Nadia Harbeck:

breaking with convention

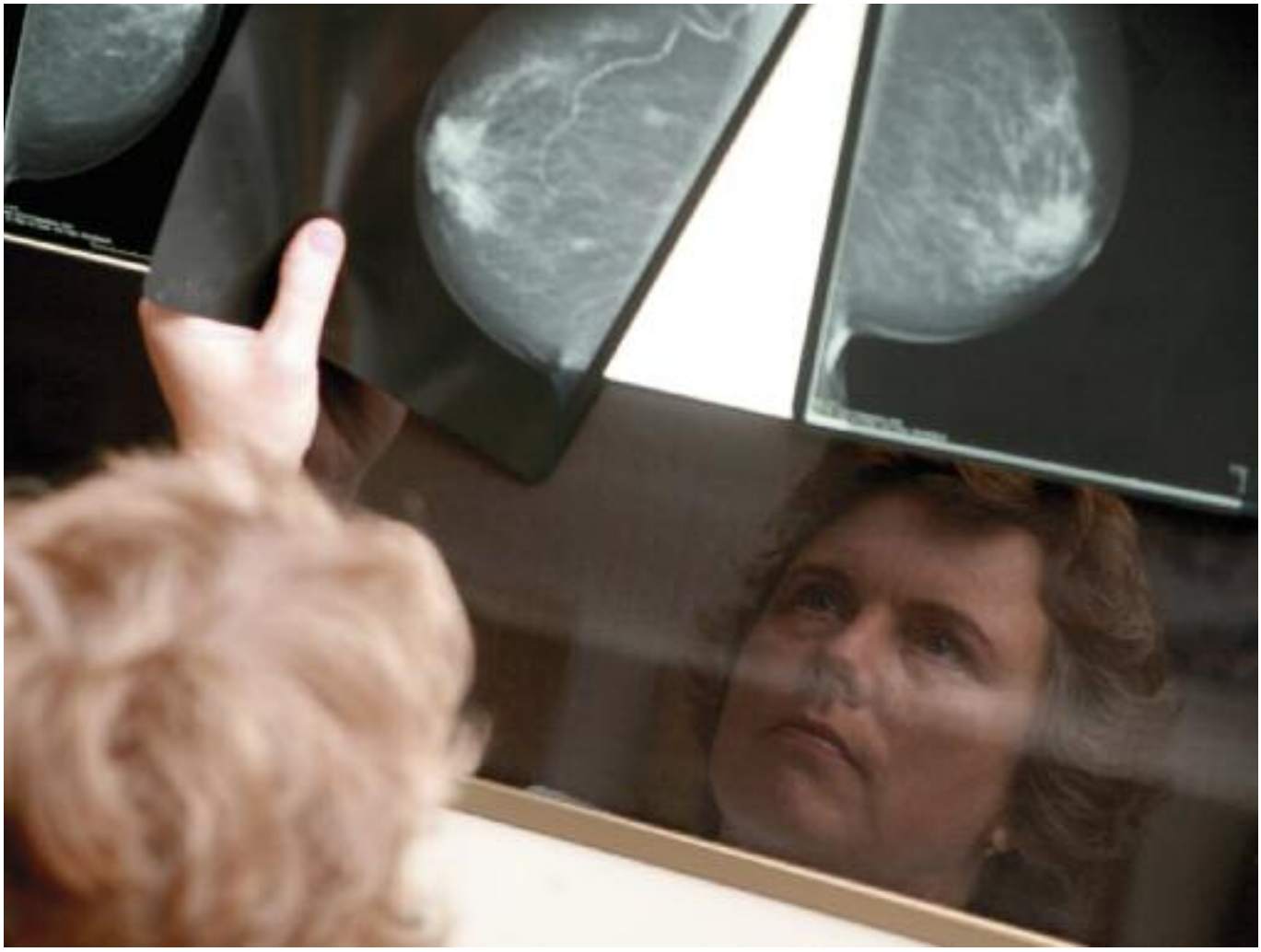
Marc Beishon

Gynaecologists don't win top awards at ASCO. German oncologists don't make it on the international stage. Women who want large families can't expect to be leaders in their field. Nadia Harbeck's high-flying career and relaxed leadership style demonstrate the great possibilities that open up if you refuse to let conventional wisdom and prejudices stand in your way.

