

## Appendix One. HER2-positive early breast cancer, its treatment and prognosis

### Breast cancer and HER2/*neu* over-expression

Health need is one of PHARMAC's nine decision criteria (<http://www.pharmac.govt.nz/pdf/231205.pdf> 'The health needs of all eligible people within New Zealand (eligible as defined by the Government's current rules of eligibility)').

Breast cancer is the most common cancer found in women. In 2003 there were approximately 2300 new cases of breast cancer and 600 deaths (NZ Cancer Registry). It is also the most common cause of cancer-related deaths in women.

The standard staging system is that of the American Joint Committee on Breast Cancer.<sup>1</sup> The system is based on tumour size (T), lymph node involvement (N), and metastatic disease (M). Breast cancer is classified according to the size of the primary tumour (T), the extent of spread to regional lymph nodes (N) and whether there are distant metastases (M) (known as the TNM [tumour, node, metastasis] classification), and may be grouped into four stages as follows:

Stage	Description
0	TisN0M0
I	T1N0M0
II	T0N1M0, T1N1M0, T2N0M0
IIIa	T2N1M0, T3N0M0
IIIb	T4 any N M0, any T N3 M0
IV	Any T Any N M1

Stages I to II describe early breast cancer (or operable breast cancer) that is locally invasive at the time of diagnosis and may or may not have spread to regional lymph nodes.

Stage III denotes locally advanced (inoperable) disease; stage IV denotes metastatic disease.

Early stage breast cancer is usually defined as stage I, II, or III. The term "primary breast cancer" is commonly applied to these stages. This denotes a tumour of less than 5cm, which may or may not involve same-side axillary lymph node(s), but with no distant metastasis; or a tumour greater than 5cm, if regional lymph nodes are not involved, without distant metastasis.

The human epidermal growth factor receptor 2 (HER 2) protein is found on the surface of certain cancer cells, produced by the HER2/*neu* gene. The HER2 protein is a receptor for a naturally-occurring growth factor, human epidermal growth factor.<sup>2</sup> When human epidermal growth factor attaches itself to HER2 receptors on breast cancer cells, it can stimulate cell division and growth. For those breast adenocarcinomas that have proportionately more HER2 receptors, the tumour is described as being HER2/*neu*-positive (IHC 3+ or FISH positive).

Such overexpression of the HER2 protein, amplification of the HER2/*neu* gene, or both occurs in approximately 15-25% of breast cancers, and is associated with aggressive behavior in the tumour. Pathological diagnosis is made by immunohistochemical staining for HER2 protein of 3+ intensity (IHC 3+) or amplification of the HER2/*neu* gene on fluorescence in situ hybridisation (FISH).

### **Agents used to treat HER2-positive breast cancer**

The availability of other treatments and clinical benefits are two of PHARMAC's decision criteria (<http://www.pharmac.govt.nz/pdf/231205.pdf> 'The availability and suitability of existing medicines, therapeutic medical devices and related products and related things'; 'The clinical benefits and risks of pharmaceuticals').

Trastuzumab is a recombinant DNA-derived humanised monoclonal antibody that selectively targets the extracellular domain of the HER2 protein.

Docetaxel and paclitaxel belong to the taxane class of anticancer drugs, shown in studies of adjuvant use in early node-positive breast cancer to have a 5 year absolute survival advantage of about 5%. Currently in New Zealand, docetaxel and paclitaxel are funded in the Pharmaceutical Cancer Basket; both medicines being available for metastatic breast cancer (Stage IV), and paclitaxel for node-positive early breast cancer.

