

# 13th St. Gallen International Breast Cancer Conference 2013: Primary Therapy of Early Breast Cancer Evidence, Controversies, Consensus – Opinion of a German Team of Experts (Zurich 2013)

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## Keywords

St. Gallen Consensus · Early breast cancer · Adjuvant therapy · Multigene signatures · Targeted therapy

## Summary

The International Consensus Conference on the treatment of primary breast cancer takes place every two years in St. Gallen, Switzerland. The panel in St. Gallen is composed of international experts from different countries. From a German perspective, it seems reasonable to interpret the voting results in the light of AGO-recommendations and S3-guidelines for everyday practice in Germany. Consequently, a team of eight breast cancer experts, of whom two are members of the international St. Gallen panel, commented on the voting results of the St. Gallen Consensus Conference (2013). The main topics at this year's St. Gallen conference were surgical issues of the breast and axilla, radiotherapeutic and systemic treatment options, and the clinical relevance of tumour biology. The clinical utility of multi-gene assays for supporting individual treatment decisions was also intensively discussed.

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## Schlüsselwörter

St. Gallen Consensus · Frühes Mammakarzinom · Adjuvante Therapie · Zielgerichtete Therapie · Multigenensignaturen

## Zusammenfassung

Alle zwei Jahre findet in St. Gallen (Schweiz) die internationale Konsensuskonferenz zur Behandlung des primären Mammakarzinoms statt. Da sich das internationale Panel in St. Gallen aus Experten unterschiedlicher Länder zusammensetzt, spiegelt der Konsensus ein internationales Meinungsbild wider. Vor diesem Hintergrund erscheint es aus deutscher Sicht sinnvoll, die Abstimmungsergebnisse für den Therapiealltag in Deutschland zu konkretisieren. Eine deutsche Arbeitsgruppe mit acht Brustkrebsexperten, von denen zwei Mitglieder des internationalen St. Gallen-Panels sind, hat daher die Abstimmungsergebnisse der St. Gallen-Konsensuskonferenz (2013) für den Klinikalltag in Deutschland kommentiert. Inhaltliche Schwerpunkte der diesjährigen St. Gallen-Konferenz waren operative Fragestellungen der Brust und der Axilla, strahlentherapeutische und systemische Therapieoptionen sowie die klinische Relevanz der Tumorbiologie. Intensiv diskutiert wurde der klinische Einsatz von Multigen-Assays, inkl. ihrer Bedeutung für die individuelle Therapieentscheidung.

## Introduction

The St. Gallen Consensus Conference on treatment of primary breast cancer is of global relevance. The panel of this year's 13th St. Gallen Consensus Conference comprised 50 experts from a total of 19 countries, including 2 representatives from Germany. The recommendations are based on the majority vote of the panellists, who represent different fields of expertise and countries from all continents with sometimes very different healthcare systems and resources. Under these circumstances, the consensus reflects an expert opinion – even if the individual opinions and thus ultimately the overall opinion are based on published, evidence-based data. It thus seems reasonable from a German perspective to comment on the voting results. In previous years – 2009 and 2011 – this interpretation taking into account the current German guideline recommendations was highly appreciated. Therefore, a team of 8 breast cancer experts commented the voting results of St. Gallen for everyday practice in Germany.

### *Basis of the St. Gallen Consensus*

This year's St. Gallen Consensus Conference concentrated on topics and issues that are currently the subject of controversial debates within the international scientific community. The aim was to search for clinically applicable recommendations of the panellists and to:

- (1) ideally reach a consensus;
- (2) take into account country-specific differences;
- (3) define issues that need to be clarified within on-going and future controlled clinical trials.

In their preparation of the St. Gallen consensus conference, the panellists agreed that controlled clinical trials are suitable to document the clinical benefit of one treatment over another and to define the average outcome improvement for patients. However, they are unable to make any definitive statements on the specific treatment benefit for an individual patient.

In summary: every treatment decision must be made individually. The basis for the treatment choices in primary breast cancer are tumour biology, tumour size, lymph node involvement and patient's preference. Tumour biology defines the response probability for a given therapy and, along with tumour size and lymph node involvement, indicates the therapeutic benefit that can be expected.

The St. Gallen panellists answered the questions with 'yes' (agreement), 'no' (rejection) or 'abstention'. The latter is meant to indicate insufficient data available or no opinion possible due to a lack of expertise in this field for the individual panellist or a conflict of interest. The votes were given with the understanding that individual deviations may be necessary in individual cases.