Those who would like to see rigid career structures for oncologists and conformity concerning the organisation of cancer centres would do well to pay a visit to the department of obstetrics and gynaecology at the Technical University Hospital in Munich. Not only is the department a leading clinical trials centre for breast cancer – an unexpected finding for an ob/gyn unit for those who do not know the German system – but it is also part of a growing network of translational research and breast care excellence in Germany, a country that has the dual challenges of a fragmented public/private healthcare system and a pretty rigid hierarchy in the medical professions.

One of the key agents of change in Munich is Nadia Harbeck, ostensibly an associate professor of obstetrics and gynaecology, but actually more or less full time on one of her 'subtitles', namely head of breast cancer systemic therapy and the clinical trials unit in the department. "In Germany it is traditional that gynaecologists have always treated breast cancer," she says. "From the woman's point of view it makes sense as we see them when they are healthy and then if they do contract breast cancer and other diseases we carry out all the diagnosis, treatment and follow-up care – it's a continuum in one clinic."

Harbeck, though, has gone much further than most gynaecologists in making the switch to oncology, including participating in research that has brought her to international attention on the largest possible stage – at the American Society of Oncology (ASCO) meeting in the US. What's more, the work for which she is best known – a prognostic biomarker for breast cancer – has been made possible largely because the continuum of care in her clinic has provided the opportunity to collect fresh tumour samples and conduct translational research that is more difficult at present in countries such as the US, thanks to different medical practices. And overall she says Germany now has an advantage in being able to carry out neoadjuvant work, in particular, because of this 'all in one' structure. This biomarker work continues in her department, together with other trials across the spectrum from prevention to metastatic treatment, while she also promotes holistic care for the cancer journey, with



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strong interest in areas such as breast awareness and psychosocial support for women with cancer.

But, as in other fields where specialists can dominate, in particular urology, Harbeck recognises that there can be tension between the role of general medical oncologists and specialists such as herself. The picture across Germany varies: at the Technical University Hospital there is a separate medical oncology department, while in other hospitals medical oncology leads on breast cancer, she notes. Further, many physicians in Germany, including gynaecologists, work as private practitioners in their own offices and clinics, and it can be challenging to integrate them with major centres.

Other specialists, in particular radiologists, are also free to practise separately. Harbeck comments on one group that recently set up its own breast unit in Munich, in part to carry out screening in line with Germany's recent rollout of a national programme. "But this means they are apart from the already established multidisciplinary 'all under one roof' breast centres such as ours – and it is not clear if this will be to the benefit of the patient. This is a hot political topic in Germany right now."

Germany has only just announced a national cancer plan – health minister Ulla Schmidt announced in June a programme for improving early detection, treatment and care, access to drugs, patient information and the communications skills of doctors. Early announcements include the establishment of more oncology 'excellence centres' and free skin cancer screening for those over 35. The

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country has also been late in establishing its breast screening programme, and is still in the process of ensuring breast units conform to recent national guidelines and those from EUSOMA (the European Society of Breast Cancer Specialists). The country has a relatively low number of patients recruited into clinical trials; only a few regions, such as Bavaria, maintain high-quality cancer registries (Harbeck regrets that a good registry in East Germany was allowed to run down after reunification); and much to do in providing better palliative care services.

This might seem surprising given the perception of Germany as a high-quality medical provider, and indeed a high spender per head on cancer services, but healthcare is driven by a network of devolved and expensive public and private insurance systems that more closely resemble the situation in the US than most other nations. Meanwhile, adds Harbeck, there is still much to do in improving research networks both among German centres and among researchers in the neighbouring German-speaking countries of Austria and Switzerland.

