T-cell infiltration and breast cancer survival in 12,439 patients. Ann Oncol. 2014;25:1536-43.
12. Loi S, Michiels S, Salgado R, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol. 2014;25:1544-50.
13. Dieci MV, Mathieu MC, Guarneri V, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in two phase III randomized adjuvant breast cancer trials. Ann Oncol. 2015;26:1698-704.
14. Salgado R, Denkert C, Campbell C, et al. Tumor-Infiltrating Lymphocytes and Associations With Pathological Complete Response and Event-Free Survival in HER2-Positive Early-Stage Breast Cancer Treated With Lapatinib and Trastuzumab: A Secondary Analysis of the NeoALTTO Trial. JAMA Oncol. 2015;1:448-54.
15. Ingold Heppner B, Untch M, Denkert C, et al. Tumor-infiltrating lymphocytes: a predictive and prognostic biomarker in neoadjuvant treated HER2-positive breast cancer. Clin Cancer Res. 2016.
16. Denkert C, Loibl S, Noske A, et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol. 2010;28:105-13.
17. Denkert C, von Minckwitz G, Brase JC, et al. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol. 2015;33:983-91.
18. Dushyanthen S, Beavis PA, Savas P, et al. Relevance of tumor-infiltrating lymphocytes in breast cancer. BMC Med. 2015;13:202
19. Loi S, Drubay D, Adams S, et al. Abstract S1-03: Pooled individual patient data analysis of stromal tumor infiltrating lymphocytes in primary triple negative breast cancer treated with anthracycline-based chemotherapy. Cancer Research. 2016;76:S1-03-S1-03.
20. Perez EA, Ballman KV, Tenner KS, et al. Association of Stromal Tumor-Infiltrating Lymphocytes With Recurrence-Free Survival in the N9831 Adjuvant Trial in Patients With Early-Stage HER2-Positive Breast Cancer. JAMA Oncol. 2016;2:56-64.
21. Issa-Nummer Y, Darb-Esfahani S, Loibl S, et al. Prospective validation of immunological infiltrate for prediction of response to neoadjuvant chemotherapy in HER2-negative breast cancer--a substudy of the neoadjuvant GeparQuinto trial. PLoS One. 2013;8:e79775.
22. West NR, Milne K, Truong PT, et al. Tumor-infiltrating lymphocytes predict response to anthracycline-based chemotherapy in estrogen receptor-negative breast cancer. Breast Cancer Res. 2011;13:R126.

23. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711-23.
24. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372:320-30.
25. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372:2521-32.
26. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373:1627-39.
27. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373:123-35.
28. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373:1803-13.
29. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646-74
30. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12:252-64.
31. Vonderheide RH, LoRusso PM, Khalil M, et al. Tremelimumab in combination with exemestane in patients with advanced breast cancer and treatment-associated modulation of inducible costimulator expression on patient T cells. Clin Cancer Res. 2010;16:3485-94.
32. Page DB, Diab A, Yuan J, et al. Pre-operative immunotherapy with tumor cryoablation (cryo) plus ipilimumab (ipi) induces potentially favorable systemic and intratumoral immune effects in early stage breast cancer (ESBC) patients. Journal for ImmunoTherapy of Cancer. 2015;3:O6.
33. Dirix L, Takacs I, Nikolinakos P, et al. Abstract S1-04: Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A phase Ib JAVELIN solid tumor trial. Cancer Research. 2016;76:S1-04-S1-04.
34. Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. J Clin Oncol. 2016;34:2460-7.
35. Emens LA, Braiteh FS, Cassier P, et al. Abstract PD1-6: Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer. Cancer Research. 2015;75:PD1-6-PD1-6.
36. Rugo HS, Delord JP, Im SA, et al. Abstract S5-07: Preliminary efficacy and safety of pembrolizumab (MK-3475) in patients with PD-L1–positive, estrogen receptor-positive (ER+)/HER2-negative advanced breast cancer enrolled in KEYNOTE-028. Cancer Research. 2016;76:S5-07-S5-07.
37. Fusi A, Festino L, Botti G, et al. PD-L1 expression as a potential predictive biomarker. The Lancet Oncology. 2015;16:1285-1287.
38. McDermott DF, Sosman JA, Sznol M, et al. Atezolizumab, an Anti-Programmed Death-Ligand 1 Antibody, in Metastatic Renal Cell Carcinoma: Long-Term Safety, Clinical Activity, and Immune Correlates From a Phase Ia Study. J Clin Oncol. 2016;34:833-42.
39. Ilie M, Hofman V, Dietel M, et al. Assessment of the PD-L1 status by immunohistochemistry: challenges and perspectives for therapeutic strategies in lung cancer patients. Virchows Arch. 2016;468:511-25
40. Patel SP, Kurzrock R. PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy. Mol Cancer Ther. 2015;14:847-56.
41. Sabatier R, Finetti P, Mamessier E, et al. Prognostic and predictive value of PDL1 expression in breast cancer. Oncotarget. 2015;6:5449-64.
42. Galluzzi L, Buque A, Kepp O, et al. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents. Cancer Cell. 2015;28:690-714.
43. Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med. 2007;13:1050-9.
44. Albert ML, Sauter B, Bhardwaj N. Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. Nature. 1998;392:86-9.
45. Fonteneau JF, Larsson M, Bhardwaj N. Interactions between dead cells and dendritic cells in the induction of antiviral CTL responses. Curr Opin Immunol. 2002;14:471-7.
46. US National Library of Medicine. ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/record/NCT02425891 2016
47. US National Library of Medicine. ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT02303366. 2016

48. Adams S, Diamond JR, Hamilton EP, et al. Abstract 1009: Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC). J Clin Oncol. 2016;34.
49. Rooney MS, Shukla SA, Wu CJ, et al. Molecular and genetic properties of tumors associated with local immune cytolytic activity. Cell. 2015;160:48-61.
50. Gennari R, Menard S, Fagnoni F, et al. Pilot study of the mechanism of action of preoperative trastuzumab in patients with primary operable breast tumors overexpressing HER2. Clin Cancer Res. 2004;10:5650-5.
51. Muller P, Kreuzaler M, Khan T, et al. Trastuzumab emtansine (T-DM1) renders HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade. Sci Transl Med. 2015;7:315ra188.
52. US National Library of Medicine. ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT02129556. 2016
53. US National Library of Medicine. ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT02318901. 2015
54. US National Library of Medicine. ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT02605915. 2016
55. Loi S, Dushyanthen S, Beavis PA, et al. RAS/MAPK Activation Is Associated with Reduced Tumor-Infiltrating Lymphocytes in Triple-Negative Breast Cancer: Therapeutic Cooperation Between MEK and PD-1/PD-L1 Immune Checkpoint Inhibitors. Clin Cancer Res. 2016;22:1499-509.
56. Luen S, Virassamy B, Savas P, et al. The genomic landscape of breast cancer and its interaction with host immunity. Breast. 2016;29:241-50.
57. Arnedos M, Filleron T, Dieci MV, et al. Genomic and immune characterization of metastatic breast cancer (MBC): and ancillary studies of the SAFIR01 & MOSCATO trials. Annals of Oncology. 2014;25:iv116 (abstr 3510).

## W Brian Fleming

W Brian Fleming was born in Zeehan, Tasmania on 13 February 1927, and was educated in Burnie, before moving to Melbourne to complete his secondary education at Scotch College, graduating in 1943.

He was able to make the wartime quota for medicine, and as medical students were exempt from call-up, began his medical training at the University of Melbourne Medical School in February 1944. Brian's clinical training was undertaken at the Royal Melbourne Hospital, and he graduated MBBS in November 1949. He became an intern at the Royal Melbourne Hospital in 1950 and a Senior House Surgeon the following year. He became a resident surgical officer in 1952 and married Margaret in July the same year.

In December 1953 Brian attained his Fellowship of the Royal Australasian College of Surgeons, and combined his surgical duties with research as the Randal and Louisa Alcock Scholar in Pathology. In May of 1954 he received his Master of Surgery by examination, and in June was appointed to his first job as a trained surgeon.