## Surgical Therapy

In St. Gallen, the surgical issues in primary breast cancer focused on the decision criteria for or against mastectomy or breast-conserving therapy (BCT). The German experts criticised the fact that the indication for neoadjuvant therapy was not discussed and refer to the current AGO recommendations [1]. Further topics comprised the adequate practice and indications for BCT and for sentinel lymph node dissection (SLND) vs. complete axillary dissection (AD)

### *Focus on Breast-Conserving Surgery*

In the votes on the absolute and relative contraindications against BCT, the German working-group strongly agreed with the majority of the decisions of the St. Gallen panel: the German working-group emphasized that there are only relative and almost no absolute contraindications for BCT. One example for a classical mastectomy indication is stage T4d. Young age of the patient (< 35–40 years old), multi-focal disease (per se), tumour location close to the nipple, extensive vascular tumour invasion, extensive intraductal component and lobular histology are neither absolute nor relative contraindications for BCT. The German working-group welcomes the outcome of the vote on lobular histology. The German experts add that the surgical goal for tumours near the nipple is a tumour free (R0) resection, which is why a mastectomy may still be necessary in certain cases. The St. Gallen panellists and the German working-group also agree that neither a positive family history nor a prognostically unfavourable tumour biology according to genomic analysis constitutes a relative contraindication for BCT.

Extensive or scattered micro-calcifications and multicentric disease were deemed relative but not absolute contraindications for BCT by the majority of the St. Gallen panellists. From a German perspective, multicentricity is not an absolute contraindication for BCT, in particular if the diagnosis was made using magnetic resonance imaging (MRI), and the other imaging results (mammography, sonography) did not indicate multicentricity. Furthermore, the German working group points out that also in case of multicentric disease the surgical goal remains R0 resection.

The St. Gallen panel sees a relative contraindication for BCT with positive margins after repeated re-excisions of the tumour. According to the St. Gallen vote, this applies regardless of a residual ductal carcinoma in situ (DCIS) or an invasive tumour. From a German perspective, in the case of R0 resection of the invasive component and just focally involved margins with DCIS residuals, BCT may still be an option and may be discussed with the patient and the radiotherapist in individual cases. Ideally, the invasive and non-invasive components should be resected with free margins, and cosmesis of the breast should be satisfactory.

Moreover, there is a relative contra-indication for BCT if the patient is unable to receive post-operative irradiation. The German working group agrees with the clear vote of the St. Gallen panellists. The German experts criticise the absence of a vote on inflammatory breast cancer (IBC, defined as signs of inflammation of the breast skin of more than 30% of the skin and histologically proven invasive cancer), which constitutes a relative contraindication for BCT according to the AGO recommendations [1]. After neoadjuvant chemotherapy with a complete pathological remission, BCT may be performed in individual cases with IBC (AGO recommendation +/-).

There were close votes on BRCA1/2 mutation carriers and surgery for primary breast cancer patients. A BRCA1/2 mutation was considered a relative contraindication for BCT with only a narrow majority. The German experts interpret this close vote as illustrative of the existing controversy. The German working group would not base the indication for or against BCT solely on BRCA 1/2 mutation status. According to the 2013 AGO recommendation this should be decided individually [1]. The German experts point out that the patient's request for a contra-lateral prophylactic mastectomy should be taken into consideration.

#### *Focus on mastectomy*

Just under two thirds of the St. Gallen panellists answered 'yes' to the question as to whether a nipple-sparing mastectomy is acceptable if the patient is not irradiated postsurgically. More than half of the panellists only accepted this in case of a tumour-free margin behind the nipple and an immediate reconstruction of the breast; regarding the latter issue, almost a third of the panellists abstained. The German working group commented that a R0 resection is always mandatory in this situation and that the indication for post-surgery radiation is independent of a primary or secondary reconstruction. If post-surgery radiotherapy to the chest wall is indicated, an immediate reconstruction, especially using implants, would not be a good choice.

The St. Gallen panellists and the German working group agreed that MRI is not a routine procedure for the decision 'BCT versus mastectomy' in newly diagnosed patients.

#### *Focus on 'Margins'*

Invasive primary breast cancer must be resected with tumour-free margins (R0). 72.9% of the St. Gallen panellists opted for no ink on the invasive tumour cells and 48.1% for a minimal surgical margin of 1 mm. This also corresponds to the requirements in the current AGO recommendations [1]. The German working group points out that, unlike with DCIS, the width of tumour free margins (1 mm or more) is not clinically relevant in patients with invasive cancer. This applies irrespective of the underlying tumour biology [2]. The St. Gallen panellists emphasise with a majority of 77.6% that tumour biology is not clinically relevant in this context. Nonetheless,

it remains unclear as to whether this also applies to patients with triple-negative primary breast cancer who have a substantially increased risk of local relapse [2, 3]. For 'DCIS' as sole diagnosis, the AGO requests a tumour-free margin of  $\geq 2$  mm in case of BCT. This is also the opinion of the majority of the St. Gallen panellists.