Indeed, as she says, because of lack of confidence in speaking English, fear of being out alone as 'one of the first', and with so much to do at home, German cancer specialists have also not ventured onto the international stage as much as they could. That certainly does not apply to Harbeck – she is already a veteran of the conference circuit, attending all the key breast events such as the San Antonio Breast Cancer Symposium, the European Breast Cancer Conference, the St Gallen consensus event and also the ASCO meeting. It was at the latter in 2001 that she received the fellowship merit award as lead author for the highest ranking abstract, which was for long-standing work on the prognostic breast cancer biomarker. "This was really unusual – a European, a German and a gynaecologist getting this award. It had never happened before and created a lot of publicity."

Harbeck could also have added being a women to that list, for not only has she carved out an unofficial specialism within gynaecology, one of Germany's core medical disciplines, she also started out at a time when men dominated this and other German medical fields – and still do to a large extent, especially at the top. "My head of department in ob/gyn here at the Technical University is a woman, Marion Kiechle, but she was the only woman director of gynaecology in any university hospital in all the German speaking countries when she was appointed in 2000, and this has not changed since," she says.

Women, adds Harbeck, do have a different leadership style, in her experience. "In my department, at least, hierarchies are not so rigid, and that makes it easier for me to travel and network, without which it would be very hard to progress with work such as our trials portfolio." Elsewhere in Germany, she says, department heads tend to run everything and take all the credit, and also give little scope for younger staff to learn the administrative side of running a unit, which can be very demotivating.

Harbeck left school with the qualifications to study medicine. Unsure what to do, she spent a year in Canada with a relative learning photography and film skills, but not wanting to end up as a wedding photographer she returned to Munich to enter medical school, with a desire to specialise in ob/gyn firmly embedded. "I always wanted to work with women – you work with both healthy and sick women, carry out surgery, administer endocrine treatments and so on – the many different disciplines make you think. It also touches women from a psychological point of view, as some diseases affect them very personally."

She duly worked her way to a full ob/gyn qualification. Choosing to combine her career with having a sizeable family – she has four children – this took her at least three years longer than her male colleagues. "It is not surprising then that a lot of women gynaecologists go off to private practice where they can work part time to accommodate

family life," she notes. "It is especially difficult for women with families to get to the top in surgical specialities."

Needing an MD thesis, Harbeck chose an oncology topic involving monoclonal antibodies that could be carried out in the clinic. It was about detecting tumour cells in the bone marrow of breast cancer patients and was supervised by Wolfgang Eiermann at Munich's other university hospital, Ludwig-Maximilians. This sparked her interest in breast cancer research, especially in early spread of the disease, and she switched to the Technical University as the then head of the ob/gyn department, Henner Graeff, was setting up a translational research unit with a dedicated laboratory. The lab is still run today by the same biochemist, Manfred Schmitt, who is one of Harbeck's key mentors and colleagues.

"Henner Graeff had the vision of a role for a physician/scientist, which was intriguing and why I came here, and he liked my background. But I was on a short-term contract – and when I left to have my first child he kept a tenured position open for me, which was very unusual then. You can't have a family and plan research if you only have two-year contracts. This was a decisive point in my career – my husband is American and I was open to anything then, including going to work in the States."