From June to December 1954 Brian served in the Royal Australian Army Medical Corps as a Major, with the British Commonwealth Force, Korea, based at the British Commonwealth General Hospital in Kure, Japan. He was discharged to the Army Reserve as a Consultant Surgeon for the Southern Command, a post he held until 1972. He was earmarked for a stint in the UN Force in Laos, prior to the Vietnam War, but fortunately Australian forces were not required. Because of his young family, he was not needed to serve in Vietnam.

After further study in the UK and USA, Brian attained his Fellowship of the Royal College of Surgeons in England in May 1955. From December 1955 he was appointed to the staff of the Royal Melbourne Hospital, and in the following year to the staff of the Footscray and District Hospital. In 1968 he received his Fellowship of the American College of Surgeons, and was appointed Head of his own Unit. As the years progressed he became recognised as a gifted specialist Head and Neck surgeon, serving both the Peter MacCallum and Royal Melbourne Hospitals in the field of cancer surgery.

The Royal Melbourne Hospital recognised Brian Fleming's exceptional leadership skills when he was appointed the Chairman of the Division of Surgery and the Head of the Medical Advisory Committee in 1975, two posts that he held until 1983. He was appointed the Head of the Head and Neck Service in 1980, and held this appointment until retirement. He was appointed to the Board of Management in 1983 and became the Junior Vice President of the Hospital in 1986. He was the Acting Treasurer in 1989 and retired from the staff of the Royal Melbourne Hospital, after 36 years' service, in 1991.

Besides his commitments to the Royal Melbourne Hospital, Brian was deeply involved in the services of cancer research and prevention outside the hospital. In the early 1970s cancer clinicians around Australia knew more about overseas practice, than about what contemporaries were doing within a few hundred kilometres. The late Noel Newton and Leicester Atkinson in Sydney sought a like mind in Melbourne and were rewarded when Brian Fleming agreed to collaborate. He helped found the Clinical Oncological Society of Australia, becoming its first President from 1974 to 1976.

Brian was invited to assist the Anti-Cancer Council of Victoria, and as their delegate became Vice President (1980-1983) and then President of the Australian Cancer Society from 1983 to 1986. Beyond that he served the Society in other ways, chairing its Medical and Scientific Committee, editing the Cancer Related Health Check-Up, advising on the National Cancer Prevention Policy, chairing a national consensus conference on Cervical Cancer Screening and serving as a member of the National Cancer Advisory Committee. He joined the Executive Committee of the Anti-Cancer Council of Victoria in 1987 and became its Vice President in 1989. He was appointed as Surgeon to the Health Department of Victoria Consultative Committee on Anaesthetic Morbidity and Mortality in 1991.

Brian was presented with the Australian Cancer Society Gold Medal for Distinguished Service in the Fight against Cancer in November 1992. On this occasion, the President Mrs Heather Wain, in presenting the Medal said "In his voluntary service to COSA, the Anti-Cancer Council of Victoria and the Australian Cancer Society Brian added a further dimension to the care and compassion he gave

to his patients. Through his selfless commitment he has aided the advancement of cancer care for the whole Australian community and upheld the noble ideals of the medical profession. His example continues through his family with a wife a former nurse, one daughter a nurse, one a science graduate, two sons who are doctors, and Melissa who decided to follow her father's artistic talent into architecture. He deservedly joins a list of distinguished Australian cancer workers which includes a number of Victorians: Sir William Kilpatrick, Don Metcalf, John Colebatch and Ken Cox; his addition to the list adds to its lustre."

Brian retired from active surgical practice and direct patient care in 1991, but continued in medico-legal practice in Melbourne and Mildura for many years. With the introduction of Workcover by the Kennett Government in December 1992, Brian was appointed a Sessional Conciliator, one of the few medically trained, and the only surgeon. He continued in this role to March 1996, and in May 1997, Brian was presented with the inaugural Head and Neck Surgery Medal by the Royal Australasian College of Surgeons Section of Head and Neck Surgery.

Despite his advancing age, the Victorian Government acknowledged Brian’s exceptional skills as a wise and fair conciliator, appointing him to Medical Panels. He was regularly asked to keep going and was reappointed on into his 70s, before finally retiring from medico-legal practice on the occasion of his 79th birthday in February 2006.

In leisure time Brian played golf and indulged in oil painting. He began exhibiting with the Australian Medical Association Arts Group in 1962, three years after its inception. He had one painting entitled "Banksia", bought by Sir Daryl Lindsay, Chairman of the Commonwealth Art Advisory Board for the Australian Government Collection, and two paintings were purchased by John McEwen, Deputy Prime Minister.

Brian was awarded the Membership of the Order of Australia (AM) on 11 June 2001, for service to medicine, particularly oncology treatment as a head and neck surgeon, and as a medical administrator.

He died after a long illness on 5th July 2016, survived by his wife Margaret, his five children Helen, Judy, Bill, Rick and Melissa, and by his seven grandchildren.

# Clinical Oncology Society of Australia Cancer Care Coordinator Position Statement Summary

The growing demand for cancer care, increasing complexity of cancer and its treatments, a shrinking workforce, and rising costs, present major challenges to the delivery of cancer care.[1] In this context, effective coordination of care across different clinicians, teams and health services is essential to high-quality cancer care.[2] Consumers consistently identify coordination of care to be a priority issue and an important influence on their cancer experience.[3] Coordination of care has also been identified as a critical element of person-centred care and is an important element of national safety and quality standards for health care services.[1,4]

Coordination of care is a complex task that requires action at a number of levels and engagement of a wide range of health professionals. The purpose of the Cancer Care Coordinator Position Statement is to outline the position of the Clinical Oncology Society of Australia (COSA) regarding the role of dedicated care coordinator positions, one key strategy that has been implemented in many health services to achieve improved care coordination. Specifically, this paper seeks to provide an overview of the role of cancer care coordinators and to provide guidance for consumers, health professionals, health service managers and funders on the effective integration of these roles into cancer care delivery. For the purposes of this document, we focus on the role of professional care coordinators who perform clinical or health service functions associated with coordination of a person's care. Issues associated with implementation of coordinator roles that involve primarily an administrative function are not addressed in this paper.

## It is COSA's position that:

- All people affected by cancer require effective care coordination.
- Effective care coordination is an essential element of person-centred care and critical to ensuring optimal cancer outcomes and delivery of high quality and efficient cancer services.
- Effective care coordination involves interventions at many levels, including the health system, health care provider and individual consumer level.
- Designated care coordinator positions should be implemented within the context of a comprehensive approach to care coordination that includes health system, health care provider and consumer level interventions.
- Care coordinator roles should be implemented following a comprehensive assessment of existing care pathways and service capabilities to inform the way in which the roles will be operationalised. This assessment should be undertaken on a regular basis to ensure care coordinator roles are responsive to new developments in cancer treatments and supportive care, and changing service needs.
- When implementing care coordinator positions, careful consideration should be given to distinguishing between roles that require coordination of a person's clinical care from roles which serve primarily an administrative function.
- Consistent with CNSA's position on the role of cancer care coordinators,[5] key elements of the care coordinator role that involves coordination of a person's clinical care and health services include:
    - Assessment and screening for clinical and supportive care needs and people at risk for adverse clinical and psychosocial outcomes
    - Facilitating delivery of cancer care consistent with established evidence based guidelines

    - Ensuring timely and appropriate referral to specialist, allied health and support services
    - Facilitating continuity of care between health professionals and across settings for care delivery
    - Providing timely and consistent education and information to patients and their families
    - Participating in service improvement activities that aim to improve coordination of care and optimise outcomes for individuals and services.
- While no studies are available to confirm the qualifications and experience required for cancer care coordinator roles, the complexity of cancer care coordinator functions requires that cancer care coordinators have sufficient experience, qualifications and capabilities that enable them to perform a broad range of clinical, supportive care and strategic roles in the cancer context.
- A shared understanding of the roles and functions of the care coordinator is required by all involved in the cancer care team, including consumers.
- Referral pathways for access to a care coordinator service should be clearly defined and based on policies and criteria that support the holistic assessment of an individual's needs.
- The effectiveness of care coordinator services should be evaluated using indicators that are relevant and sensitive to the specific nature of this care coordination strategy.
- Care coordinators require a supportive professional practice environment and adequate professional development opportunities to enable them to function optimally.
- Ongoing efforts are required to ensure care coordinator roles evolve in response to changing service needs.