#### *Indication for an Axillary Dissection?*

The St. Gallen panellists agreed that in patients with 1 or 2 positive sentinel lymph nodes (SN) receiving a mastectomy axillary dissection (AD) must be completed. Over 90% of the panellists opted for a complete axillary dissection if no irradiation is planned post-surgery and 50% opted for AD in patients with mastectomy and with post-surgery irradiation. The German working group stresses that a complete axillary dissection should be performed independently of whether or not the patient is irradiated after mastectomy. AD can only be omitted in case of 1 or 2 involved sentinel lymph nodes according to the ACOSOG Z 0011 study criteria [4] (BCT, tangential field radiation, adequate systemic therapy) and not in patients with mastectomy (with or without post-surgery irradiation). Adjuvant irradiation of the axilla in case of positive sentinel lymph nodes is not an evidence-based alternative to axillary dissection. 72.7% of the St. Gallen panellists voted against AD in patients with BCT plus adjuvant irradiation, if only 1–2 SN are involved. According to the German experts, with reference to the current AGO recommendations [1], this is an individual decision that should be discussed with the patient individually. AD is no longer routine practice in this situation (AGO +/-).

The majority of the St. Gallen panellists agreed that patients with BCT require a complete axillary dissection if they have clinically apparent lymph nodes (cN1) or  $\geq 3$  involved sentinel lymph nodes. The German working group agrees. According to the German experts these patients were not enrolled into the ACOSOG Z0011 study [4].

More than half of the St. Gallen panellists (59%) see an indication for complete AD if the number of positive lymph nodes is relevant for adjuvant chemo- or radiotherapy. This vote was controversially discussed among the German experts. According to the current AGO recommendations [1], the chemotherapy indication does not primarily depend on number of positive lymph nodes, but rather on the underlying tumour biology. Nonetheless, AD can be performed if the type of chemotherapy depends on the absolute number of positive lymph nodes.

#### **Focus on radiotherapy**

##### *Radiation after Breast-Conserving Surgery*

The German working group agreed with the majority of the St. Gallen panellists (68%) that not all patients with BCT need adjuvant radiotherapy. However, the German

experts point out that this patient group is not clearly defined. Omission of irradiation may be justifiable in elderly and co-morbid patients with a limited life expectation (< 10 years) and low-risk cancer.

A majority of the St. Gallen panellists (59.2%) considered hypofractionated ('short course') irradiation with 45 Gy administered in 15 fractions, a standard option for all BCT patients with primary breast cancer. Over two thirds of the St. Gallen panellists (72.2%), however, saw hypofractionated irradiation as a standard option for selected patients. The German working group welcomes both votes. From a German perspective, consideration of this recommendation by German radiotherapists is highly desirable. The recommendation is based on the current updated results of the START trials from the United Kingdom [5]. The indication should correspond to the inclusion criteria of these trials. Hypofractionated irradiation is also an option if boost irradiation is planned. Here, too, the German working group agreed with the St. Gallen vote.

Exclusive intraoperative (partial breast) irradiation is not standard of care in case of breast-conserving surgery. This is clearly stated in the current AGO recommendations (AGO: -) [1] and is also in line with the St. Gallen vote. Exclusive intraoperative irradiation may only be an option in case of favourable tumour biology. In the AGO recommendations 2013 [1], intraoperative irradiation is an option for replacing an external postoperative boost (AGO +).

#### *Radiation of the Thoracic Wall and Regional Nodes after Mastectomy*

In patients after mastectomy, adjuvant irradiation is the standard of care in case of at least 4 positive lymph nodes (chest wall and supraclavicular field (SICF)). Over 95% of the St. Gallen panellists voted in favour of this. In case of 1–3 positive lymph nodes, adjuvant irradiation to the chest wall is not routinely indicated – unless there are additional risk factors such as large tumour size, unfavourable tumour biology, or young age (< = 40 years). The German working group agrees with the vote and adds that in particular young women with unfavourable tumour biology should additionally receive postmastectomy radiotherapy (PMRT).

According to the St. Gallen vote, PMRT is also indicated in patients with positive SN but no AD. The German working group does not agree because adjuvant radiotherapy cannot substitute an otherwise indicated AD. From a German perspective, adjuvant radiotherapy is not an alternative to a complete AD in case of positive SN.

PMRT is standard of care for patients with large primary tumours of > 5 cm, independent of the nodal status. The German working group agrees, referring to the AGO recommendations [1]. In case of pT3/4 carcinomas, the AGO strongly recommends PMRT (AGO ++). Only in patients with pT3

pN0 R0, PMRT can be omitted if no additional risk factors are present (AGO +/-).