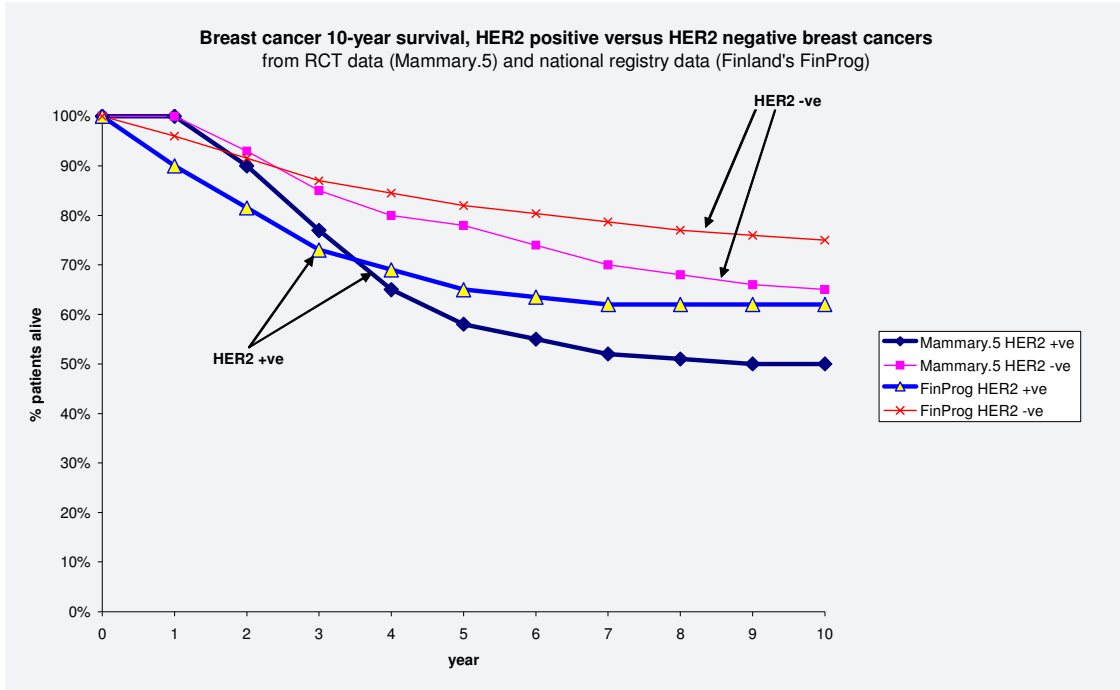
Adjuvant treatment for early breast cancer includes radiotherapy and/or cytotoxic chemotherapy after removal of the primary cancer by surgery. Women may also receive aromatase inhibitor and tamoxifen hormone therapy alongside cytotoxic chemotherapy regimens. Current standard therapy for early breast cancer in New Zealand is surgery followed by an anthracycline-containing a chemotherapy regimen.

### **Overall survival for HER2-positive early breast cancer s**

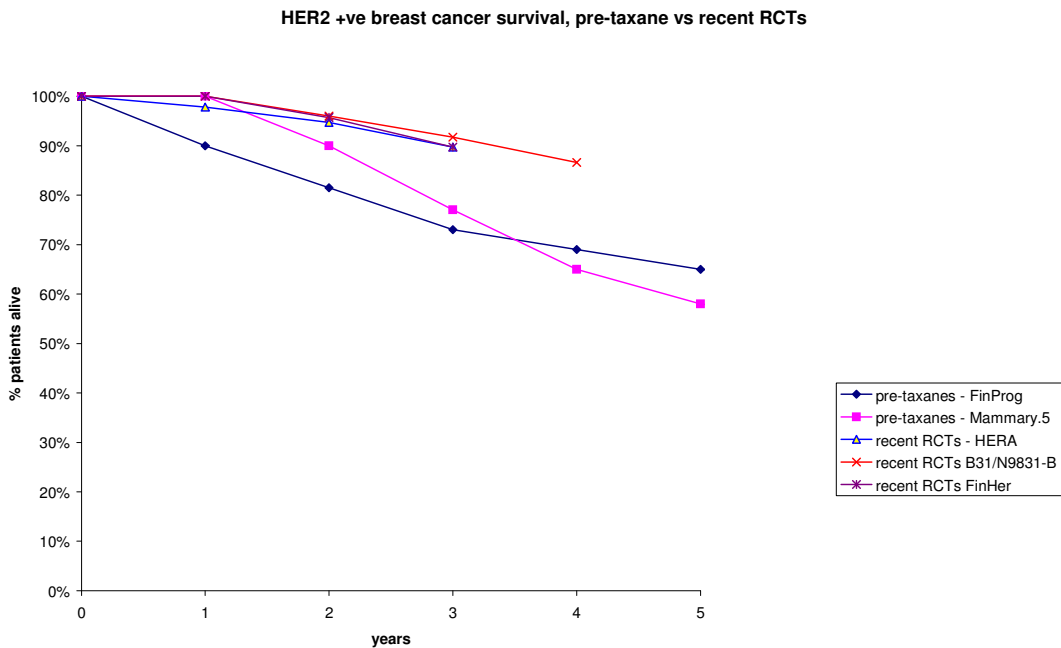
Health need is one of PHARMAC's nine decision criteria (<http://www.pharmac.govt.nz/pdf/231205.pdf> 'The health needs of all eligible people within New Zealand (eligible as defined by the Government's current rules of eligibility)').