## COSA calls for:

- Appropriate resourcing of interventions to improve the coordination of cancer care at all levels, including resourcing for dedicated cancer care coordinator positions and administrative support to enable coordinators to achieve optimal outcomes.
- The development of a national framework for cancer care coordinator positions, which provides guidance for workforce planning in relation to these roles and which describes the experience, qualifications, capabilities, principles, role responsibilities, expected outcomes and key performance indicators for these positions. This framework should be flexible to accommodate local circumstances and clearly define minimum standards associated with implementation of the roles to minimise unacceptable variation.
- Application of the Oncology Nursing Society Nurse Navigator Core Competencies[6] and/or the Canadian practice framework for Nurse Navigators[7] to inform the design, implementation and evaluation of care coordinator roles (in the absence of an Australian Framework).
- Ongoing efforts to ensure care coordination is a major priority for health services and embedded as part of standard practice.
- The development of a systematic process where indicators of effective care coordination are routinely incorporated into cancer data systems and used to drive service improvements.

## References

1. IOM (Institute of Medicine). Delivering high-quality cancer care: Charting a new course for a system in crisis. Washington, DC: The National Academies Press, 2013.
2. Bowles EJA, Tuzzio L, Wiese CJ, et al. Understanding high-quality cancer care: a summary of expert perspectives. Cancer. 2008;112(4):934-42.

3. Clinical Oncology Society of Australia, Cancer Council Australia and National Cancer Control Initiative. Optimising cancer care in Australia. Melbourne: National Cancer Control Initiative, 2003.
4. Australian Commission on Safety and Quality in Health Care. National Safety and Quality Standards 2012, Available at: http://www.safetyandquality.gov.au/publications/national-safety-and-quality-health-service-standards/
5. Cancer Nurses Society of Australia Position Statement for Care Coordinators 2008. Available at: http://www.cnsa.org.au/documents/item/46
6. Oncology Nursing Society. Oncology Nurse Navigator Core Competencies. 2013. Available at: https://www.ons.org/sites/default/files/ONNCompetencies_rev.pdf
7. Cook S, Fillion L, Fitch M, et al. Core areas of practice and associated competencies for nurses working as professional cancer navigators. Canadian Journal of Oncology Nursing. 2011;44-52.

# Cancer Council Australia Student Essay Competition 2016: How best to teach and learn about cancer in medical schools: moving towards a patient-centred approach that reflects the needs of Australia

Robert J McRae
MBBS candidate, School of Medicine Sydney, University of Notre Dame Australia.
Email: robert.mcrae1@my.nd.edu.au

**Abstract**
Cancer has recently overtaken heart disease to become the number one cause of mortality both globally and in Australia. As such, adequate oncology education must be an integral component of medical school if students are to achieve learning outcomes that meet the needs of the population. The aim of this review is to evaluate the current state of undergraduate oncology education and identify how Australian medical schools can improve oncology learning outcomes for students, and by derivative, improve health care outcomes for Australians with cancer. The review shows that oncology is generally not well represented in medical school curricula, that few medical schools offer mandatory oncology or palliative care rotations, and that junior doctors are exhibiting declining oncology knowledge and skills. To address these issues, Australian medical schools should implement the Oncology Education Committee's Ideal Oncology Curriculum, enact mandatory oncology and palliative care clinical rotations for students, and in doing so, appreciate the importance of students' differing approaches to learning.

*"To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all."*
— Sir William Osler

Cancer has recently overtaken heart disease to become the number one cause of mortality both globally and in Australia,[1] yet is still not a core clinical rotation in most medical schools. Australians are living longer than ever, and because cancer is positively associated with ageing, its incidence in Australia continues to rise. The oncology specialty has undergone rapid and remarkable change over the last 50 years, leading to significant improvements in the prevention, diagnosis, and treatment of cancer. A knock-on implication of such rapid change, however, is determining how to best teach and learn about cancer and integrating these principles into medical education.

Improving outcomes for patients affected by cancer starts with undergraduate medical education curricula. Because cancer has the ability to immensely impact every aspect of a patient's life, an ability to treat not only the disease, but the whole person, must be a fundamental outcome of medical education. Such a patient-centred approach necessitates the presence of patients, yet most medical schools do not have core (mandatory) oncology or palliative care rotations in their curricula, nor do their curricula adequately weigh oncology in teaching time or assessment.[2] It must be questioned, therefore, whether medical schools are adequately addressing the medical needs of our population. As such, after reviewing the current state of undergraduate medical education in Australia, this essay will outline how integrating core clinical rotations and improving oncology curricula are essential steps to providing the best possible learning and teaching environment for cancer education.

## The current state of undergraduate medical education

Australia's system of medical education was historically based on that of the UK's, which after decades of disorder eventually evolved into what is today called a two-phase pre-clinical and clinical structure. Medical schools in Australia generally provide basic science education in the first one or two years through lectures, tutorials, and workshops that cover physiology, anatomy, pharmacology, and other key disciplines. For many medical schools, the problem-based learning model maintains its

position as the glue that binds together each of these components, notwithstanding its oft-discussed limitations.[3-5] Clinical concepts are slowly introduced during this pre-clinical phase, and developing students are gradually exposed to patients in usually graceless clinical encounters. It is these patient encounters, however, that bring the basic sciences to life for medical students.

After completing the pre-clinical phase of their education, students become immersed in the clinical world of medicine, spending the majority of their time in hospitals, outpatient clinics, general practices, and community health organisations that focus on specialties chosen by universities. The clinical years of medical school provide an opportunity to apply basic science knowledge to dynamic, real clinical situations and environments. Equally important, students have the chance to learn and practice skills that cannot be mastered in classrooms or workshops. For example, 'breaking bad news', a theme often discussed in medical education,[6,7] presents a host of difficulties for the clinician as she or he grapples with how to provide distressing information to patients or families. Whilst pre-clinical education tells the student to, for example, avoid jargon and provide written materials, no amount of classroom teaching can fully prepare for managing distressed, sometimes despondent, patients. As such, the clinical years of a student's education allow not just an application of knowledge, but the development of human skills and abilities that are essential to the doctor wishing to provide patient-centred care.[8]

## The key issues in oncology education

### *1. Oncology is under-represented in medical school curricula*

By the age of 85, half of Australian men and a third of Australian women will be diagnosed with cancer.[9] In 2013, more than 44,000 Australians died from cancer, and in 2020 alone, there will be 150,000 new diagnoses of cancer in our country.[9] Indigenous Australians have a 30 per cent higher cancer mortality risk, despite having a slightly lower incidence rate than non-Indigenous Australians.[10] Clearly, the impact of cancer in Australia is immense, and should be reflected in the time devoted to teaching and learning about its management. However, it is not.

Effectively teaching and learning about cancer requires robust oncology coverage in medical school curricula, which continues to be an issue in Australia and around the world (e.g. Canada,[12] Poland,[13] Greece,[14] and Scandinavia[15]).[11] The poor uptake of standardised and properly weighted oncology curricula has been demonstrated in a study of undergraduate training programs that showed oncology contributed to less than 10 per cent of the curriculum and final assessment for most medical schools, far less than its impact on health in society.[16] Similarly, only three out of five European universities were found to have a stated oncology curriculum, and even fewer had departments of oncology.[17]

The lack of adequate cancer education curricula has also been acknowledged by oncologists and students alike. In Argentina, four out of five oncologists believe that cancer curricula in universities are incomplete.[18] A review of oncology curricula in European undergraduate medical schools shows that only 20 per cent of fifth and sixth year medical students rated their clinical exposure to oncology as 'satisfactory', while over 40 per cent had received less than 20 hours of total teaching time throughout their entire degree.[2] With over 14 million new cases of cancer worldwide in 2012 alone, and a further 8.2 million deaths,[19] the emphasis on oncology in medical schools is manifestly inadequate and a barrier to providing an environment for quality cancer education.