PMRT is not a standard therapy in case of pathologically tumour-free lymph nodes (pN0). The St. Gallen panellists and the German working group agree that this also applies if < 8 lymph nodes had been removed. Moreover, PMRT – regardless of nodal status – is not necessarily indicated in young patients (< 40 years) or if a G3 tumour, lympho-vascular invasion, HER2 positivity or triple negative breast cancer (TNBC) are present. The German experts agree and add that an indication in node-negative patients for PMRT should be based on additional risk factors (see above).

#### *Irradiation of the Nodal Areas*

The St. Gallen panellists and the German working group agree that the indication for adjuvant irradiation of the nodal areas does not depend on the intrinsic sub-type of breast cancer or on the response to neoadjuvant chemotherapy (NACT). The German experts point out that there are no data, and therefore the decision needs to be made individually. There is also a consensus that adjuvant irradiation of the nodal areas is not automatically indicated and does not necessarily include the axilla and the internal mammary lymph nodes. Moreover, the St. Gallen panellists rejected by a majority that irradiation of supraclavicular fields (SICF) (82%) and the internal mammary lymph nodes (70%) needs to be routinely performed in case of an indicated nodal irradiation (53%). With reference to the AGO [1], the German experts recommend SICF irradiation for patients with pN2a and (p)N3a-c tumours and only in individual cases in stage pN1a. SICF irradiation is also recommended if level III lymph nodes are affected or if axillary surgery cannot reach R0 margins.

#### **Focus on Pathology**

##### *Difference between Luminal A and Luminal B Carcinomas*

For practical purposes, in order to reliably distinguish between luminal A and luminal B type breast cancer (HER2-negative), the proliferation marker Ki-67 can be used in addition to the hormone receptor status (ER, PgR). The St. Gallen panellists and the German working group were in agreement that tumour grade only constitutes an unsatisfactory substitute for Ki-67. However, the German experts add that the Ki-67 value should be consistent with grade in order to make a therapeutic decision; especially G3 should correlate with a high Ki-67 value.

According to the majority vote of the St. Gallen panellists (60%), the use of molecular diagnostics for distinction between luminal A and luminal B tumours is not necessary in everyday practice. The German experts agree and add that



there is no routine indication for gene signatures in Germany. There is a consensus that a molecular and histopathological diagnosis should always be performed in a quality-controlled pathology laboratory to obtain reliable test results.

#### *HER2 Positivity*

Patients with a positive HER2 status (HER2 overexpression) additionally require an anti-HER2 therapy. HER2-positive breast cancer is defined as  $\geq 30\%$  of immuno-histochemically proven tumour cells stained positive for HER2 (IHC3+) and/or a FISH ratio of  $\geq 2.0$ . In case of an HER2 expression of  $> 10\%$  to  $< 30\%$  (IHC2+), an additional FISH analysis is recommended. If there is amplification in the FISH analysis, heterogeneity of HER2 overexpression is not therapeutically relevant. For an anti-HER2 therapy, hormone receptor status, proliferation activity of the tumour and polysomy 17 are not relevant. The German working group agrees with the St. Gallen panel on all of these points.

#### *Chemotherapy Indication*

The St. Gallen panel and the German working group agree that the intrinsic breast cancer sub-type has an influence on the indication for adjuvant chemotherapy. The intrinsic sub-type can be classified reliably by the criteria of St. Gallen 2011 – based on the hormone receptor and HER2 status, grade, and Ki-67. Classification using multi-gene expression analyses is not indicated for every day practice. From a German perspective, however, the cut-off value of Ki-67 for high proliferation still remains unclear. The cut-off value of 14% as defined by the 2011 St. Gallen Consensus was questioned by this year's St. Gallen panel and is also not sufficiently validated from a German perspective. An increase in the cut-off value to 20% is currently being discussed. This was also suggested by the St. Gallen panel this year. From the German experts' perspective, the Ki-67 value represents a continuum.

#### *Clinical Relevance of Multi-Gene Assays*

In hormone-sensitive primary breast cancer (ER+ and/or PgR+), the question remains if patients also need chemotherapy in addition to endocrine therapy. Over 97% of the St. Gallen panellists rejected an additional multi-gene assay for the majority of patients after the clinical and pathological determination of the intrinsic sub-type. No additional multi-gene assay is routinely indicated in case of a positive oestrogen (ER) and/or positive progesterone (PgR) receptor status. This also applies – according to a simple majority of the St. Gallen panellists – to patients with a luminal B sub-type (HER2-negative). From a German perspective, a multi-gene assay is only justified if the intrinsic classification – luminal B or luminal A – is uncertain and the chemotherapy indication strongly depends upon it.

