

A definition for aggressive disease in patients with HER-2 negative metastatic breast cancer: an expert consensus of the Spanish Society of Medical Oncology (SEOM)

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Abstract

Purpose To converge on an expert opinion to define aggressive disease in patients with HER2-negative mBC using a modified Delphi methodology.

Methods A panel of 21 breast cancer experts from the Spanish Society of Medical Oncology agreed upon a survey which comprised 47 questions that were grouped into three sections: relevance for defining aggressive disease, aggressive disease criteria and therapeutic goals. Answers

were rated using a 9-point Likert scale of relevance or agreement.

Results Among the 88 oncologists that were invited to participate, 81 answered the first round (92%), 70 answered the second round (80%), and 67 answered the third round (76%) of the survey. There was strong agreement regarding the fact that identifying patients with aggressive disease needs to be adequately addressed to help practitioners to decide the best treatment options for patients with HER2-negative mBC. The factors that were considered to be strongly relevant to classifying patients with aggressive HER2-negative mBC were a high tumor burden, a disease-free interval of less than 12–24 months after surgery, the

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presence of progressive disease during adjuvant or neoadjuvant chemotherapy and having a triple-negative phenotype. The main therapeutic goals were controlling symptoms, improving quality of life and increasing the time to progression and overall survival.

Conclusions High tumor burden, time to recurrence after prior therapy and having a triple-negative phenotype were the prognostic factors for which the greatest consensus was found for identifying patients with aggressive HER2-negative mBC. Identifying patients with aggressive disease leads to different therapeutic approaches.

Keywords Metastatic breast cancer · HER2-negative · Aggressive disease · Consensus

Introduction

Metastatic breast cancer (mBC) remains an incurable disease in a large majority of affected patients. The median overall survival for HER2-positive mBC patients has almost tripled over the past decade [1]. Because the HER2 signal is constitutively activated in these cancers, strategies aimed at maintaining a blockade of the HER2 signaling cascade using several lines of treatment continue to improve survival [2]. Significant improvements have also been reported among endocrine-sensitive MBC patients [3], and the introduction of new agents that target endocrine resistance is fueling future improvements [4–6]. However, for HER2-negative MBC patients who are not candidates for endocrine therapy, chemotherapy is the only option. No particular chemotherapeutic agent or regimen has been able to provide consistent gains in survival in these patients.

The HER2-negative MBC population that is treated using chemotherapy under a wide range of scenarios includes patients with triple-negative tumors (TNBCs) and ER-positive tumors that have developed resistance to endocrine therapies in addition to aggressive situations in which a rapid response is needed. International clinical guidelines do not very precisely define these scenarios, which are referred to as “aggressive disease” or “visceral crisis”. Some well-known factors are associated with poor prognosis, including TNBC, liver metastases and short disease-free intervals [7, 8]. However, because “aggressive disease” is a multifactorial concept that encompasses different domains (e.g., visceral disease, tumor burden, histopathology, and disease progression), predicting when a HER2-negative mBC will rapidly progress and, therefore,

benefit from chemotherapy is not always a straightforward process in clinical practice.

For real-life issues that need to be addressed in routine clinical practice but for which there is not enough evidence, expert opinions can be assembled using a systematic approach aimed at generating a consensus. Our aim was to converge on an expert opinion for defining aggressive disease in patients with HER2-negative mBC using a modified Delphi survey.

Materials and methods

To develop a modified Delphi survey [9], a panel of 21 breast cancer experts from the Spanish Society of Medical Oncology (SEOM) was assembled.

This panel of experts reviewed the literature and discussed the structure of the survey and the wording of its questions and the procedure that would be used to rate the answers given in the survey. A plenary meeting and four teleconferences in smaller groups were held to determine the final content of the survey, which was then approved by the panel of experts. The survey was divided into the following three sections (for the full questionnaire, see the Supplementary data, Tables S1–S5): relevance to defining aggressive disease; aggressive disease criteria, including information on high tumor burden, time to progression criteria, histopathology, and patient clinical status; and therapeutic goals.