### *2. Oncology education is lacking a patient-centred approach*

Historically, medical training up until around 1850 was exclusively delivered through an apprenticeship-based system:[20] on-the-job teaching with real patients, in real clinical environments. The following century saw a strong movement away from the apprenticeship approach as the scientific underpinnings of pathology emerged, and subsequently relied heavily on a lecture-based approach.[21] Since around 1950, however, universities have again emphasised the importance of bedside teaching and clinical contact, by reducing the lecture component of education and focusing on delivering knowledge and skills through clinical experiences.[21] This change is grounded in research: though lectures may provide students with knowledge, the application of this knowledge to patients cannot be taught effectively through a lecture.[21]

While medical schools have acknowledged the value of clinical rotations for disciplines like psychiatry, women's health and paediatrics, they seem to have overlooked the importance of dedicated oncology

and palliative care rotations. The Medical Deans Australia and New Zealand's most recent publicly available report of medical undergraduate clinical training shows that in 2008, only two of 19 medical schools in Australia offered an oncology rotation as part of the core curriculum, while a further two offered a core palliative care rotation.[22] As such, only around one in 10 students will experience dedicated oncology exposure in a clinical setting, and another one in 10 will experience a palliative rotation, which is disproportionate given the prevalence of cancer in Australia and the reality that almost all doctors will be involved in managing patients with cancer at some stage in their career.

### *3. Doctors are exhibiting declining oncology knowledge and skills*

The result of inadequate medical school curricula and clinical rotations in oncology and palliative care are inevitability found in our practising doctors. A survey of interns in Australia and New Zealand comparing interns from 2001 to those from 1990 demonstrated that the 2001 intern group had received less exposure to cancer patients than those from the 1990 group.[23] For example, less than half of the 2001 group had performed a physical examination on a patient with prostate or rectal cancer, fewer than the 1991 group. Similarly, an ability to perform a Papanicolaou smear had reduced in the 2001 intern group compared to the 1991 group, as had the ability to recognise melanoma lesions.[23] The authors also found that the 2001 intern group regarded their oncology teaching as being poorer than those in the 1991 group. With melanoma, prostate, and colorectal cancers accounting for three of the five most common cancers in Australia,[9] a declining screening and diagnostic ability amongst Australian doctors is an unacceptable outcome.

As may be expected, the outcomes of limited undergraduate oncology education are also carried through to the careers of oncologists, with Australian medical, surgical, radiation, and gynaecological oncologists reporting via survey that significant variability of knowledge and opinion existed, as well as being overall poorly informed about cancer epidemiology.[11]

## Addressing the key issues in oncology education

### *1. Implement curricula that reflect the health needs of our population*

In 1989, Australian medical schools received guidelines for an 'ideal' oncology curriculum based on the outcome of a national survey about cancer education, and published by the Australian Cancer Society.[24] After further research and the backing of the International Union Against Cancer, these guidelines eventually progressed into the Ideal Oncology Curriculum (IOC), a set of guidelines made available to all medical schools almost 10 years ago by the Cancer Council's Oncology Education Committee. Despite this, uptake of the IOC by Australian universities has been limited despite having many years to achieve integration, a reality perhaps more common in academia than we would like to believe.[24]

More complete implementation of the IOC will provide medical schools with a solid framework for designing standardised, well-researched oncology curricula and will make Australia one of the few countries in the world with a coordinated effort towards national undergraduate cancer education. The best way to teach oncology is to start with addressing the health needs of our population, which requires increasing cancer curricula in medical schools.

### *2. Implement a patient-centred approach with core oncology and palliative care clinical rotations for every student*

Oncology and palliative care rotations should be integrated as core rotations for every student during the clinical years of undergraduate medical education if we are to provide the best environment for teaching and learning about cancer. The addition of the 'five essential cancer clinical experiences for medical students' to the IOC demonstrates the importance of this hands-on, patient-centred approach to teaching and learning. They are:[24]

1. Talking with and examining people affected by all stages of cancer;
2. Talking with and examining people affected by all common cancers;
3. Observing all components of multidisciplinary cancer care;
4. Seeing shared decision-making between people with cancer and their doctors; and
5. Talking with and examining dying people.

The IOC's essential clinical experiences, as expected, necessitate hands-on training with patients. The opportunity to talk with and examine dying patients is generally reserved for palliative wards, while being able to talk with and examine patients affected by all stages of cancer and all common cancers requires significant time in oncology wards or outpatient clinics. With the majority of Australian medical students missing out on rotations through oncology and palliative care wards and outpatient clinics, achieving the IOC's recommended clinical experiences becomes difficult, if not impossible. And, because poor coverage of specialties in the undergraduate curricula can lead to a decreased level of interest in those specialties,[25] there are also implications for meeting the projected shortage of medical oncologists in Australia.[26]

Breast cancer, one of the most commonly diagnosed cancers in Australia,[9] has been shown to be better managed by students who have had clinical experiences with patients. A study of University of Western Australia (UWA) students demonstrated that after the introduction of short clinical attachments in cancer medicine and palliative care during the clinical undergraduate years, interns were reported as being better prepared to care for patients with cancer, compared to the national intern average.[27] Fewer UWA students responded that their training had been 'poor or very poor' when considering management of incurable cancer or patients dying from cancer, and more UWA students reported that they would refer a patient with a new diagnosis of breast cancer for multidisciplinary review. Multiple other studies have demonstrated that using actual patients in the delivery of breast examination education improves examination skills and breast lump detection,[28,29] further demonstrating the benefits of a patient-centred approach with clinical teaching and learning.

Excellent communication skills are essential for all medical students and are perhaps most important when dealing with patients with cancer. The IOC details a range of communication skills that are required for addressing the psychosocial aspects of cancer, counselling, patient education, and the communication of bad news. The development of such skills requires continued patient contact and could be achieved by having every student complete oncology and palliative care rotations in medical school. A review of reflections from University of New South Wales students shows that after a four week oncology and palliative care rotation, students improved their communication skills by having the opportunity to 'just listen' to patients' stories, allowing them to be empathetic and utilise communication strategies like 'silence periods'.[30] Students also recorded improvements in confidence in managing patients, as well as enhancing their approach to providing whole-person care.

### *3. Recognise that different students have different approaches to learning*

The huge variety in instructional preferences, cognitive styles, and learning styles observed in students dictates that the 'best' way to learn and teach is to provide students with flexible, adaptable environments, such as those found in clinical rotations.[21] While students are forced to adapt (with varying degrees of success) to their lecturers' respective styles in the pre-clinical years, clinical rotations afford students a certain freedom around how they learn.

When on clinical rotations, it is common for students to attach themselves to clinicians who they perceive to be effective teachers, and avoid those who do not match their individual learning preferences.[21] Such a relationship is nurtured through the cognitive apprenticeship learning model, allowing students to articulate what they are learning to their mentor, and to be coached by their mentors. It allows teachers to be good role models for students, and in return, provides students with someone to model their learning and behaviour on.[31] Being immersed in the clinical environment with both patients and clinicians also demonstrates the doctor-patient relationship to students, an essential learning objective.[21] Thus, clinical rotations in oncology allow each student to apply their individual learning styles while completing important learning tasks, providing them with constructive cancer education.

## Conclusion

Cancer is the number one cause of death in Australia, yet our medical schools still have not modernised their approach to curricula and clinical rotations to better reflect the reality of twenty-first century health. Meanwhile, research from Australia and around the world confirms that medical students, junior doctors, and in some cases, specialist oncologists, are falling behind in their understanding of cancer diagnosis, patient management, and clinical skills. Despite acknowledging the importance of patient contact in other specialties, medical schools still have not implemented core

oncology or palliative care rotations for their medical students. Medical school curricula remain lacking in oncology content and assessment in spite of having one of the world's oldest, most researched, and most developed guidelines, the Oncology Education Committee's Ideal Oncology Curriculum. But, we must remain optimistic. Many of Australia's medical schools are young, agile, and possess the capacity to update curricula and in conjunction with health care providers, implement oncology and palliative care clinical rotations, providing medical students and educators alike with the environment to best teach and learn about cancer.

## Acknowledgements

A sincere thank you to the team at Cancer Council Australia for the opportunity to attend the WHO Medical Sciences Summer School in Groningen, the Netherlands.