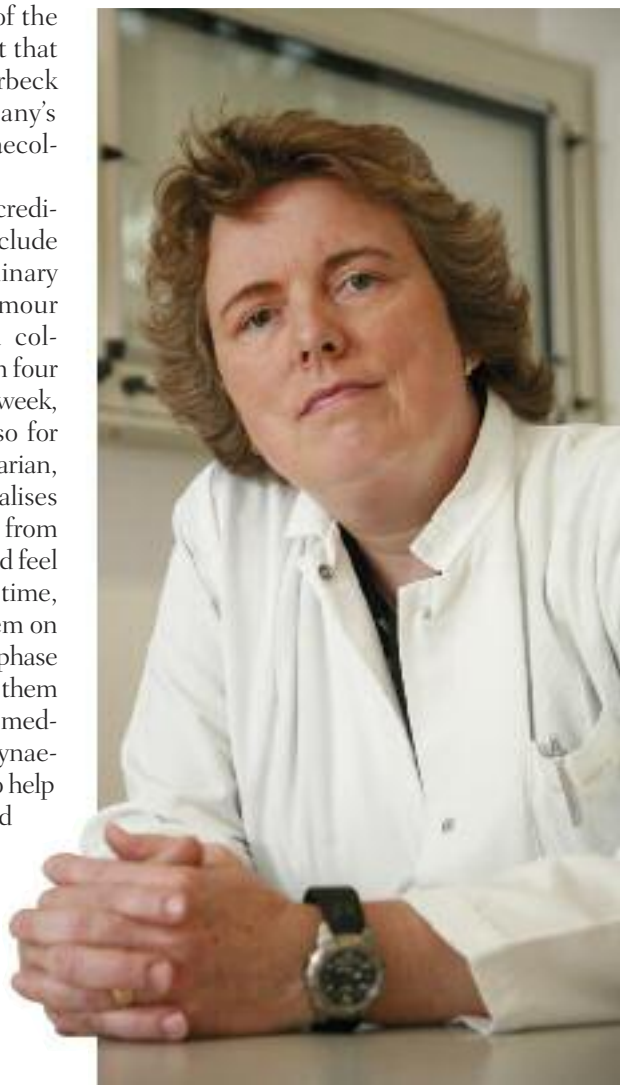
So Harbeck's research career was safeguarded – and has continued through three more children. About 10 years ago she also moved full time in the clinic away from surgery and day-to-day ob/gyn work to focus on systemic therapy and building up the department as a top breast unit.

As she says, there can't be too many internationally known oncologists who have delivered babies and carried out breast cancer surgery and many other procedures such as hysterectomies, and who are now investigating novel therapies. The experience, she feels, gives her a more profound insight into the needs of women, which helps in her work with breast cancer patients of all age-groups.

Her main achievements, then, fall into the two camps of research and trial work, and building up the department as one of Germany's main cancer centres, especially for breast cancer. As trial work is a parameter for accreditation, the two reinforce one another. "In 2005 we were certified as a breast centre by the German authorities – two organisations have jointly drawn up specifications, namely the German Cancer Society and the Society of Senology, but they differ from EUSOMA's guidelines. We do struggle with EUSOMA because it requires that medical oncologists be part of the unit and does not accept that I have the expertise." Harbeck herself sits on Germany's AGO breast cancer gynaecology guidelines group.

The breast centre accreditation does, of course, include the usual multidisciplinary structures such as tumour boards – Harbeck and colleagues run no fewer than four early morning meetings a week, mostly for breast but also for other cancers such as ovarian, which a colleague specialises in. Medical oncologists from elsewhere, she says, would feel superfluous most of the time, "But we consult with them on difficult cases, and in our phase II trials we also work with them closely – I try to partner a medical oncologist with a gynaecologist as investigators, to help bridge the gap and avoid confrontation.

"It is sometimes hard to explain to colleagues abroad how we do things here and that



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I don't want to export our system – but I do want the recognition that I am an equal in the medical oncology field in breast cancer, even though I did a different specialist degree. I don't think it is what you did 10 years ago but what you specialise in now that counts." In fact, Harbeck also faces some opposition from within the ob/gyn world too – not all are too keen to see their field extended and sub-specialised so far in the direction of systemic treatment of early and metastatic breast cancer.

Meanwhile, she considers the introduction of certified breast centres will radically change the landscape of breast care in Germany. "The estimate is we need 200 centres to provide good care – we are at around 150 now. Smaller hospitals that see only a low number of cases should not carry on with breast cancer work – but it will probably be the insurance companies that decide the issue as they won't offer reimbursement to non-conforming places."

It is important also, she adds, to implement a structure where the patients of private practitioners are referred to breast centres, but are then returned to the care of the referring physician.