Eighty-eight Spanish oncologists who are dedicated to treating patients with breast cancer were invited to participate by e-mail. They were asked to complete the survey on a web site that was specifically designed to anonymously collect the answers. After the first round, the results were presented to the participants at ten regional meetings that were coordinated by the panel of experts. During these regional meetings, the oncologists had time to discuss their points of view and to suggest the rewording of questions that they considered to be ambiguous or unclear. At the end of these regional meetings, the participants again anonymously completed the second round of the survey at the survey web site.

After the second round of acquiring the answers, the panel of experts discussed the rewordings that were suggested in the regional meetings, and some of the questions were modified as a result of these suggestions. Then, the participants were asked to anonymously complete the third round of the survey, which included only the modified questions.

The answers were rated using a 9-point Likert scale. Some of the questions asked about the relevance of certain factors (1 = poorly relevant to 9 = strongly relevant), and others graded agreement with different statements

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(1 = fully disagree to 9 = fully agree) (for the full questionnaire, see the Supplementary data, Tables S1–S5). Using a cut-off point described elsewhere [10], consensus was determined to have been achieved when $\geq 75\%$ of the answers were located within three consecutive points of the Likert scale (Supplementary data, Fig. 1). In addition to the proportion of consensus and its localization on the 9-point Likert scale, the median was also estimated to determine the strength of the consensus [10].

Results

Among the 88 oncologists that were invited to participate, 81 answered the first round (92%), 70 answered the second round (80%) and 67 answered the third round (76%) of the survey. The results of each round are provided in the Supplementary data (Tables S1–S5). Below, we provide the final results of the last round of the survey.

Relevance to defining aggressive disease

The majority of the respondents indicated that it is strongly relevant to define aggressive disease in an HER2-negative mBC first-line chemotherapy setting (98.6% answered 7–9; median 8), and most of the respondents agreed that the

distinction of an aggressive profile guides strategies toward different therapeutic approaches in clinical practice (97.2% answered 7–9; median 8) (Table 1).

There was consensus in considering symptomatology (100% answered 7–9; median 8) and therapeutic goals (91.4% answered 7–9; median 7) as strongly relevant factors when deciding on a therapeutic strategy (Table 1). During the therapeutic decision-making process, the social and healthcare situation of the patient was considered to be a moderately relevant factor (78.6% answered 5–7; median 5), whereas no consensus was achieved regarding the relevance of patient preferences and opinions (72.9% answered 7–9; median 7) (Table 1).

Aggressive disease criteria

High tumor burden criteria

There was no consensus regarding whether the terms “high tumor burden” and “visceral crisis”, which are widely used in clinical guidelines, should be considered equivalent concepts (72.9% answered 1–3; median 3) [Table 2]. Answers also did not converge when participants were asked to determine the relevance of using a cut-off point of at least three affected organs when defining high tumor burden (62.8% answered 5–7; median 5) (Table 2). The

Table 1 Need for defining aggressive disease

	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c
	Fully disagree		Mostly disagree		Neither agree nor disagree		Mostly agree		Fully agree		
From a clinical perspective, it is relevant to make a distinction between patients with a more or less aggressive profile in a 1st line chemotherapy setting for HER2-negative mBC	–	–	–	–	–	1	13	26	30	98.6	8
In your clinical practice, identifying patients with aggressive breast cancer leads to a different therapeutic approach	–	–	–	–	1	1	14	30	24	97.2	8
	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c
	Poorly relevant		Slightly relevant		Moderately relevant		Fairly relevant		Strongly relevant		
In the 1st line setting for HER2-negative mBC with aggressive criteria, how relevant are the following factors to your therapeutic decisions?											
The overall clinical situation of the patient (regarding symptomatology)	–	–	–	–	–	–	19	29	22	100	8
The overall situation of the patient, regarding their social/ healthcare and family situation	1	1	5	7	27	10	18	1	–	78.6	5
The therapeutic goal that you have planned	–	–	–	–	4	2	31	21	12	91.4	7
The opinion/preference of the patient	–	–	–	3	7	9	24	17	10	72.9	7