Recent data indicate that large improvements have occurred over that last decade or so in breast cancer survival<sup>3</sup>, pre-dating the use of trastuzumab. Epidemiological survival estimates for HER2-positive early breast cancer (50-60% 10-year survival) may be overly pessimistic, by not necessarily differentiating between early and late stage disease and not incorporating important recent gains with taxane chemotherapy.

According to historical registry data from Finland (FinProg<sup>4</sup>), and a large randomised controlled trial comparing two regimens of conventional chemotherapy (Mammary.5, Pritchard et al NEJM 2006<sup>5</sup>), around 50-60% of patients with HER2-positive breast cancer are still alive by 10 years (see graph on the following page).

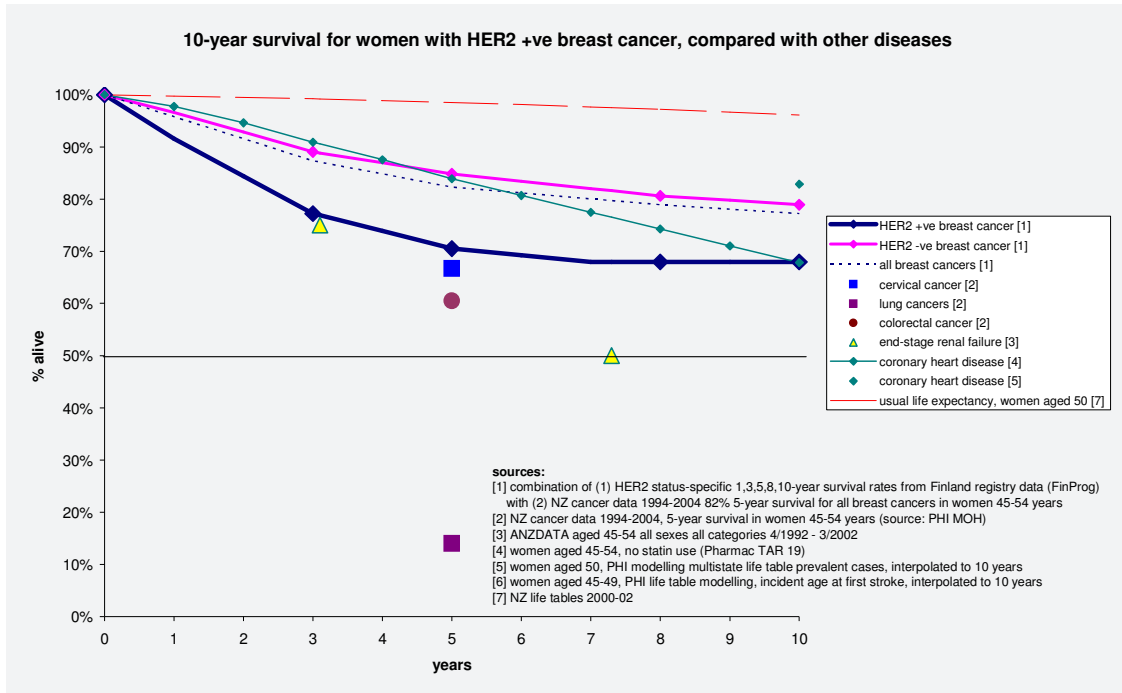


Both sets of data pre-date the use of taxanes, and survival rates nowadays are likely to be appreciably better, as suggested by survival in the standard treatment arms of more recent RCTs (e.g. HERA,<sup>6</sup> B31/N9831-C,<sup>7</sup> FinHer<sup>8</sup>). Albeit that trial eligibility criteria may exclude patients with poorer overall prognoses, and hence their overall survival will be better, the following graph indicates the extent of survival improvements in these trials compared with the above older series not using taxanes.