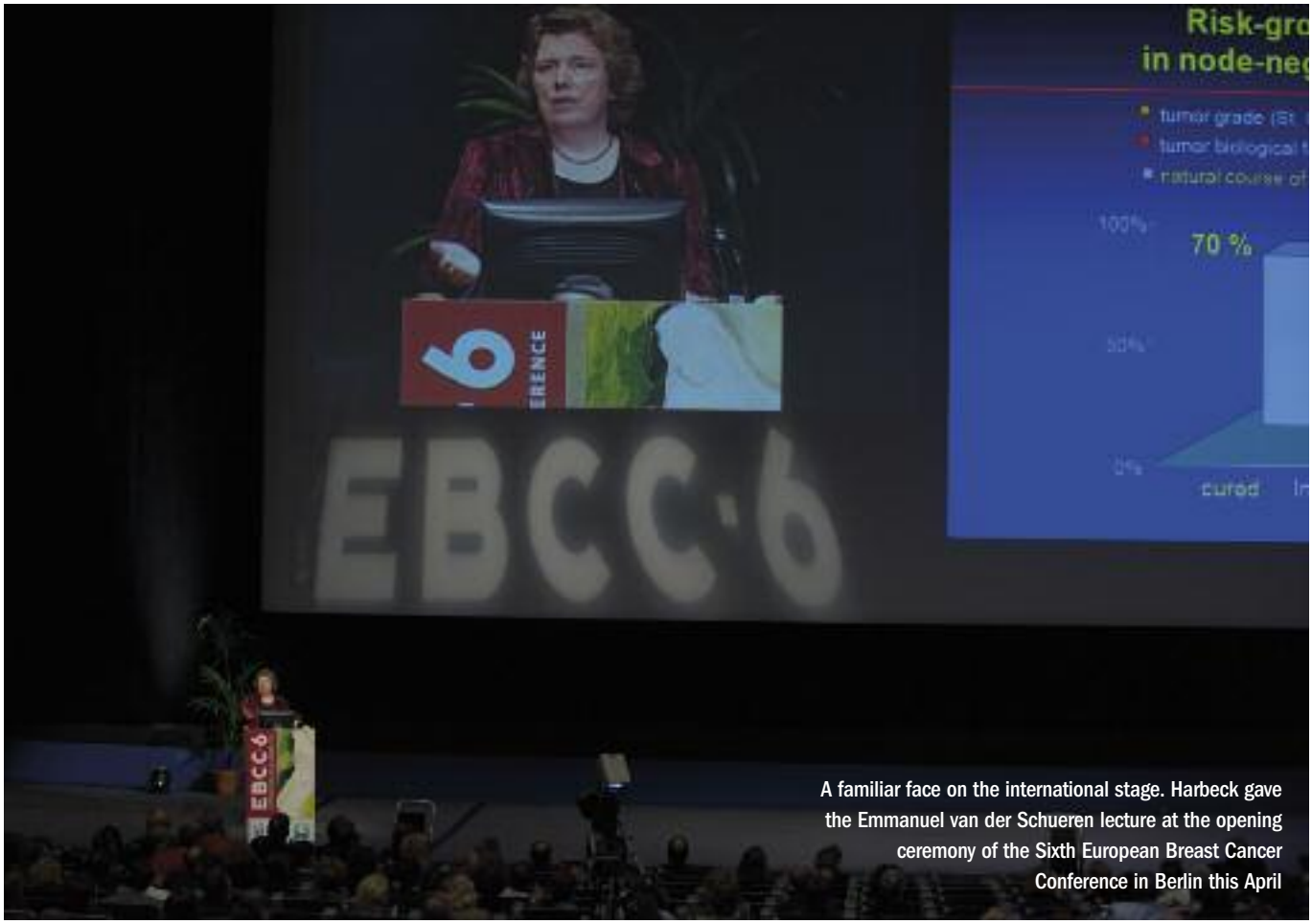
Harbeck's department also carries out a good deal of second opinion work, seeing patients directly – but she feels that moves to implement a mandatory second opinion system where only the paperwork is received, which is partly driven by insurance companies seeking to avoid expensive therapies, is politically controversial. "Who is going to take responsibility if the patient relapses – and can you really give second opinions for individual patients just by following guidelines and published evidence?" That said, guidelines are critical: "We have seen changes in treatment patterns and better outcomes in both breast and ovarian cancer for those who follow guidelines, and overall, despite what some of our journalists like to say, treatment in experienced German centres is not any worse than in the US. You do not have to go to America to get the best care."