^a Absolute frequencies. The absolute frequencies of the 3 consecutive responses that were most frequently answered are included in italics

^b Overall proportion of the 3 consecutive responses that were most frequently chosen. This proportion is written in a bold text whenever consensus was achieved ($\geq 75\%$ in 3 consecutive responses)

^c Median

Table 2 Tumor burden

	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c
	Fully disagree		Mostly disagree		Neither agree nor disagree		Mostly agree		Fully agree		
Do you think that the definitions of “high tumor burden” and “visceral crisis”, as provided in different national/international guidelines, are equivalent terms?	16	17	18	4	7	2	4	1	1	72.9	3
	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c
	Poorly relevant		Slightly relevant		Moderately relevant		Fairly relevant		Strongly relevant		
In your clinical practice, to define high tumor burden, how relevant is the fact that there are at least 3 affected organs?	–	4	11	6	24	5	15	5	–	62.8	5
	≤1/3 ^a		>1/3; <2/3 ^a		≥2/3 ^a		% ^b		M ^c		
Which threshold of liver affection do you consider to define high tumor burden?			47		21		69.1		>1/3 <2/3		
	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c
	Poorly relevant		Slightly relevant		Moderately relevant		Fairly relevant		Strongly relevant		
How relevant is the presence of ...											
Bilirubin >1.5 UNL	1	2	6	–	10	7	22	14	4	65.1	7
GOT, GPT >2.5 LNL	1	1	2	2	9	11	28	13	3	74.3	7
Altered prothrombin time	–	–	2	–	–	4	14	25	25	91.4	8
Severity of asthenia	–	1	8	5	17	13	21	4	–	73.8	6
Severity of anorexia	1	1	9	7	20	15	14	3	–	70.0	5
Pain at right hypochondrium	–	1	15	2	20	15	14	3	–	70.0	5
Multiple and bilateral pulmonary nodules	–	2	7	4	29	17	8	3	–	77.1	5
Lymphangitic carcinomatosis	–	–	–	–	1	–	–	20	49	98.6	9
Symptomatic pleural effusion	–	3	6	5	18	19	14	3	2	72.8	6
Severity of dyspnea	–	–	–	–	–	4	16	31	19	94.3	8
Severity of cough	1	5	8	4	21	20	8	3	–	94.3	5
Pleuritic pain	–	5	11	3	19	21	11	–	–	72.8	5
Multiple brain metastases, regardless of symptomatology	–	–	–	1	–	3	22	25	19	94.2	8
Leptomeningeal carcinomatosis, regardless of symptomatology	–	–	–	–	–	1	3	15	51	98.6	9
Significant symptomatology, regardless of the number of brain metastases	–	–	2	1	3	4	22	23	15	85.7	8
Bone events: fractures, bone collapses, antalgic radiotherapy or use of 3rd-step analgesics	–	3	6	3	12	9	23	6	3	67.7	6
Bone metastases and symptomatic hypercalcemia	1	1	2	3	9	13	24	9	5	68.6	7
Bone marrow infiltration with peripheral consequences	–	–	–	–	–	1	5	22	41	98.5	9
Symptomatic pericardial effusion	–	–	–	1	2	4	14	24	25	90	8
Symptomatic peritoneal carcinomatosis	–	–	1	–	2	4	25	28	10	90	8
Widespread skin disease and/or symptomatic skin disease	1	1	7	4	12	18	17	9	1	67.1	6
Ganglionic involvement with plexopathy (axillary plexus/brachial plexus)	–	–	11	7	13	12	14	10	3	55.7	6