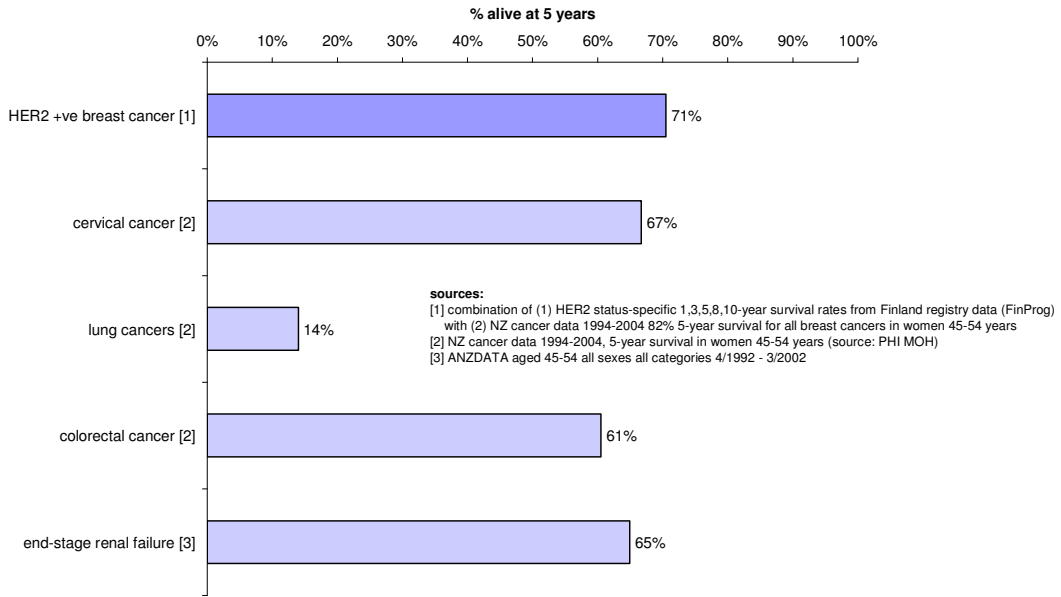
Combining these HER2-positive-specific patterns<sup>9</sup> with New Zealand overall breast cancer survival figures for women aged 45-54<sup>10</sup> suggests HER2-positive breast cancer may now have at least a 70% 5-year survival.<sup>1</sup>

The above survival estimates for early HER2-positive breast cancer (71% 5-year survival)<sup>11</sup> compares with, for example, a 14% 5-year survival rate for lung cancer,<sup>12</sup> 61% for colorectal cancer<sup>12</sup> and 67% for cervical cancer for women aged 50,<sup>12</sup> and 65% for end-stage renal failure (both sexes)<sup>13</sup> (see graphs).