Likewise, a multi-gene assay is not indicated in patients with hormone-sensitive HER2-negative breast cancer and positive lymph nodes. The German experts add that in case of lymph node involvement, chemotherapy is recommended. This is different in primary breast cancer patients with only 0–3 involved lymph nodes and a positive ER status without HER2 overexpression. In this case, a simple majority of the St. Gallen panellists sees an indication for a multi-gene assay. The German working group sees an indication for a multi-gene assay mostly in the sub-group of patients with G2 carcinomas, a mid-range Ki-67 value (15–20%) and slightly positive ER/PR as the chemotherapy indication in these patients is uncertain. From a German perspective, uPA/PAI-1 measurement is a valid and evidence-based alternative to the multi-gene assay in N0 patients. For patients with node-negative G2 cancer this assay is widely used in Germany, but was not discussed by the St. Gallen panellists.

#### *Different Multi-Gene Assays*

Different multi-gene assays are used in ongoing clinical trials. The most widely used genomic test is currently the 21-gene recurrence score (RS) (Oncotype DX<sup>®</sup>). Accordingly, the majority of the St. Gallen panellists see the 21-gene RS as the only option for routine use for HR-positive patients and an unclear chemotherapy indication. Further options, such as the PAM50 assay, the 70-gene signature (Mammaprint<sup>®</sup>), the EPclin score (EndoPredict<sup>®</sup>) and Mammostrat<sup>®</sup>, were rejected by the majority of the St. Gallen panel with respect to indicate (or spare) adjuvant chemotherapy.

The German working group does not agree with these votes and points out that Oncotype DX and EndoPredict have a similar 'level of evidence' (loe) according to the actual AGO recommendations. Furthermore there are no prospectively validated data for any of these multi-gene assays. Oncotype DX, EndoPredict, Mammaprint, Pam50 and Mammostrat should thus only be used in individual cases [1] until prospective validation is available. Again the German experts point out that uPA/PAI-1 is a well-validated test method for node-negative G2 cancer to confirm a chemotherapy indication. PAM50 and EPclin are tests retrospectively validated on tumours from the ATAC and ABCSG studies. They are able to distinguish between patients with a good and a poor prognosis. However, data showing that those patients with a poor prognosis derive benefit from adjuvant chemotherapy are still missing. Consequently, both tests are not suitable to verify a chemotherapy indication. Prospective validation is also lacking for the 70-gene signature. The German experts explicitly warn against 'test hopping'. It has been demonstrated that tests may show different results in 20–30% even if they were performed on the tumour material from the same patient (uPA/PAI-1 and Oncotype DX in the Plan B Study [8] as well as Pam 50 and Oncotype DX [9]). uPA/PAI-1 and Oncotype DX showed a good correlation only in the high-risk group.

## Molecular Diagnostics ...

### ... for Hormone-Sensitive Primary Breast Cancer

The St. Gallen panellists voted by a majority that molecular diagnostics in patients with hormone-sensitive primary breast cancer are not necessary in the following cases:

- very small tumours ( $\leq 1$  cm), where no chemotherapy is indicated at all;
- large tumours (e.g.  $> 5$  cm), where there is an indication for chemotherapy;
- inflammatory carcinomas that also always have a chemotherapy indication;
- very low oestrogen receptor expression (e.g. 5%), as chemotherapy is indicated in addition to endocrine treatment.

While the German working group agrees with each of the St. Gallen votes, it points out that tumour size per se is not a sufficiently validated factor for a chemotherapy indication alone and that other factors need to be taken into consideration.

The St. Gallen panellists did not vote in favour of the statement that molecular diagnostics can be omitted in patients with hormone-sensitive primary breast cancer and 1–3 involved lymph nodes because these patients require chemotherapy anyway. The German working group points out that 1–3 involved lymph nodes constitute a relative but not an absolute chemotherapy indication. This chemotherapy indication should be decided upon individually – depending on tumour biology. The decision for or against chemotherapy should be based on additional factors.

In the case of 4 or more involved lymph nodes, however, molecular testing is not necessary as there is a chemotherapy indication, as the St. Gallen panellists and the German experts established unanimously. The German experts add that the 21-gene RS has not yet been prospectively validated in node-positive patients.

The German working group and the St. Gallen panel are not in agreement regarding patients with hormone-sensitive primary breast cancer and a G3 tumour, as well as very young women ( $< 35$  years old) and the use of molecular diagnostics: the majority of the St. Gallen panellists decided that molecular diagnostics may be useful in these cases. The German working group does not see an indication for molecular testing in either case. From a German perspective, there is a chemotherapy indication for a G3 tumour and in very young women.