^a Absolute frequencies. The absolute frequencies of the 3 consecutive responses that were most frequently answered are included in italics

^b Overall proportion of the 3 consecutive responses most frequently chosen. This proportion is written in bold text whenever consensus was achieved (≥75% in 3 consecutive responses)

^c Median

Table 3 Tumor burden actors: localization and associated symptomatology

Localization	Grade of relevance on a 9-point Likert scale (1 = poorly relevant; 9 = strongly relevant)		
	Strongly to fairly relevant (≥75% answered 7–9)	Fairly to moderately relevant (≥75% answered 5–7)	No consensus (<75% collapsing in three consecutive points)
Liver	Liver impairment Altered prothrombin time		Bilirubin >1.5 UNL GOT, GPT <2.5 LNL Severity of asthenia Severity of anorexia Pain at right hypochondrium
Pleuropulmonary	Lymphangitic carcinomatosis Severity of dyspnea	Multiple and bilateral pulmonary nodules Severity of cough	Symptomatic pleural effusion Pleuritic pain
Central nervous system	Multiple brain metastases Leptomeningeal carcinomatosis Clinically significant symptomatology		
Bone			Bone events: fractures, bone collapses, antalgic radiotherapy, use of 3rd-step analgesics Bone metastases and symptomatic hypercalcemia
Other localizations	Bone marrow infiltration with peripheral consequences Symptomatic pericardial effusion Symptomatic peritoneal carcinomatosis		Widespread and/or symptomatic skin disease Ganglionic involvement with plexopathy (axillary plexus/brachial plexus)

relevance the participants gave to different localizations and associated symptomatology when defining aggressive disease in this setting is summarized in Tables 2 and 3. When defining high tumor burden, the presence of the following characteristics/factors was considered to be strongly relevant (Tables 2 and 3): >1/3 liver infiltration, altered prothrombin time, pulmonary lymphangitic carcinomatosis, severity of dyspnea, multiple brain metastases (regardless of the symptomatology), leptomeningeal carcinomatosis (regardless of the symptomatology), brain metastases with significant symptomatology (but regardless of the number of lesions), bone marrow infiltration with decreased peripheral blood cells, symptomatic pericardial effusion, and symptomatic peritoneal carcinomatosis.

Time to progression criteria

The majority of the respondents indicated that a disease-free interval of <12 months after surgery (92.8% answered 7–9; median 8) and the presence of progressive disease during adjuvant or neoadjuvant chemotherapy (100% answered 7–9; median 9) were strongly relevant factors (Table 4). Similar consensus was also achieved for a disease-free interval of <24 months (81.4% answered 7–9;

median 7) (Table 4). The temporal criterion for rapid progression was defined as a time to clinical impairment of 2–3 months (14.5% answered 2 months; 82.6% answered 3 months) (Table 4).

Histopathology criteria

A triple-negative breast cancer (TNBC) phenotype was considered to be a strongly relevant factor by all respondents (100% answered 7–9; median 8) (Table 5). No consensus was achieved regarding the value of ki67 as a marker of aggressive disease in a biopsy or re-biopsy (68.5% answered 5–7; median 5) (Table 5).

Patient clinical status

More than 75% of the participants (89.1%) (Table 5) viewed a deterioration in performance status caused by a tumor that led to an ECOG 3 as the criterion for defining aggressive disease.

A wide variety of answers were given when the participants were asked to determine the relevance of being younger than 35 years old, and no consensus was achieved for this question (Table 5).