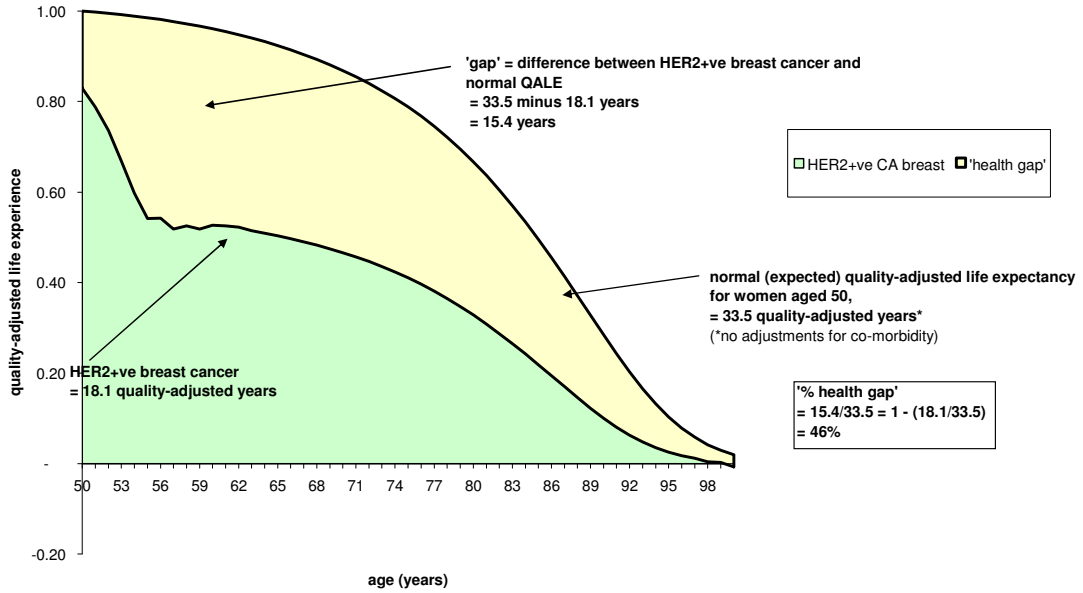


<sup>i</sup> combination of (1) HER2 status-specific 1,3,5,8,10-year survival rates from Finland cancer registry data (FinProg) with (2) calculated NZ cancer data 1994-2004 82% 5-year survival for all breast cancers in women 45-54 years (personal communication Martin Tobias, Public Health Intelligence, Ministry of Health)

**5-year survival for women aged 50, for HER2+ve breast cancer and other diseases**



**'Health need' - estimated quality-adjusted survival patterns for HER2+ve breast cancer, compared with expected**



## References

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- <sup>1</sup> Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, Borgen PI, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol*. 2002 Sep 1;20(17):3628-36. <http://jco.ascopubs.org/cgi/content/full/20/17/3628>
- <sup>2</sup> The human epidermal growth factor receptor 2 (HER 2/*neu*) protein belongs to a family of four transmembrane receptor tyrosine kinases that mediate the growth, differentiation, and survival of cells.
- <sup>3</sup> 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. *Lancet*. 2005 May 14-20;365(9472):1687-717.
- <sup>4</sup> FinProg data (<http://www.finprog.org>)—HER2-positive vs. HER-2 negative. See Lundin J, Lundin M, Isola J, Joensuu H. A web-based system for individualised survival estimation in breast cancer. *BMJ*. 2003 Jan 4;326(7379):29. <http://www.bmj.com/cgi/content/full/326/7379/29>
- <sup>5</sup> Pritchard KI, Shepherd LE, O'Malley FP, Andrulis IL, Tu D, Bramwell VH, Levine MN; National Cancer Institute of Canada Clinical Trials Group. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med*. 2006 May 18;354(20):2103-11. <http://content.nejm.org/cgi/content/full/354/20/2103>. from Figure 1. Relapse-free Survival (Panel A) and Overall Survival (Panel B) among Women with Breast Cancer, According to HER2 Amplification Status on FISH.
- <sup>6</sup> Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A. et al. 2 year follow up of trastuzumab (Herceptin) after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007;369:29-36. <http://www.thelancet.com/journals/lancet/article/PIIS0140673607600282/fulltext>
- <sup>7</sup> Romond, EH, Perez EA, Bryant J. et al., Trastuzumab plus Adjuvant Chemotherapy for Operable HER-2 positive breast cancer. *N Engl J Med* 2005;353(16):1659-1672. <http://content.nejm.org/cgi/content/full/353/16/1673>
- <sup>8</sup> Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, et al; FinHer Study Investigators. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006;354(8):809-20. <http://content.nejm.org/cgi/content/full/354/8/809>
- <sup>9</sup> HER2 status-specific 1,3,5,8,10-year survival rates from Finland registry data (FinProg).
- <sup>10</sup> calculated NZ cancer data 1994-2004 82% 5-year survival for all breast cancers in women 45-54 years (personal communication Martin Tobias, Public Health Intelligence, Ministry of Health).
- <sup>11</sup> combination of (1) HER2 status-specific 1,3,5,8,10-year survival rates from Finland registry data (FinProg) with (2) calculated NZ cancer data 1994-2004 82% 5-year survival for all breast cancers in women 45-54 years (personal communication Martin Tobias, Public Health Intelligence, Ministry of Health)
- <sup>12</sup> NZ cancer data 1994-2004, 5-year survival in women 45-54 years (personal communication Martin Tobias, Public Health Intelligence, Ministry of Health)
- <sup>13</sup> ANZDATA aged 45-54 all sexes all categories 4/1992–3/2002. ANZDATA 25th Annual Report Chapter 14 Integrated survival. [http://www.anzdata.org.au/anzdata/AnzdataReport/25thReport/files/Ch.14%20%20Integrated%](http://www.anzdata.org.au/anzdata/AnzdataReport/25thReport/files/Ch.14%20%20Integrated%20)