The research that has captured Harbeck's attention is on the plasminogen activator system – a complex enzyme system where it has been found that increased levels of an activator, uPA, and also its inhibitor, PAI-1, in primary breast cancers correlate with aggressive tumours and poor outcomes. As she explains, work on uPA goes back to the 1980s, where Joe Duffy, of St Vincent's University Hospital, Dublin, demonstrated the effect of high uPA activity, while Manfred Schmitt in Munich developed an ELISA (Enzyme Linked ImmunoSorbent Assay) to measure the levels of uPA and PAI-1. The uPA enzyme degrades the extracellular matrix and so tumour cells can escape and metastasise – and the inhibitor also has a similar effect and helps tumour cells migrate, which is counter-intuitive, but was shown to be true.

"Various groups around Europe, helped by the then Receptor and Biomarker Group [now Pathobiology Group] of the European Organisation for the Research and Treatment of Cancer [EORTC], also found the same bad prognosis, and Fritz Janicke, then here in Munich, led the first clinical trial of these biomarkers, (Chemo N0). The results were published in 2001 in the *Journal of the National Cancer Institute*."

That trial should sound familiar in its aim to *Cancer World* readers, as it concerns selecting which women with node-negative breast cancer would best benefit from adjuvant chemotherapy, through risk stratification – the same aim of the much discussed MINDACT and TAILOR*x* trials, which instead use gene signatures to help distinguish high- and low-risk groups. But the uPA/PAI-1 work relies on a simpler and cheaper protein measurement that Harbeck says is easier to replicate and now has a robust quality control methodology.

"When Fritz Janicke left, I took over as clinical lead on the project and did my professorial thesis on the system," says Harbeck. "The ASCO merit award was for a meta-analysis on behalf of the EORTC



A familiar face on the international stage. Harbeck gave the Emmanuel van der Schueren lecture at the opening ceremony of the Sixth European Breast Cancer Conference in Berlin this April

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Receptor and Biomarker Group, where we showed that uPA and PAI-1 were ready for routine testing of primary breast cancer as level 1 evidence. No one had ever done such an analysis of a prognostic factor on over 8,000 patients – it was the first in any cancer I think – and the ASCO organisers emailed me twice to check the details were true." So far these biomarkers are the only ones proved in a prospective trial in breast cancer. As an aside, she also mentions the support she's received from Martine Piccart-Gebhart, current president of the EORTC, in developing her international work.

As she adds, the uPA/PAI-1 work is also an excellent example of translational research in action. "We went from bed to bench and back again. We had the clinical indication first, the scientist explained how it worked, and then we did the trial that proved that high levels of these factors are bad for patients. We have been a step ahead of the gene signature work with level 1 evidence – i.e. ready for use in the clinic – and we also have a second clinical trial (NNBC-3) now in train with 3,000 patients in 150 centres that will be finished early next year."

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Role model. Harbeck – pictured here with children (from the left) Lara, Julian, Emma and Daniel, and husband Ronald – is living proof that, with a bit of give and take, it is perfectly possible to combine family with a successful career in oncology

The uPA/PAI-1 biomarker system is, says Harbeck, now routinely used in clinics in Germany and elsewhere (about half of the current trial sites use the system in the clinic). As a consequence, about 35%–40% of node-negative breast cancer patients are spared adjuvant chemotherapy, but wider application is constrained by the need for medical oncologists to access fresh tumour tissue and also have available the ELISA. "The Americans don't have it – after the surgeon takes out the tumour, samples end up in formalin, and the company making the ELISA test has not marketed it heavily." The fresh tissue constraint is shared with the MINDACT gene signature trial, but not with TAILORx, which is designed to work with formalin-fixed, paraffin-embedded tissue specimens.

Further, because it is deemed 'impractical', the biomarker is acknowledged but not recommended in the influential St Gallen breast cancer treatment consensus, nor is it used by the Adjuvant Online resource (www.adjuvantonline.com), according to Harbeck, who is in discussion with Adjuvant Online on how to integrate her data.

"Some say, 'If your biomarker is so good how come it's not in St Gallen?' But half of the St Gallen panel come from the US so it's not surprising they don't yet recommend it. We had a big boost last year, though – uPA/PAI-1 is now in ASCO's guidelines, which shows how scientifically independent they are. And the company making the ELISA is looking for approval from the US Federal Drug Administration based on our German data."