Table 4 Temporal criteria related to the progression of the disease

	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c				
	Poorly relevant		Slightly relevant		Moderately relevant		Fairly relevant		Strongly relevant						
How relevant is the presence of a disease-free interval (DFI) <24 months after surgery for the primary tumor?	–	1	1	1	6	12	30	15	4	81.4	7				
	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c				
	Fully disagree		Mostly disagree		Neither agree nor disagree		Mostly agree		Fully agree						
Do you agree that a DFI <12 months is preferable to a DFI <24 months in identifying patients with aggressive disease?	–	–	1	–	2	2	11	25	29	92.8	8				
	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c				
	Poorly relevant		Slightly relevant		Moderately relevant		Fairly relevant		Strongly relevant						
How relevant is the presence of progressive disease during adjuvant or neoadjuvant chemotherapy?	–	–	–	–	–	–	2	8	59	100	9				
							≤1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	≥6 ^a	Months	% ^b	M ^c
In your clinical practice, which temporal criteria do you consider when defining rapid progression (meaning clinical progression, ECOG = 2)							–	10	57	2	–	–		97.1	3

^a Absolute frequencies. The absolute frequencies of the 3 consecutive responses that were most frequently answered are included in italics
^b Overall proportion of the 3 consecutive responses most frequently given. This proportion is written in bold text whenever consensus was achieved (≥75% in 3 consecutive responses)
^c Median

Table 5 Aggressive disease-histopathological and patient clinical status criteria

Histopathological criteria	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c
	Poorly relevant		Slightly relevant		Moderately relevant		Fairly relevant		Strongly relevant		
In your clinical practice, to define high tumor burden, how relevant is having a triple-negative phenotype?	–	–	–	–	–	–	20	19	31	100	8
Ki67 levels as an indicator of aggressiveness in biopsy/re-biopsy in an advanced disease setting?	2	5	6	2	22	14	12	6	1	68.5	5
Patient clinical status	0 ^a	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	ECOG		% ^b		M ^c
In your clinical practice, at which ECOG do you consider a patient to have aggressive disease?	–	–	4	57	3	–				89.1	3
	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c
	Poorly relevant		Slightly relevant		Moderately relevant		Fairly relevant		Strongly relevant		
How relevant is the fact that a patient is <35 years old?	2	1	6	3	21	9	16	5	6	66.6	6

^a Absolute frequencies. The absolute frequencies of the 3 consecutive responses that were most frequently answered are included in italics
^b Overall proportion of the 3 consecutive responses most frequently given. This proportion is written in bold text whenever consensus was achieved (≥75% in 3 consecutive responses)
^c Median

Therapeutic goal

The therapeutic goal in patients with aggressive mBC was considered to be very different than the goals in other settings (92.5% answered 6–8; median 7) (Table 6). There was consensus in scoring the following therapeutic goals as strongly relevant in an aggressive mBC setting (Table 6): control of symptoms, improving quality of life, increasing overall survival, increasing time to progression, and overall objective response (complete response and partial response).

On the contrary, no consensus was achieved in grading the relevance of clinical benefit (stable disease >6 months) in this setting (Table 6).

Discussion

There was clear agreement that identifying patients with aggressive disease needs to be adequately addressed to determine the best treatment options for patients with HER2-negative mBC. The factors that were considered to be strongly relevant when classifying patients with aggressive HER2-negative mBC were high tumor burden, a disease-free interval of less than 12–24 months after surgery or the presence of progressive disease during adjuvant or neoadjuvant chemotherapy, and having a triple-negative phenotype. The relevance of “high tumor burden” was mainly driven by the following factors: >1/3 of the liver infiltrated, altered prothrombin time, lymphangitic

carcinomatosis, severity of dyspnea, multiple brain metastases (regardless of the symptomatology), meningeal carcinomatosis, brain metastases with significant symptomatology (regardless of the number of lesions), bone marrow infiltration with peripheral expression, symptomatic pericardial effusion, and symptomatic peritoneal carcinomatosis.

The respondents also agreed that the immediate therapeutic objective in patients with HER2-negative mBC and aggressive disease can be coincident with other scenarios, and that the main therapeutic goals should be the following: controlling symptoms, improving the quality of life and increasing the time to progression and overall survival. However, the clinical benefit ratio, which is usually employed as a parameter for efficacy in hormone receptor-positive mBC, was not considered to be relevant in this context.

