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Consensus from the 2025 International Symposium on Breast Diseases of Inland São Paulo: Management of HER2-Positive Breast Cancer

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ABSTRACT

Objective: To present the expert panel recommendations derived from the panel discussion *"Management of HER2-Positive Breast Cancer"*, held during the 2025 International Symposium on Breast Diseases of Inland São Paulo (SIMIP), addressing critical controversies in treatment. **Methods:** Priority topics were discussed in evidence-based lectures, followed by technical debates and anonymous electronic voting among 110 panelists. Consensus was defined as agreement of ≥75%. Panelists were predominantly mastologists (101), of whom 94 were from São Paulo (Southeast) and seven from other regions: one from Bahia (Northeast), two from Rio Grande do Sul (South), one from Minas Gerais, two from Goiás (Central-West), and one from Ceará (Northeast). The panel also included six oncologists, two pathologists, and one radiotherapist, all from São Paulo. Panelists disclosed no relevant conflicts of interest related to human epidermal growth factor receptor 2 (HER2)-targeted therapies. Lectures were based on selected literature from existing clinical practice guidelines and pivotal clinical trials; no prior systematic review was conducted. The number of respondents varied across questions because voting participation was optional for each item, and the exact number of votes for each question was presented in the respective results tables. The questionnaire consisted of single-choice, forced-response items using binary or categorical formats, depending on the topic (not a Likert scale). The consensus process followed a structured expert panel methodology with anonymous electronic voting, but the number of respondents per question could vary. **Results:** The majority of respondents (64%) concluded that there is no standardization for HER2-low and ultra-low categories. For adjuvant therapy, 67% defined >5 mm (starting at T1bN0) as the threshold for indication. Neoadjuvant chemotherapy was recommended for tumors ≥2 cm by 68% of specialists. The HER2 genomic/prognosis test (DX) does not significantly alter management, according to 55% of votes. **Conclusions:** These expert consensus statements reflect current evidence and the majority views of the panel, supporting the management of HER2-positive breast cancer, with emphasis on multidisciplinary evaluation. Standardization of HER2-low and ultra-low categories and the clinical utility of HER2DX require further validation. These statements represent the majority opinion of Brazilian specialists and are intended to support clinical reasoning rather than define mandatory protocols or formal clinical practice guidelines.

KEYWORDS: breast cancer; HER2-positive; neoadjuvant chemotherapy; expert consensus statements; panel recommendations; consensus.

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INTRODUCTION

HER2-positive breast cancer represents a biologically aggressive subtype that has benefited from targeted therapies, significantly improving prognosis. Despite advances, uncertainties persist regarding optimal indications for upfront surgery, criteria for adjuvant therapy in small tumors, the role of genomic tools such as HER2DX, and the applicability of emerging HER2-low and ultra-low categories[1-15].

During the 2025 SIMIP, experts reviewed these controversies based on updated evidence and Brazilian real-world practice. This publication synthesizes key lecture messages, supporting evidence, audience voting results, and clinical implications, distinguishing majority views from the broader literature context.

METHODS

Plenary sessions were structured around four thematic axes:

1. Standardization of HER2-low and ultra-low categories;
2. Threshold for adjuvant therapy in early-stage HER2-positive disease;
3. Indication of neoadjuvant chemotherapy;
4. Impact of the HER2DX genomic test.

Each topic had a 10-minute evidence-based lecture, a 50-minute debate, and anonymous electronic voting. Results were tabulated and considered consensual at ≥75% agreement.

Panel composition, conflict-of-interest status, and literature basis are as described above.

Voting participation was optional per question; therefore, the number of respondents varied and was reported in each results table.

The questionnaire consisted of single-choice, forced-response items using binary or categorical response formats (not Likert scale).

The consensus process followed a structured methodology with anonymous electronic voting, but the number of respondents per question could vary.