### Influence of the Stroma

Pathological properties of the stroma, such as lymphocyte infiltration, microvascular density and p16 staining of the stroma, have no influence on treatment decisions. The St. Gallen panellists agreed upon this by a clear majority and the German working group also agrees.

## Adjuvant Antihormonal Treatment

### Pre-menopausal Patients

For premenopausal patients with hormone-sensitive primary breast cancer, tamoxifen is standard. The German working group agrees with the majority of the panellists in St. Gallen. A combination with ovarian suppression (OFS) was rejected by the majority and the panel's vote was divided in the case of patients under 40 years of age: half voted for the addition of OFS, half against. The German experts specify that, according to the studies available, the combination of tamoxifen plus OFS (mainly gonadotropin releasing hormone (GnRH) analogues) is not superior to tamoxifen. According to the current AGO recommendations, the addition of OFS to tamoxifen may be an option only for patients with a low or intermediate risk who have not received any additional chemotherapy. Young age (e.g.  $< 40$  years old) per se is not a reason to perform OFS in addition to tamoxifen. 70% of the St. Gallen panellists rejected the exclusive use of OFS (without tamoxifen) as a therapeutic option. The German working group disagrees and refers to the AGO recommendations [1]. The exclusive use of OFS is an option for patients with a contraindication to tamoxifen. This is a better option than no endocrine therapy at all.

From a German perspective, tamoxifen for 10 years should be discussed also with every premenopausal patient, weighing benefits against risks. For patients with an increased relapse risk (e.g. N+) and those without significant side effects from tamoxifen, the longer duration of the therapy is an important new therapeutic option. In the AGO recommendations, administration of tamoxifen is recommended for up to 10 years. The German working group agrees with the St. Gallen vote.

The majority of the St. Gallen panellists rejected the use of aromatase inhibitors (AI) in premenopausal patients in addition to OFS. However, it is an option if there are contraindications to tamoxifen (e.g. thrombosis, embolism). This corresponds to the evaluation according to the AGO recommendation (AGO +/-) [1]: the AI/OFS combination is an option for premenopausal patients in individual cases. The German working group agrees, but points out that OFS is also an option in patients with contraindications to tamoxifen (see above).

### Postmenopausal Patients

The votes on endocrine treatment in postmenopausal patients focused on the use of tamoxifen and AI with particular emphasis on therapy duration. The St. Gallen panellists voted with a clear majority (93.6%) that the exclusive administration of tamoxifen still constitutes an option for postmenopausal patients with hormone-sensitive primary breast cancer. The German working group agrees. There can be an indication for tamoxifen alone in the case of older patients, intolerance to AI, pronounced osteoporosis or low relapse risk (small tumour, N0, G1/2).

If an AI is indicated, 47.5% of the St. Gallen panellists would already administer it upfront and 50% would not. The German working group agrees with the narrow majority of 50% of the panellists who do not see any compelling 'upfront' indication for AI in general. However, if there is a risk situation (pN+), the St. Gallen panellists (87.2%) and the German experts agreed that upfront AI is indicated.

They were also in agreement on the following votes: after upfront administration of the AI, it can be switched to tamoxifen. A majority of the St. Gallen panellists answered 'yes' to the question as to whether patients who had already received anti-hormonal therapy for 5 years should be offered further treatment with an AI for node-positive but not for node-negative patients. The German working group agrees with this statement but points out that no valid data on the use of an AI for > 5 years are available so far. The decision should thus be made individually by weighing the benefits against risks.

Further endocrine treatment with an AI is both an option after 5 years of tamoxifen and after tamoxifen and a switch to AI within the first 5 years. Once again, the German experts pointed out that no data are available from controlled clinical trials that justify the use of an AI beyond 5 years. Accordingly, both the St. Gallen and the German experts rejected further treatment with AI for patients who already received an AI 'upfront' for 5 years. They agreed that in the case of contraindications against AI and after upfront administration of tamoxifen over 5 years, tamoxifen can be used subsequently for (another) 5 years. The AGO recommends to give tamoxifen to patients at increased risk of relapse for up to 10 years (AGO++) [1].

Several studies with longer endocrine treatment are ongoing. Also there is a need for multigene signatures to predict late relapse.

## Adjuvant Chemotherapy

### Chemotherapy Indication

The St. Gallen panellists and the German working group agree that high grade (G3 tumour), an increased Ki-67 value, low ER expression and invasive ductal triple negative breast cancer (TNBC: ER-, PgR-, HER2-) are indicators for adjuvant chemotherapy. For Ki-67, the lack of methodological standardization and the cut-off value controversy are problematic. The individual high-risk classification obtained by the two genomic tests, 21-gene RS (Oncotype DX) and 70-gene test (Mammaprint) were deemed additional indicators for chemotherapy. There was no voting on other molecular tests (Pam 50, EndoPredict) for evaluation of chemotherapy indication.