The portfolio of trials in Munich – some 15 currently – is keeping Harbeck very busy; paperwork and organising and motivating junior doctors and remote participants in outlying clinics is an exhausting business, even though she has the help of her colleagues and a university trials centre. One of her key achievements is turning the trials work in her department from an informal, after-hours approach into a fully fledged functional trials unit with study nurses and a growing portfolio. She would like to see more clever trials that target subgroups such as those with hard-to-treat triple-negative disease, and she is also an investigator for therapies such as Avastin (bevacizumab), which are starting to be used more widely across several tumour types. "But companies need to invest more in predictive biomarkers so we can see what compounds are best used in which patient," she says. She has recently applied for a large grant for combining targeted therapy with molecular imaging in line with this need to develop markers for drugs such as Avastin.

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She adds that one other reason to travel so much – especially to the US – is to meet top industry and academic decision makers to discuss clinical trials and biomarkers.

But a few German oncologists making international commitments is not sufficient to raise the bar generally for German oncology, she feels. She is pleased to report that there is now a national translational research network for gynaecological cancers (TRAFO), for which she is deputy chair, while she is also the scientific co-chair of a new translational research meeting for breast cancer, COMBAT, which has been deliberately set up as a German-speaking networking event (its inaugural event is in Frankfurt this November).

Naturally, though, she sits also on the scientific committee of the ASCO-NCI-EORTC Annual Meeting on Molecular Markers in Cancer, which will be held in Florida this year, having had its first meeting in Nyborg, Denmark, in 2000. She also told the uPA/PAI-1 story this year at the Breast Cancer Conference in Berlin as an invited lecturer at the opening ceremony. Harbeck is also one of the editors in chief of *Breast Care*, a journal set up in 2006 that has both English and German contributions, and she seems tireless in writing up treatment standards and new developments.

Harbeck is keen to stress that she is not single-minded about treatment and survival. "I do try to be as patient-oriented as I can, for example by introducing counselling and a specialist breast care nurse to the clinic, but it is a struggle, as we have to raise outside funds for much of this. I'm also researching breast self-awareness – women need to learn about self-examination and we are evaluating what this brings to their awareness. A technique called MammaCare, which comes from the US, can help them do it better, and we are also doing this with breast cancer patients – they don't like to touch themselves, but they need to feel a new lump.

She is firmly on the side of the screening programme, feeling that its late introduction has cost women's lives in Germany, and comments that the old trials that have been criticised need to be interpreted within the time they were initiated, and some of their flaws may not be relevant any more, given the introduction of digital mammography and a thorough double-reading procedure.

Harbeck has a close non-medical colleague in Renate Haidinger, a breast cancer survivor who first set up a support group in Munich and then co-founded Brustkrebs Deutschland (Breast Cancer Germany). Haidinger gives counselling sessions at the Munich clinic and has also worked with Harbeck on writing up patient experiences with treatments such as Femara (letrozole) (*Breast Can Res Treat* 105:91–103). There are other breast cancer advocacy groups in Germany, and Harbeck's wish is that they would collaborate more closely and also look outside the country, in an echo of the situation on the medical side.

The pan-European advocacy group, Europa Donna, does not have a big local presence in Germany, she says, despite German MEP Karin Jöns being a past Europa Donna president.

For her own part, Harbeck is determined to be a role model for younger women wanting to pursue a clinical research career. "There was no one like me when I was starting out – now I write at the top of my CV that I have four kids, so women can ask me how I did it." Those children are aged 16, 14, 9 and 4, and husband Ronald Kates, who was a relativity physicist in the US, works now as freelance mathematician and indeed is a co-author on many of Harbeck's papers. "He does my bio-maths," she says.

Harbeck's immediate plans are to continue to develop the breast unit part of the clinic, and she indicates she might move to head up her own breast centre if there was an opportunity to set up a genuinely holistic facility. She will of course be at every major breast meeting in the next few years – and if you see her, some words of warning: don't ask who is looking after her children…