A controversial issue when identifying patients with aggressive disease is defining high tumor burden and determining whether this term is different from visceral crisis. During the meetings, most of the oncologists agreed that these were different terms because high tumor burden is related to the number and volume of metastases, whereas visceral crisis usually refers to symptomatic visceral disease or, in cases of hepatic involvement, a relevant analytical abnormality. Therefore, high tumor burden is not always an indicator of aggressive disease, whereas visceral crisis nearly always leads to rapid progression. However, in this survey, there was no consensus in differentiating high tumor burden from visceral crisis, although a trend was

Table 6 Therapeutic goal

	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c
	Totally similar		Very similar		Neither similar nor different		Very different		Totally different		
Do you think that the immediate therapeutic goal in patients with aggressive disease is ^a :	–	–	–	1	–	10	39	13	4	92.5	7
In your clinical practice, how relevant is it...	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	% ^b	M ^c
	Poorly relevant		Slightly relevant		Moderately relevant		Fairly relevant		Strongly relevant		
...to achieve an objective response (CR or PR)?	–	–	–	1	5	4	32	15	10	85.1	7
...to achieve a clinical benefit (disease stabilization >6 months)?	–	3	4	2	10	8	22	15	2	68.1	7
...to control symptoms?	–	–	–	–	1	1	23	23	18	96.9	8
...to improve quality of life?	–	–	–	1	2	2	25	21	15	94.2	8
...to increase time to progression?	–	–	1	–	5	2	30	22	6	87.9	7
...to increase overall survival?	–	–	1	–	5	2	24	20	15	88.1	8

^a Absolute frequencies. The absolute frequencies of the 3 consecutive responses that were most frequently answered are included in italics
^b Overall proportion of the 3 consecutive responses most frequently given. This proportion is written in bold text whenever consensus was achieved (≥75% in 3 consecutive responses)
^c Median

observed in round 2 towards differentiating these terms (Table 2; Table S2).

When defining high tumor burden, there was no consensus for considering a threshold of at least three affected organs, which is opposed to what has been described in the literature [11]. The discussants argued that although the number of metastases is widely used to exclude aggressive disease in clinical trials, in clinical practice, the localization rather than the number of metastases is more important. When the respondents were asked to rate the different disease localizations, the involvement of the central nervous system was considered to be strongly relevant in terms of both the presence of metastases of tumors in addition to symptomatology. Liver disease, whenever it affects more than 1/3 of the liver, was also considered to be strongly relevant. Among the known markers of liver function, only altered prothrombin time was rated as strongly relevant.

There was consensus in defining TNBC as a strong prognostic indicator of aggressiveness because it has been widely described in the literature [7, 12–14]. No consensus was achieved regarding Ki-67, which is consistent with the lack of standardized methods, and the lack of a cut-off point to be used in clinical practice [15, 16]. Some authors have suggested a role for Ki-67 as a prognostic marker of early breast cancer [17]. Others have suggested that it could be useful for supporting treatment decision-making in HR-positive breast cancer (e.g., endocrine therapy vs chemotherapy) [18]. During the regional meetings, most of the oncologists stated that given the lack of clear recommendations regarding when and how to rate ki-67 levels, they do not routinely ask to use this biomarker in their clinical practice in metastatic patients. Also, this marker is not usually determined in a biopsy of a metastatic lesion.

Disease progression within 24 months post-treatment or at any time during adjuvant or neoadjuvant chemotherapy has been previously described as relevant prognostic indicator of aggressive disease [7, 14], and a consistently high consensus was achieved for both of these items in our survey.

The respondents answered that the therapeutic goals in patients with HER2-negative aggressive disease should not be substantially different from the goals in other settings. When rating the relevance of different therapeutic goals, controlling symptoms and improving the quality of life achieved the highest consensus. On the contrary, no consensus was achieved for clinical benefit, which is more frequently used in other clinical contexts, such as the maintenance of endocrine therapy.