The lymph node status has no predictive value, but is still regarded as a prognostic factor. A positive nodal status ('any

positive node') is therefore insufficient as a sole factor for a chemotherapy indication. If, however, at least 4 lymph nodes are histologically affected, patients are at increased risk and chemotherapy needs to be given. Lympho-vascular invasion in itself does not constitute a chemotherapy indication. In young patients (i.e. < 35 years old), the German experts recommend weighing benefits against risk in consultation with the informed patient. This is in line with a highly ambivalent St. Gallen vote (more than half voted against chemotherapy solely based on the young age).

### Luminal A Sub-Type

Numerous votes in St. Gallen focussed on the influence of the intrinsic breast cancer sub-type on the choice of cytostatic therapy. Luminal A breast cancers belong to the highly endocrine sensitive tumours. The St. Gallen panellists and the German experts agreed that the luminal A subtype is less sensitive to chemotherapy and thus should rather be treated by endocrine therapy alone. In the case of an increased risk, however, there may be a chemotherapy indication. In this case, from a German perspective it is inadequate to preferentially treat the patients with a less intensive regimen, such as 4×AC, 6×CMF or 4×TC. The German working group thus disagrees with the majority St. Gallen vote (62%), which deemed less intensive chemotherapy to be sufficient for luminal A breast cancer. The German experts explain their disagreement with the St. Gallen vote by stating that a chemotherapy indication requires an increased risk of relapse, which in turn requires chemotherapy with optimum efficacy. The patients should receive an anthracycline/taxane-based combination or sequence for at least 18–24 weeks.

### Luminal B Sub-Type

Hormone-receptor-positive patients with luminal B breast cancer (HER2-negative) have an increased risk of relapse and are sensitive to chemotherapy because of their increased proliferation rate. Patients with luminal B breast cancer (HER2-negative) thus need to receive chemotherapy prior to endocrine treatment. The Ki-67 measurement is useful according to the St. Gallen panellists to define the 'luminal B' sub-type. The majority of the St. Gallen panellists see the Ki-67 cut-off value at  $\geq 20\%$ . The majority of the German experts are also in favour of  $\text{Ki-67} \geq 20\%$  as a threshold, but stress the continuum of the value.

The St. Gallen panellists voted by a majority in favour of anthracycline and taxane based regimen for patients with a luminal B sub-type for at least 6 cycles in case of a chemotherapy indication. The German group agrees and point out that an 18–24-week course of therapy is standard. Dose-dense chemotherapy can be indicated in the case of at least 4 involved lymph nodes. In the event of a luminal B tumour with HER2 overexpression, the patients require chemotherapy with trastuzumab.

### *HER2-Positive Sub-Type*

Patients with HER2-positive primary breast cancer require anti-HER2-therapy in addition to chemotherapy. The St. Gallen panellists and the German experts agree that there is no preferred chemotherapy regimen in case of HER2-positivity but that chemotherapy should contain an anthracycline and a taxane. The majority is in favour of a simultaneous taxane and trastuzumab administration. Also from a German perspective, the trastuzumab therapy should be carried out simultaneously with the taxane.

### *Invasive Ductal Triple Negative Breast Cancer*

Patients with triple negative breast cancer (TNBC) have an unfavourable prognosis. The St. Gallen panellists voted in favour of treating these patients with chemotherapy that contains an anthracycline and taxane. Alkylating agents in high doses or platinum salts, however, should not be recommended. Whether patients with invasive ductal TNBC should preferentially be treated with dose-dense chemotherapy was rejected by the St. Gallen panellists: 38.3% voted in favour and 48.9% rejected preferential dose-dense chemotherapy. The German experts agreed with the individual votes on invasive ductal TNBC. While benefits from dose-dense therapy could be demonstrated in a German phase III trial also for patients with TNBC [10], no preferred indication for a dose-dense therapy can be derived.

### *Other Criteria for Special Chemotherapy Regimen?*

The chemotherapy decision is fundamentally influenced by tumour-related characteristics. The St. Gallen panellists and the German working group agreed that, on top of this, potential co-morbidities play a key role for the chemotherapy indication and the choice of regimen. Moreover, the biological age of the patient should be taken into consideration. The preservation of the ovarian function and fertility that is often desired by young patients is not always possible. The German experts point out that specific preservation of fertility as well as ovarian function cannot be guaranteed. Every chemotherapy can compromise fertility. However, there are chemotherapies that are potentially more harmful to the ovaries than others. If justifiable, the cyclophosphamide dose should be kept as low as possible and preferably an anthracycline and taxane-containing regimen should be used. From a German perspective, it should be noted that the efficacy of the treatment is important particularly in young women and should have priority. Possible alopecia is not a reason against an effective chemotherapy. The intrinsic sub-type does not influence the type of chemotherapy. However, the German experts refer to the current AGO recommendations [1] regarding chemotherapy in certain sub-types. There is also no specific chemotherapy regimen that should preferably be used in BRCA mutation carriers.