## References

1. Stewart BW, Wild C. International Agency for Research on Cancer and World Health Organization. 2014. World cancer report 2014. Lyon, France, Geneva, Switzerland: International Agency for Research on Cancer. WHO Press.
2. Pavlidis N, Vermorken JB, Stahel R, et al. Oncology for medical students: a European School of Oncology contribution to undergraduate cancer education. Cancer Treat Rev. 2007;33(5):419-426. doi:10.1016/j.ctrv.2007.02.005.
3. Neville AJ. Problem-based learning and medical education forty years on. A review of its effects on knowledge and clinical performance. Med Princ Pract. 2009;18(1):1-9. doi:10.1159/000163038.
4. Koh GC, Khoo HE, Wong ML, et al. The effects of problem-based learning during medical school on physician competency: a systematic review. CMAJ. 2008;178(1):34-41. doi:10.1503/cmaj.070565.
5. Colliver JA. Effectiveness of problem-based learning curricula: research and theory. Acad Med. 2000;75(3):259-266.
6. Bousquet G, Orri M, Winterman S, et al. Breaking Bad News in Oncology: A Metasynthesis. J Clin Oncol. 2015;33(22):2437-2443. doi:10.1200/JCO.2014.59.6759.
7. Kiluk JV, Dessureault S, Quinn G. Teaching Medical Students How to Break Bad News with Standardized Patients. J Cancer Educ. 2012;27(2):277-280. doi:10.1007/s13187-012-0312-9.
8. Cuff PA, Vanselow NA, and Institute of Medicine (U.S.). Committee on Behavioral and Social Sciences in Medical School Curricula. Improving medical education : enhancing the behavioral and social science content of medical school curricula. Washington, D.C: National Academies Press. 2004.
9. AIHW. 2016. Australian Cancer Incidence and Mortality books. http://www.aihw.gov.au/acim-books/. Accessed 28 March 2016.
10. AIHW. 2014. Cancer in Australia: an overview 2014: Canberra: AIHW.
11. Tattersall MH, Langlands AO, Smith W, et al. Undergraduate education about cancer. A survey of clinical oncologists and clinicians responsible for cancer teaching in Australian medical schools. Eur J Cancer. 1993;29A(11):1639-1642.
12. Cheung WY, Fishman PN, Verma S. Oncology education in Canadian undergraduate and postgraduate training programs. J Cancer Educ. 2009;24(4):284-290. doi:10.1080/08858190902973143.
13. Matkowski RJ, Szelachowska K, Szewczyk U, et al. Improvements in undergraduate oncology education introduced at Polish medical universities between 2004 and 2010 under Poland's "National Program for Combating Neoplastic Diseases". J Cancer Educ. 2014;29(3):428-433. doi:10.1007/s13187-014-0633-y.
14. Karamouzis MV, Ifanti AA, Iconomou G, et al. Medical students' views of undergraduate Oncology education: A comparative study. Educ Health (Abingdon). 2006;19(1):61-70. doi:10.1080/13576280500534552.
15. Brincker H. Undergraduate oncology education in Scandinavia. J Cancer Educ. 1988;3(2):97-101. doi:10.1080/08858198809527919.
16. Tam VC, Berry S, Hsu T, et al. Oncology education in Canadian undergraduate and postgraduate medical programs: a survey of educators and learners. Curr Oncol. 2014;21(1):e75-88. doi:10.3747/co.21.1667.
17. Peckham M. A curriculum in oncology for medical students in Europe. Acta Oncol. 1989;28 (1):141-147.

18. Estevez RA, de Estevez OT, Cazap EL, et al. Undergraduate teaching of oncology in Argentina. J Cancer Educ. 1988;3(2):111-115. doi:10.1080/08858198809527923.
19. UK, Cancer Research. Worldwide cancer statistics. http://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer. Accessed 8 March 2016.
20. Geffen L. A brief history of medical education and training in Australia. Med J Aust. 2014;201(1 Suppl):S19-22.
21. Norman GR, van der Vleuten C, Newble D. International handbook of research in medical education. Kluwer international handbooks of education, vol. 7. Dordrecht ; Boston: Kluwer Academic. 2002.
22. Zealand, Medical Deans Australia and New. National Clinical Training Review Report. 2008. http://www.medicaldeans.org.au/projects-activities/completed-projects/national-clinical-training-review/. Accessed 7 March 2016.
23. Barton MB, Tattersall MH, Butow PN, et al. Cancer knowledge and skills of interns in Australia and New Zealand in 2001: comparison with 1990, and between course types. Med J Aust. 2003;178(6):285-289.
24. Committee, Oncology Education. 2014. Ideal Oncology Curriculum. http://wiki.cancer.org.au/oncologyformedicalstudents/Ideal_Oncology_Curriculum. Accessed 2 March 2016.
25. Compton MT, Frank E, Elon L, et al. Changes in U.S. medical students' specialty interests over the course of medical school. J Gen Intern Med. 2008;23(7):1095-1100. doi:10.1007/s11606-008-0579-z.
26. Blinman PL, Grimison P, Barton MB, et al. The shortage of medical oncologists: the Australian Medical Oncologist Workforce Study. Med J Aust. 2012;196(1):58-61.
27. Starmer D, Jamrozik K, Barton M, et al. Evaluating curriculum changes in undergraduate cancer education. J Cancer Educ. 2004.19(3):156-160. doi:10.1207/s15430154jce1903_9.
28. Pilgrim C, Lannon C, Harris RP, et al. Improving clinical breast examination training in a medical school: a randomized controlled trial. J Gen Intern Med. 1993;8(12):685-688.
29. Heard JK, Cantrell M, Presher L, et al. Using standardized patients to teach breast evaluation to sophomore medical students. J Cancer Educ. 1995;10(4):191-194. doi:10.1080/08858199509528370.
30. Kearsley JH, Lobb EA. "It is not a disease we treat, but a person": medical students' reflections on their first rotations to an oncology and palliative care unit. J Palliat Care. 2013;29(4):232-236.
31. Swanwick T and Association for the Study of Medical Education. Understanding medical education : evidence, theory, and practice. Second edition. Aufl. Chichester, West Sussex: John Wiley & Sons Inc. 2014.

# Centre for Behavioural Research in Cancer (CBRC), Victoria

## Information needs are associated with anxiety and depression in caregivers of renal cell survivors

Cancer caregivers often experience unmet supportive care needs and higher rates of psychological and physical morbidity than the general population. Most studies exploring caregivers' unmet needs have focused on more common cancers such as lung and colorectal, which often involve complex treatments and longer caregiving periods. Renal cell carcinoma, a relatively less common cancer, is mostly diagnosed at an early stage, and involves less complex treatments with relatively shorter caregiving periods. However, it is unclear whether the caregivers of renal cell carcinoma survivors have the same level of unmet needs as caregivers of other cancer survivors and how these needs impact on their psychological distress. In a study funded by the Victorian Cancer Agency, Dr Devesh Oberoi, A/Prof Vicki White and colleagues examined the association between unmet needs and psychological distress among 196 renal cell carcinoma caregivers in Victoria who participated in a telephone interview. Sixty-four percent of caregivers had at least one unmet need and 29% reported 10 or more unmet needs. Elevated anxiety and depression were found in 29% and 11% of the sample respectively, on par with levels found for caregivers of more common cancers. Unmet information needs were associated with 1.6 and two times higher odds of elevated anxiety and depression respectively. Findings suggest that improving the provision of information to renal cell carcinoma caregivers by health professionals may help to reduce caregivers' unmet needs and psychological distress. This paper is published in *Supportive Care in Cancer*.

# Newcastle Cancer Control Collaborative (New-3C), NSW

## How can we improve patient-centred decision making in cancer care?

Patient-centred decision making is a key characteristic of a high quality healthcare system. Clinicians and patients need to work together and incorporate the best available evidence regarding different healthcare options with patients' goals and concerns. Actively involving patients in decisions regarding their care can increase patients' knowledge, satisfaction and overall quality of life. A number of interventions have been developed to help patients make difficult healthcare decisions. One such strategy are decision aids. Decision aids provide patients with tailored information regarding their healthcare decisions and help them become more involved in the decision making process. Decision aids have been shown to improve patient outcomes, including increased knowledge and decreased decisional conflict. However, decisions aids are not commonly used in clinical practice.