One of the main limitations of our results is that they were obtained using a questionnaire in which different factors were addressed individually, whereas in clinical practice, all of the potential factors must be assessed

globally. Therefore, during the meetings, it was noted by most of the attendants that although some factors were scored as irrelevant in the questionnaire, they can potentially become relevant in clinical practice when they co-exist with other factors. Another limitation of using a questionnaire is the potential effect of the order of the questions. The panel of experts thought that this could have happened in the therapeutic goal section. Therefore, they decided to change the order of the questions in round 3 (i.e., “Do you think that the main therapeutic goal in patients with aggressive disease is totally different, very different...” was the last question of this section in rounds 1 and 2, but it was the first question of this section in round 3). As a result, the answers in round 3 moved slightly to the right side of the 9-point scale (9 = “totally different”). However, because the wording of this question was also changed (“main therapeutic goal” was substituted with “immediate therapeutic goal”), we could not determine whether the order of the questions was or was not meaningful.

To our knowledge, this is the first study that has aimed to define aggressive disease in patients with HER2-negative mBC based on clinical factors that can be easily assessed in daily clinical practice. Nevertheless, given the limitations that are inherent to an expert consensus survey, the factors that have been identified in this study should be validated in further appropriately designed prognostic studies.

In conclusion, high tumor burden, time until recurrence after prior therapy and having a triple-negative phenotype are the prognostic factors for which the greatest consensus was found in identifying patients with aggressive HER2-negative mBC. Identifying patients with aggressive disease leads to different therapeutic approaches, including a switch in the main therapeutic goals toward the control of symptoms and the improvement of quality of life without discarding overall response, time to progression and overall survival. Although this work suggests how the aggressiveness of this disease is identified in clinical practice, further prognostic research is needed to validate these findings.

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Compliance with ethical standards

Conflict of interest A. González has received honoraria for lectures and advisory boards from Roche; A. Lluch has received consultant fees from Novartis, Roche, Pfizer; E. Aba has received honoraria for advisory boards from Roche and Celgene, and honoraria for lectures

from Roche, Novartis, and Celgene; J. Albanell has received honoraria for advisory board from Roche; I. Álvarez has received honoraria for consultancy, lectures and clinical research from Roche, AstraZeneca, Novartis, and Lilly; F. Ayala has received honoraria for consultancy and advisory boards from Novartis and Celgene, and has received support for travel, accommodations and expenses from Roche and Celgene; A. Barnadas has received honoraria for advisory board from Pfizer, Astra Zeneca, and Roche, for speaker bureau from Pfizer, Astra Zeneca, Roche, and Novartis; J. Cortés has received consultancy fees from Roche/Genentech and Celgene, honoraria for lectures from Celgene, Novartis, Eisai, and Roche/Genentech, and has ownership interest in MedSIR; J. de la Haba has received honoraria for advisory boards from Roche, Pierre-Fabre, Genomics Health, Astra Zeneca, Celgene, Agendia, and GSK, and has received honoraria for lectures from Roche, Astra Zeneca, Agendia, Celgene, Pierre-Fabre, and Novartis; E. Martínez has received honoraria for lectures and advisory board from Roche; M. Muñoz has received consultancy fees from Roche; A. Redondo has received honoraria for advisory boards from Roche, and Astra Zeneca, honoraria for lectures from Roche, Astra Zeneca, and Pharmamar, and research grants from Roche; A. Llombart has received honoraria for advisory boards from Roche, Pfizer, Lilly, Novartis, and AstraZeneca, honoraria for lectures from Roche, Astra Zeneca, Novartis, Pfizer, and Celgene; A. Antón L. Calvo, E. Ciruelos, J.M. López-Vega, I. Peláez, Á. Rodríguez, C.A. Rodríguez, and A. Ruíz have declared no conflict of interest.

Ethical standards The manuscript does not contain clinical studies or patient data.

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