### **Anti-HER2 Therapy**

72.5% of the St. Gallen panellists see an indication for an anti-HER2 therapy with trastuzumab in case of HER2-positive primary breast cancer with an invasive tumour of 5 mm or larger; 17.5% see an indication for anti-HER2 therapy irrespective of the size of the primary tumour. Trastuzumab should be used simultaneously with taxanes, but not necessarily simultaneously with anthracyclines. For both votes, there was a clear majority on the St. Gallen panel. The German experts also agree with both votes. If there are contraindications to chemotherapy, 50% of the St. Gallen panellists voted for and 50% against the exclusive treatment with trastuzumab (without chemotherapy). The German working group points out that there are no data and no registrational approval for administration of trastuzumab without chemotherapy ( $\pm$  anti-hormonal treatment).

### **Neoadjuvant Systemic Therapy**

#### *Neoadjuvant Chemotherapy*

Half of the St. Gallen panellists (50.9%) consider improvement of the local (surgical) therapeutic options as the primary goal of neoadjuvant chemotherapy (NACT). The German experts would like to extend this statement. The response associated with the NACT enables early evaluation of individual benefit from systemic therapy and thus contributes to a stronger individualisation of the treatment. Moreover, NACT facilitates prognostic evaluation. Achieving a pathological complete remission (pCR) is regarded as a strong prognostic marker for long-term survival in the case of HER2-positive tumours and TNBC.

Patients who achieve a pCR after NACT do not require any further chemotherapy post-surgery (adjuvant). According to the St. Gallen vote, this is also true for patients who have not achieved a pCR after NACT. The German experts agree in both cases, but admit that there is no indication for further adjuvant chemotherapy in the case of no pCR if all chemotherapy cycles were administered preoperatively. If not all cycles had been administered preoperatively, the chemotherapy should be completed in the adjuvant setting even if a pCR has been achieved. Future studies need to verify if further chemotherapy is needed in this situation. In summary, all chemotherapy cycles should be administered preoperatively.

#### *HER2-Positive Breast Cancer*

In case of HER2-positive primary breast cancer, the patients need an anti-HER2 therapy as part of the neoadjuvant therapy in addition to chemotherapy. A dual HER2 blockade is currently not indicated, formal approval is pending.



### *Neoadjuvant Endocrine Therapy*

There is a broad consensus that exclusive neoadjuvant endocrine therapy may be a reasonable therapeutic option for postmenopausal patients with highly hormone-sensitive breast cancer (high hormone receptor expression, low proliferation index). The German experts agree. A majority (62.2%) of the St. Gallen panellists voted in favour of continuing neoadjuvant treatment therapy to its maximum response instead of limiting it to 3 or 4 months. The German working group agreed with the majority vote.

### **Adjuvant Use of Bisphosphonates**

The questions in St. Gallen focussed on the bisphosphonate zoledronate. The majority of the St. Gallen panellists (70%) voted against adjuvant administration of zoledronic acid (every 6 months) in addition to adjuvant endocrine therapy to prolong disease-free survival. The German experts agree. The St. Gallen panellists rejected adjuvant treatment with zoledronic acid both for premenopausal patients who receive adjuvant tamoxifen ± GnRH agonists and postmenopausal patients with hormone-sensitive breast cancer. The German experts agree. They see an exception for premenopausal patients who meet the inclusion criteria of the ABCSG 12 study [11, 12]. However, it should be pointed out that bisphosphonates were given for 3 years. In postmenopausal patients, the German experts disagree with the St. Gallen vote based on the clinical data available. The AGO (AGO +) [1] recommends adjuvant administration of zoledronate (AGO EG +) for postmenopausal patients with ER-positive breast cancer.

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There is currently no adjuvant indication for the RANK ligand denosumab. Data that justify a substitution of denosumab for zoledronate as adjuvant treatment are not available yet. The issue should be clarified in studies.

### **Follow-Up Examination**

Patients with breast cancer should undergo regular follow-up examinations after the end of the primary treatment (surgery, radiation and chemotherapy, antibody and/or antihormone therapy). This requires personal visits to the physician and should not be carried out over the telephone. However, colleagues from Great Britain see a possibility for follow-up visits by specialised nurses. For the time being, such a situation is hardly conceivable for Germany, but should be verified in studies. With the exception of mammography and breast ultrasound, routine imaging is not indicated for patients without symptoms during follow-up.

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