We undertook a literature review to examine where decision aid research has been directed to and where the focus of future research should lie. Changes in the volume of research on the effectiveness of cancer-related decision aids were examined across three time points and eligible articles were categorised by cancer type and decision type. We then compared the number of studies that assessed the effectiveness of cancer-related decision aids to the number of studies that assessed implementation strategies which aimed to increase the use of decision aids by healthcare providers. Medline, Embase, PsychInfo and Cochrane Database of Systematic Reviews were searched. Eligible papers were those published in any country in 2000, 2007 or 2014. These years were chosen given the release of two influential reports on patient-centred care by the US National Cancer Board and the Institute of Medicine in 1999 and 2001.

Over the three time points assessed, increasing research effort has been directed towards examining the effectiveness of decision aids in improving patient outcomes. The number of studies testing cancer screening or prevention decision aids increased statistically significantly; the number of studies testing cancer treatment decision aids did not. Most studies assessed the effectiveness of decision aids for prostate, breast or colon cancer. This is not surprising as these are among the most common cancer types worldwide. However, there are other cancer types which often include difficult decisions for patients. For example, lung cancer patients might have to trade off slightly higher survival rates with severe treatment side effects. Only two studies assessed the effectiveness of implementation strategies to increase the use of decision aids by healthcare providers.

More research is needed on other cancer populations and other decision types, such as treatment decisions. This data may be useful in designing decision support that suits the needs of different patient populations. The next step must be to translate the evidence of decision aids' effectiveness into meaningful benefits for patients by implementing decision aids into clinical practice. This will help improve patient-centred decision making in routine cancer care. This review has recently been published in *BMC Medical Informatics and Decision Making (*Herrmann A, Mansfield E, Hall AE, Sanson-Fisher R, Zdenkowski N. (2016). Wilfully out of sight? A literature review on the effectiveness of cancer-related decision aids and implementation strategies. BMC medical informatics and decision making, 16(1), 1-9. doi: 10.1186/s12911-016-0273-8).

# Behavioural Research and Evaluation (BREU), South Australia

## Investigating iHOPE: An online peer-led program for cancer survivors

With the rising number of people surviving and living with cancer, the need for post-treatment support options is increasing. We conducted a literature review that revealed a burgeoning body of research regarding promising psychosocial and positive psychology interventions designed to help people cope with the detrimental biopsychosocial effects of chronic disease. Some of these interventions have been developed into online programs, but there is little information about their uptake in the community.

One example related to cancer is the iHOPE program (Help to Overcome Problems Effectively). iHOPE is an online, group-based, peer-led, positive psychology support program that aims to provide participants with the knowledge and confidence to cope with surviving cancer. iHOPE is an online version of the HOPE program, a face-to-face version used by Macmillan Cancer Support in the UK. Pilot tests of iHOPE in the UK appear promising (i.e. it is reportedly effective, relevant, engaging, and easy to use), however the feasibility of using iHOPE with an Australian population has yet to be tested.

Consequently, Cancer Council SA is undertaking a project to collect feedback from potential Australian users of iHOPE, to determine if the program is relevant, engaging, and easy to use. The study involves conducting interviews (approximately 30-45 minutes) to seek feedback on iHOPE's main activities (i.e. grateful expression and goal setting) and the peer-led and interactive nature of the course. To date, four semi-structured interviews have been conducted with cancer survivors who were not currently in active treatment. Findings will be disseminated in due course.

## National Primary Schools SunSmart survey

Primary schools provide suitable grounds for implementing policy development as a skin cancer control strategy. In addition, policy can assist in creating sustainable change for sun protective environments in primary schools. Cancer Councils nationally recognise the importance of policy development to promote healthy sun protection policies and practice in primary schools and encourages schools to become members of the National SunSmart School Program. This program awards recognition to primary Schools that meet SunSmart recommendations in both practice and policy.

As part of providing ongoing monitoring of primary school sun protection practices and policies, as well as to monitor the impact that the SunSmart program has on these practices, Cancer Council SA works with the national schools and early childhood centres working group to conduct the National Primary Schools SunSmart Survey across Australia.

Funded by Cancer Council Australia with in-kind contribution provided by the Behavioural Research and Evaluation Unit, this survey is conducted on behalf of all state and territory Cancer Councils. The primary aim of the survey is to determine common sun protection policies and practices in primary schools across Australia and to examine the variation in these by factors such as SunSmart status, and over time. This will be the fifth round of the survey having previously been conducted in 1998, 2002, 2005 and 2011. Data collection has recently commenced, with data analysis and reporting to occur in the first half of next year. Key areas of focus in the survey includes policy development, regulation of hat wearing, shade provision, sunscreen provision, scheduling of outdoor activities, incorporation of sun protection into the curriculum and school's SunSmart status.

# Western Australian Cancer Prevention Research Unit (WACPRU), Curtin University

## Drinking ourselves sick

In a heavy drinking culture such as Australia, it is difficult to convince drinkers that alcohol is toxic. Over three decades ago, alcohol was classified as a category one carcinogen by the International Agency for Research on Cancer. This means the alcohol-cancer link in humans is certain, and hence that individuals should take appropriate preventive action. However, alcohol intake levels in Australia are still high and the task remains to convince drinkers that alcohol consumption increases their risk of cancer and other diseases and thus that they should reduce their intake.

In collaboration with Cancer Council WA, WACPRU has investigated Australian drinkers' current alcohol-related beliefs, including their understanding of the alcohol-cancer link. The study also assessed the extent to which heavier drinkers understand that they are at increased risk of alcohol-related harm relative to their peers who drink more moderately. More than 2000 adult drinkers from around the country participated in an online survey that asked them to report their alcohol consumption levels and tested their understanding of the relationship between alcohol and the following diseases: cancer, heart disease, high blood pressure, stroke and liver damage. The results indicated that two-thirds of the sample were aware of the association between liver damage and alcohol consumption, but only around half were aware of the association between alcohol and the other diseases. Cancer had the lowest level of awareness, indicating that this should be a particular area of attention in future health communications.

When the self-reported alcohol consumption levels of the survey respondents were compared to the National Health and Medical Research Council's guidelines for low-risk drinking, 80% reported intake levels above the high-risk thresholds for short and/or long-term alcohol related harm (i.e. more than four drinks on a single occasion or an average of more than two drinks per day). Of these high-risk drinkers, just over half did not consider their drinking to be harmful. This outcome highlights the need to ensure all drinkers are aware of current alcohol consumption guidelines and are able to compare their own intake to these guidelines to better understand their level of risk. The extent to which alcohol is embedded in Australian culture means that drinkers are unlikely to be receptive to such information, making it essential for messages to be carefully developed and tested prior to dissemination. A further complicating factor is that alcohol harm minimisation messages are countered by extensive alcohol advertising. Alcohol advertisements are carefully crafted to depict alcohol consumption as a highly enjoyable and socially rewarding experience. High levels of alcohol-related harm in the community combined with the low levels of understanding of the long-term health risks associated with alcohol consumption demonstrated in this study suggest that drinkers should be exposed to fewer messages from the alcohol industry and more messages informing them of the association between alcohol and diseases such as cancer.

This results of this study have been published in *Addiction Research & Theory*. The study was funded by the Western Australian Health Promotion Foundation.

# Cancer Council Australia

## Clinical prostate test guidelines receive GP college endorsement

The Royal Australian College of General Practitioners has formally endorsed the clinical guidelines for PSA testing and early management of test-detected prostate cancer developed by Prostate Cancer Foundation of Australia (PCFA) and Cancer Council Australia.

PCFA and Cancer Council Australia worked in partnership to develop the guidelines through a rigorous process involving experts from all clinical disciplines that participate in the clinical management of test-detected prostate cancer patients.

The guidelines were published in January following the National Health and Medical Research Council (NHMRC) approving the guidelines' recommendations.

RACGP is the latest medical college to endorse the guidelines, which provide health professionals with evidence-based recommendations for using the prostate specific antigen (PSA) blood test to assess prostate cancer risk and manage test-detected patients.