STANDARDIZATION OF HER2-LOW AND ULTRA-LOW IN CLINICAL PRACTICE

Introduction

The HER2-low and ultra-low categories have emerged to identify tumors with low HER2 gene protein expression but without gene amplification. While HER2-low is conventionally defined by immunohistochemistry (IHC) scores of 1+ or 2+ without amplification confirmed by fluorescence *in situ* hybridization (FISH), the standardization of this classification — as well as the definition of HER2-ultra-low — remains under debate and evolution[1].

Evidence summary

- HER2-low is typically defined as tumors with IHC 1+ or IHC 2+ without HER2 gene amplification.
- HER2-ultra-low has been proposed to describe tumors with even lower expression levels (generally IHC 0 with minimal reactivity), but no universal consensus exists on specific criteria[2].
- Variability in IHC test interpretation and the absence of uniform criteria contribute to the lack of robust standardization in clinical practice[3].
- Clinical interest stems from trials such as DESTINY-Breast04 (demonstrating benefit of trastuzumab deruxtecan in HER2-low metastatic disease) and DESTINY-Breast06 (evaluating HER2-ultra-low disease)[4,5] (Table 1).

Practical recommendations (based on panel majority)

- Due to the lack of standardization (64% majority view), clinicians should acknowledge limitations in test interpretation.
- Therapeutic decisions should integrate comprehensive evaluation, including prognostic factors beyond HER2 classification, via multidisciplinary discussion.
- Updates from international clinical practice guidelines should be monitored, as this field is evolving[1,3].

Discussion

The panel majority (64%) highlighted the absence of standardization, aligning with challenges reported in the literature but falling short of consensus (≥75%). This view emphasizes caution in applying these categories without further validation, distinguishing it from minority opinions favoring early adoption.

THRESHOLD FOR ADJUVANT THERAPY IN EARLY-STAGE HER2-POSITIVE DISEASE

Introduction

Adjuvant therapy with trastuzumab has significantly altered the natural history of HER2-positive breast cancer, reducing recurrence risk and improving survival[6]. However, in very small tumors (particularly T1a, ≤5 mm), the excellent prognosis raises questions about the benefit versus toxicity.

Evidence summary

- Meta-analyses show a 30% reduction in recurrence with trastuzumab, particularly for tumors >1 cm[6].

Table 1. Panel voting results.

Response	Percentage (%)
Yes (standardization exists)	36
No (no standardization)	64

- In pT1aN0 tumors (≤5 mm), disease-free survival is ~87%, with high breast preservation rates[7].
- Risk factors such as high grade, HER2+++, and Ki-67 index ≥20% may warrant therapy even in small tumors[7,8].
- Trials such as HERA and BCIRG 006 confirm benefits in larger tumors, while APT and ATEMPT support less toxic regimens for ≤3 cm tumors[9-12] (Table 2).

Practical recommendations (based on panel majority)

- Adjuvant therapy is not routinely recommended for HER2+ T1aN0 (≤5 mm) tumors without unfavorable factors (e.g., high grade, high Ki-67 index, hormone receptor-negative); a 67% majority supports threshold at >5 mm.
- Trastuzumab-based regimens should be considered for ≥T1b tumors.
- Treatment is best individualized through multidisciplinary evaluation, factoring tumor biology, comorbidities, age, and preferences.

Discussion

The panel majority (67%) favored a >5 mm threshold, supporting de-escalation in small tumors, consistent with evidence but below consensus level. Statements on less intensive regimens (e.g., paclitaxel + trastuzumab) reflect literature context rather than direct voting endorsement.

INDICATION OF NEOADJUVANT CHEMOTHERAPY IN HER2-POSITIVE DISEASE

Introduction

Neoadjuvant chemotherapy (NAC) in early-stage HER2-positive disease balances systemic benefits with tumor reduction for surgery, response monitoring, and escalation if residual disease[13].