The guidelines have also received formal endorsement from the Urological Society of Australia and New Zealand, the Royal College of Pathologists of Australasia, the Faculty of Radiation Oncology (the Royal Australian and New Zealand College of Radiologists) and the Australian College of Rural and Remote Medicine.

## Cancer Council and Australian Cancer Survivorship Centre – On the Road to Recovery CALD project stage two and three

*On the road to recovery* is a collaboration designed to produce translated booklets to assist cancer patients and survivors from cultural and linguistically diverse communities.

Developed by Cancer Council in conjunction with the Peter MacCallum Cancer Centre, the project has been supported with funding from Cancer Australia.

Stage one of the project saw production booklets on cancer survivorship in Cantonese, Mandarin and Greek, drawing from Cancer Council's 'Understanding Cancer' series, including: *Living well after cancer; Emotions and cancer; Coping with cancer fatigue; Cancer, work and you; Cancer care and your rights; and Understanding complementary therapies.*

Stage two originally included the publication of bilingual booklets for the Arabic and Vietnamese speaking communities. It has now been expanded to include a bilingual Italian cancer factsheet.

Stage three has also commenced to develop resources for Hindi and Filipino speaking communities.

Booklets are available from the Australian Cancer Survivorship Centre, Peter MacCallum Cancer Centre, through Cancer Council 13 11 20 Information and Support, or online in PDF format at cancer.org.au/publicationsCALD.

For details contact Jane Roy on 02 8063 4100 or jane.roy@cancer.org.au

## Clinical Guidelines Network

Cancer Council Australia aims to produce concise, clinically relevant and up-to-date electronic clinical practice guidelines for health professionals, accessible on its wiki platform at wiki.cancer.org.au

For more information or to be added to the mailing list for notification of guidelines open for public consultation or guidelines launches, please email guidelines@cancer.org.au.

***Guidelines in development***

| Guideline | Status |
|---|---|
| National Cervical Screening Program: Guidelines for the management of screen detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding | Email guidelines@cancer.org.au to be notified when the guidelines are published. |
| Clinical practice guidelines for the prevention, diagnosis and management of lung cancer | Systematic reviews in progress |
| Clinical practice guidelines for the diagnosis and management of melanoma | First set of draft content went to public consultation May/June and post public consultation in progress. Email guidelines@cancer.org.au to be notified when the final content will be published. Further systematic reviews in progress |
| Clinical practice guidelines for the prevention, early detection and management of colorectal cancer | Systematic reviews in progress |
| Clinical practice guidelines for the management of sarcoma in AYA | Systematic reviews in progress |
| Clinical practice guidelines for Surveillance Colonoscopy | Guidelines revision commissioned by Department of Health. Planning is progress. |

***Cancer Council Australia guidelines***

| Guideline | Last updated |
|---|---|
| Clinical practice guidelines for PSA testing and management of test-detected prostate cancer | August 2015 |
| Clinical practice guidelines for the diagnosis and management of Barrett's oesophagus and early oesophageal adenocarcinoma | September 2014 |
| Clinical practice guidelines for the treatment of lung cancer | December 2012 (update in progress) |
| Management of apparent early stage endometrial cancer | March 2012 |
| Clinical practice guidelines for surveillance colonoscopy | December 2011 |
| Clinical practice guidelines for the management of adult onset sarcoma | February 2015 |
| Clinical practice guidelines for the management of locally advanced and metastatic prostate cancer | April 2010 |

***Clinical Oncology Society of Australia guidelines***

| Guideline | Last updated |
|---|---|
| Clinical practice guidelines for teleoncology | December 2015 |
| Diagnosis and management of gastroenteropancreatic neuroendocrine tumours guidance | August 2012 |
| Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer | August 2013 |
| Early detection of cancer in AYAs | May 2012 |
| AYA cancer fertility preservation | September 2012 |
| Psychosocial management of AYA cancer patients | June 2012 |

***Other guidelines***

| Guideline | Last updated |
|---|---|
| Cancer pain management | August 2013 |

# Clinical Oncology Society of Australia, COSA

## COSA Annual Scientific Meeting (ASM)

Hopefully readers will still have time to register for the 2016 COSA ASM when this edition of *Cancer Forum* is published. Held on the Gold Coast from 15 to 17 November 2016, the theme of "Partners for Progress in Breast Cancer Research and Care" is fitting for our collaboration with the ANZBCTG for a conference program dedicated to breast cancer. The full program and registration information is available at www.cosa2016.org

Venues, dates and themes for future COSA ASMs are now confirmed as follows:

- 2017, 13-15 November, Sydney International Convention Centre – immunotherapy, with a subtheme on quality and safety in cancer care
- 2018, 13-15 November, Perth Convention and Exhibition Centre – gastro-intestinal cancers and mesothelioma, with possible sub themes of prevention, technology and genomics
- 2019, 12-14 November, Adelaide Convention Centre – prostate cancer and geriatric oncology

## Cancer Survivorship 2017

COSA is now partnering with the Flinders Centre for Innovation in Cancer to co-host the biennial Cancer Survivorship Conference. The 2017 event will be held at the Adelaide Convention Centre, Thursday 2 and Friday 3 February. This exciting partnership will help ensure this conference is closely aligned with the national directions for cancer control and continues to expand its reach and relevance to a diverse range of cancer health professionals, policy makers and to all those affected by cancer.

The theme "Cancer Survivorship 2017: Pathways to better policy and practice" will focus our thinking on how we can translate the growing evidence in this area into day to day applications. The program will explore diverse perspectives from Australia, the UK and US to identify how we can accelerate progress collaboratively, share learnings and promote best practice.

Unlike the COSA ASM, delegates to this conference include not only health professionals and researchers but also cancer survivors and representatives from cancer advocacy groups.

## Other educational opportunities for COSA members

The COSA Cancer Care Coordination Group has trialled a highly successful webinar program to assist in achieving the Group's professional development goals. To date the Group has conducted two webinars: the pilot webinar was held in October 2015 on the topic of "*Indigenous Cancer Care"* with the aim of highlighting the relationship between individual, social and health system issues that can impact on the delivery of cancer care for Aboriginal and Torres Strait Islander patients*;* and the second in July 2016 titled "*Care, Complexity & Clarity"* presented elements of a current research project that set out to develop and pilot test a clinically relevant nurse-sensitive index for use with cancer patients in ambulatory settings. The webinars reached 150 registrants at over 90 sites. COSA and the Cancer Care Coordination Group are currently investigating further webinars on topics of relevance to COSA members.

## Australasian Tele-Trial Model

Under the leadership of Professor Sabe Sabesan, and in consultation with clinical trial sponsors, clinicians, health administrators and regulatory bodies, COSA recently published a national guide for implementing the Australasian Tele-Trial Model – a model to enable cancer patients to access clinical trials closer to home using tele-health.

Access to clinical trials for people diagnosed with cancer is a core component of providing optimal cancer care through specialist cancer centres, hospitals and other treatment facilities. Patients living outside major metropolitan centres face many barriers accessing clinical trials, including the limited availability of trial sites close to home and the increased cost and inconvenience of travel to major centres where the trials are taking place. While it may be reasonable to establish clinical trials units in large regional cancer treatment centres, the logistics of maintaining a suitably trained workforce and undertaking the ethical and regulatory responsibilities of clinical trials may be difficult in smaller rural and regional sites with limited resources and low patient numbers.

System improvement using the model is unlikely to be achieved without added cost and additional resources for the sponsors, hospitals and governments. Simplification and streamlining of site accreditation and selection processes, monitoring requirements, ethics, governance and contractual matters are needed to reduce cost and workload, and to expedite approval processes. COSA will now work with relevant stakeholders to ensure adoption of the Australasian Tele-trial Model is part of standard practice by cooperative trials groups, industry, researchers, governments, regulatory bodies, hospitals and insurers.

The Australasian Tele-trial Model is available to download from the publications page of the COSA website www.cosa.org.au

## Working with Cancer Council Australia

In COSA's role as medical and scientific advisors to Cancer Council Australia, we often collaborate on submissions to government. Since the last report we have submitted the following joint submissions from Cancer Council Australia and COSA:

1. Submission to the Review of the Radiation Oncology Health Programs Scheme (April 2016)
2. Comment on the National Patient Information and Consent Form (PCIF) Project documents (July 2016)

Cancer Council Australia and COSA's joint Position Statement on the Medical use of cannabis was updated in July 2016 to report on national and state changes in public policy in this area. Our joint position remains unchanged.