Evidence summary

- The European Society for Medical Oncology (ESMO) 2024 recommends NAC for tumors ≥2 cm and/or with positive axilla nodes[1].
- The APT trial supports upfront surgery + adjuvant paclitaxel + trastuzumab for ≤3 cm node-negative tumors (93% disease free survival at 7 years)[11].

Table 2. Panel voting results.

Threshold for adjuvant indication	Percentage (%)
>5 mm (T1bN0 and larger)	67
>10 mm (T1cN0 and larger)	20
>20 mm (T2N0 and larger)	9
All sizes (even ≤5 mm)	4

- The KATHERINE trial shows trastuzumab emtansine (T-DM1) benefit post-NAC residual disease[13].
- Benefits increase with tumor size per trials[9-11] (Table 3).

Practical Recommendations (Based on Panel Majority)

- Recommend NAC for HER2+ tumors ≥2 cm (T2) and/or clinically positive axilla (68% majority).
- For tumors <2 cm and cN0 (especially hormone receptor-positive, low-risk), consider upfront surgery + adjuvant therapy.
- A multidisciplinary team should be involved to enable tumor reduction, pathological complete response (pCR) assessment, T-DM1 escalation if residual disease is present, and reconstructive planning.

Discussion

The 68% majority for tumors ≥2 cm aligns with international clinical practice guidelines, though below consensus. This reflects balanced evidence on the risk-benefit profile, separate from minority views on lower thresholds.

IMPACT OF THE HER2DX TEST ON SURGICAL AND SYSTEMIC MANAGEMENT IN HER2-POSITIVE DISEASE

Introduction

The HER2DX test integrates 27 genes and clinical factors for prognostic assessment in stage I–III HER2-positive breast cancer, potentially guiding therapy[14,15].

Evidence summary

- The test predicts pCR, possibly aiding surgical selection, although with limited direct impact.
- HER2DX may inform systemic de-escalation in high-response cases.
- Once the test is not yet standard, it requires prospective validation (Table 4)[14].

Practical recommendations (based on panel majority)

- HER2DX does not currently warrant changes to surgical or systemic plans (55% majority); therefore, decision should rely on clinical and pathological criteria.

Table 3. Panel voting results.

Tumor size threshold for NAC	Percentage (%)
≥5 mm	0
≥1 cm	16
≥1.5 cm	16
≥2 cm	68

NAC: Neoadjuvant chemotherapy.

Table 4. Panel voting results.

Impact on management	Percentage (%)
Changes only surgical	2
Changes only systemic	34
Changes both	9
Does not change	55

- To use HER2DX as complementary prognostic tool via multidisciplinary integration.
- To await prospective studies for broader adoption.

Discussion

The majority opinions are aligned with literature trends but frequently did not reach the ≥75% consensus threshold. This highlights ongoing uncertainties and the need for further validation.

These statements represent the majority opinion of Brazilian specialists and are intended to guide clinical reasoning rather than define mandatory protocols.

Limitations

These recommendations reflect Brazilian expert perspectives and may not be generalizable internationally. No systematic review or health-economic assessment was conducted. Participation rates varied across voting questions.

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AUTHORS' CONTRIBUTION

ECP: Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. FB: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing. MM: Conceptualization, Methodology, Validation, Writing – review & editing. JTAN: Investigation, Methodology, Validation, Writing – review & editing. GMT: Investigation, Validation, Writing – review & editing. FB: Conceptualization, Methodology, Validation, Writing – review & editing. BBG: Data curation, Visualization, Writing – original draft, Writing – review & editing. DAB: Conceptualization, Methodology, Validation, Writing – review & editing. LFO: Investigation, Methodology, Validation, Writing – review & editing. SW: Investigation, Validation, Writing – review & editing. RA: Investigation, Validation, Writing – review & editing. FFP: Conceptualization, Methodology, Validation, Writing – review & editing. ATH: Supervision, Validation, Writing – review & editing.

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