For more information about COSA activities please visit www.cosa.org.au

**Marie Malica**
Executive Officer, COSA

# Faculty of Radiation Oncology, RANZCR

## Medicare Benefits Schedule Review

The review of the radiation oncology items within the Medicare Benefits Schedule (MBS) is well underway. Our College has a number of members (from both radiation oncology and radiology) on the MBS Oncology Clinical Committee (OCC) which includes both medical and radiation oncology, of the MBS Review Taskforce

The Faculty is providing input into the MBS review through its MBS Review Working Group, chaired by Dr Liz Kenny. One of the first tasks of the radiation oncology working group has been to review a list of infrequently used/potentially obsolete radiation oncology items identified by the Department of Health (DoH).

The Faculty recommended to the OCC that a two-part payment model (planning/dosimetry, and per attendance treatment/verification) with added levels of complexity would be an appropriate funding model. The Faculty is now in the process of drafting a proposal for the most suitable levels of complexity for both radiation therapy and brachytherapy. The proposal will be provided to the OCC for consideration.

The Faculty is keen to see the MBS items for radiation oncology simplified and more reflective of current practice. To this end, we will continue to work closely with the DoH and the MBS Review Taskforce, to hopefully ensure the ongoing provision of accessible and affordable quality radiation oncology services to our patients.

## Radiation Oncology Practice Standards

The Radiation Oncology Practice Standards (the Standards), which were published in 2011, provide a framework of requirements to assist radiation therapy facilities to achieve best practice across various domains (e.g. machine calibration, documentation, safety and quality improvement). The Faculty has been advocating for the implementation of the Standards in all facilities in Australia and New Zealand. However, Queensland is the only jurisdiction which has formally adopted the Standards to date.

In response to the MBS Review Consultation at the end of 2015, the Faculty listed mandatory national implementation of the Standards as one of the priorities for government consideration.

The Radiation Oncology Tripartite Committee has established a Standards Working Group to progress the implementation of the Standards. As a first step, the group has developed a self-assessment tool to assist facilities in reflecting on their own quality management systems and assessing how well they currently comply with the Standards.

The Standards Working Group is also exploring the opportunity of working with the Australian Council on Healthcare Standards (ACHS) to map the Radiation Oncology Practice Standards against the National Standards, and develop an accreditation plan.

## Targeting Cancer Campaign

The Radiation Oncology Targeting Cancer campaign aims to increase awareness of radiation therapy as an effective, safe and sophisticated treatment for cancer, among cancer patients and their families, as well as health professionals, in particular general practitioners (GPs). The campaign has made steady process in various areas, including GP education programs and social media presence.

GP Education Evenings provide GPs with the opportunity to learn about the role of radiation therapy for their patients at their local radiation therapy departments. To complement this, several GP-focused articles on radiation therapy have been published in *Australian Doctor* and *Australian Family Physician*.

A/ Prof Sandra Turner, the clinical lead of the Targeting Cancer campaign, has been talking about modern radiation therapy for prostate cancer at the HealthEd seminars held in major capital cities in Australia. These seminars, scheduled between August and November 2016, have attracted several thousand GPs.

HealthEd is the biggest health professional education provider in Australia and these one-day seminars provide practical, clinical, up to date information for GPs. This is an incredible opportunity to

reach out to the larger GP community and improve their knowledge of radiation therapy, to help ensure that cancer patients are fully informed about all their treatment options.

We are delighted that the Targeting Cancer website won the **Best in Class** award in the Interactive Media Awards for Healthcare category, and was the **Gold Winner** for the prestigious Sydney Design Awards in the EdTech category. It is hoped that the website will become the most trusted source of information about radiation therapy for cancer patients and their families, as well as for other health professionals, especially GPs.

Please like Targeting Cancer on Facebook, or follow @targetingcancer on Twitter, and help us promote radiation therapy as a safe and cost-effective cancer treatment option.

## Prostate Testing for Cancer and Treatment Trial (ProtecT)

The results of the prostate testing for cancer and treatment (ProtecT) trial were recently published in two papers in the *New England Journal of Medicine*. This trial, which compared prostate cancer treatment options head-to-head, showed that curative radiation therapy was equally likely to control the cancer as surgical prostate removal. There was also no difference in overall quality of life between radiation therapy and surgery, but less urinary incontinence and sexual problems after radiation therapy.

This study strongly supports the importance of patients with localised prostate cancer knowing about all their treatment options by talking to a radiation oncologist as well as an urologist before they decide on a treatment or to proceed with surveillance. A/Prof Sandra Turner was interviewed by ABC News 24 on 16 September, to talk about the study findings. More details and the interview are available from the Targeting Cancer website.

**Dr Dion Forstner**
**Dean, Faculty of Radiation Oncology**

# Medical Oncology Group of Australia, MOGA

Associate Professor Chris Karapetis became the new Chairman of the Medical Oncology Group of Australia (MOGA) on 3 August 2016. He has been a member of the MOGA Executive since 2012 with the specific task of oversighting the Australia-Asia Pacific Clinical Oncology Research Development (ACORD) Workshop for the Association and as ACORD Deputy Convenor including participating in the 2012, 2014 and most recently the 2016 Workshops as a Faculty member. In October he cycled 360kms across Cambodia to fight gastro-intestinal cancer to raise funds to support the Australasian Gastro-Intestinal Trials Group (AGITG) Innovation Fund, with a team of like-minded adventurers. In taking on this new challenge he said, “As a clinical researcher, I am grateful for the contribution patients make to research and the courage they show in joining trials.”

Associate Professor Karapetis is the Head of the Department of Medical Oncology at the Flinders Medical Centre and the Network Director for Cancer Services in the Southern Area Local Health Network of Adelaide, South Australia. He is also the Director of Clinical Research in Medical Oncology at the Flinders Medical Centre and the Flinders Centre for Innovation in Cancer. He has been the principal investigator on over 120 clinical trials. His interest in clinical research developed following a research fellowship at Guy’s Hospital in London. He has established research interests in the areas of lung cancer, gastro-intestinal malignancy, molecular targeted therapies, predictive biomarkers, epidemiology and clinical research methodology.

Congratulations and plaudits go to Professor Martin Stockler based at the Cancer Trails Centre in Sydney on convening a stimulating but exhausting 2016 ACORD Workshop (11-16 September, Magenta Shores, NSW Central Coast) with 70 participants from across South-East Asia and 25 top-line international faculty supported by eight junior faculty who are successful program alumni. ACORD goes from strength to strength and has an important place in clinical trials training in Australia and our region, of which we can all be proud. The Association is grateful for the extensive support and assistance this project receives from all our collaborators above all those close to home, including the NSW Cancer Institute, Cancer Council Australia, The Facility of Radiation Oncology and the Clinical Oncology Society of Australia.

On Saturday 1 October The Federal Minister for Health, The Hon Sussan Ley MP Undertook a media stop at the Peter MacCallum Cancer Centre to provide details on the announcement that Tamoxifen (Nolvadex) had been added to the Public Benefits Schedule and was available as a preventative treatment for around 250,000 Australian women whose breast cancer risk is more than 1.5 times the average population. MOGA, the Breast Cancer Network of Australia, Peter MacCallum and patients collaborated to advocate for this access to tamoxifen as a preventative treatment over the last four years. MOGA’s campaign to seek an expansion of the extant listing was led by Professor Kelly-Anne Phillips with support from the Oncology Drugs Working Group with Chair, A/Prof Gary Richardson and A/Prof Rosemary Harrup as the MOGA Chair. AstraZeneca also worked closely with MOGA from the get-go and contributed a large amount of staff time and resources to put provide the requisite research information and data to support the MOGA submission. This landmark win for Australian breast cancer specialists and their patients was widely reported in the media nationally. Organizing this highly successful media event with the Minister on the day of the Grand Final in Melbourne proved to be a worthwhile challenge.