Editorial

TJ Tumori Journal

Tumori Journal
2022, Vol. 108(3) 196–203

DOI: 10.1177/03008916211062642
journals.sagepub.com/home/tmj
SAGE

Role and evaluation of pathologic response in early breast cancer specimens after neoadjuvant therapy: consensus statement

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Abstract

Pathologic evaluation of early breast cancer after neoadjuvant therapy is essential to provide prognostic information based on tumor response to treatment (pathologic complete response [pCR] or non-pCR) and to inform therapy decisions after surgery. To harmonize the pathologist's handling of surgical specimens after neoadjuvant therapy, a panel of experts in breast cancer convened to developed a consensus on six main topics: (1) definition of pCR, (2) required clinical information, (3) gross examination and sampling, (4) microscopic examination, (5) evaluation of lymph node status, and (6) staging of residual breast tumor. The resulting consensus statements reported in this document highlight the role of an accurate evaluation of tumor response and define the minimum requirements to standardize the assessment of breast cancer specimens after neoadjuvant therapy.

Keywords

Pathologic response, neoadjuvant therapy, breast cancer, consensus

Date received: 4 October 2021; revised: 6 November 2021; accepted: 8 November 2021

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Introduction

Preoperative (neoadjuvant) treatment strategies in breast cancer were originally implemented for patients with inoperable locally advanced disease.[1] In the past decade, neoadjuvant therapies (NAT) have been increasingly used also for patients with resectable early breast cancer (EBC).[2,3] The first goal of NAT is to reduce the tumour size, allowing for breast-conserving surgery (BCS) or nipple-sparing mastectomy in patients not eligible for BCS. Moreover, it can lead to a potential de-escalation of axillary surgery, with a reduction in morbidity. Additional advantages of this approach are the possibility to evaluate treatment efficacy at an early disease stage, providing prognostic information based on tumour response to NAT, and informing therapeutic decisions in patients with no or partial response.[4,5] The achievement of these clinical benefits requires accurate management of women with EBC, including (1) a complete biological characterization of the tumour on the diagnostic biopsy; (2) a multidisciplinary team for the choice of treatment in all women with newly diagnosed breast cancer; and (3) an accurate and standardized evaluation of pathologic response on the surgical specimen post-NAT. Pathologic complete response (pCR) after NAT is considered a valid endpoint for the approval of new drugs for the treatment of women with EBC, and several studies and meta-analyses have demonstrated the association between pCR and long-term clinical benefits at the individual level, especially for specific breast cancer subtypes.[6–10] Although recommendations have been developed to guide pathologic characterization of breast specimens in neoadjuvant clinical trials,[11] there is considerable variability in the definition and evaluation of pCR in clinical practice. Given the value of pCR as a surrogate endpoint for clinical outcomes, a standardized and reproducible approach is required to ensure its accurate assessment. This consensus aims to harmonize pathologists' procedures in the evaluation of surgical specimens after NAT, fostering the implementation of optimum diagnostic and therapeutic strategies for women with EBC eligible for presurgical systemic treatment.

Methods

The consensus statement was developed by a scientific board comprising an oncologist, a surgeon, and 10 pathologists with expertise in breast cancer. The consensus was focused on six topics: (1) definition of pCR; (2) clinical information required for the evaluation of breast cancer surgical specimens after NAT; (3) gross examination and sampling and (4) microscopic examination of breast cancer specimens after NAT; (5) evaluation of lymph node status after NAT; and (6) staging of residual breast tumour after NAT. These topics were discussed during a virtual meeting together with a review of available scientific evidence to define the minimum requirements for the pathologic evaluation of surgical breast cancer specimens from patients who received presurgical systemic treatment. The consensus document was reviewed and approved by the Associazione Italiana Oncologia Medica (AIOM) and Gruppo Italiano di studio della Patologia Mammaria–Società Italiana di Anatomia Patologica (GIPAM–SIAPEC/IAP) and it has been published on the AIOM website (Raccomandazioni & Position Paper).[12] The resulting consensus statements are reported here.

What is the definition of pCR?

The pathologic assessment of surgical samples after NAT represents the gold standard for the definition of pCR. Clinical evidence of complete regression does not imply the presence of pCR. A residual tumour is detected in approximately 30%–50% of patients with clinicoradiologic complete response and pCR is observed in approximately 20% of patients with clinicoradiologic suspicion of residual disease.[13,14] However, different definitions of pCR have been employed. The US Food and Drug Administration (FDA) recognizes two definitions of pCR for clinical trial design: (1) absence of invasive and in situ tumour in the surgical breast tissue specimen and all examined lymph nodes (ypT0/ypN0) after NAT; (2) absence of residual invasive tumour in the breast cancer specimens and all examined lymph nodes after NAT even if residual in situ tumour is detected in the breast (ypT0/Tis, ypN0).[6] The presence of residual in situ tumour has no impact on patient survival[15] (Box 1).

What information should be provided/available to the pathologist for an accurate evaluation of breast cancer surgical specimens after NAT?

Accurate evaluation of surgical samples after NAT requires pathologists to be provided with detailed clinical information. The pathologist must at least be aware the sample is a post-NAT surgical specimen and receive information regarding the site and size of the pretreatment tumour, especially in case of wide excision or mastectomy. However, this information is not always available at the time of gross evaluation of the specimen. Some clues that may lead the pathologist to suspect the patient received NAT include a diagnostic biopsy performed months before the surgery and a surgical specimen with no evidence of tumour. If not provided, the pathologist should ask for all the data that are required for the accurate handling of post-NAT specimens. The pre-NAT tumour site may be marked by clip if previously placed, or identified through the imaging scans performed before and after NAT. Furthermore, it would be useful to know the hormone receptor and HER2 status of the tumour at diagnosis to properly guide the specimen sampling. Lastly, it is useful to know whether the patient has been enrolled in a clinical

Box 1. Consensus: definition of pathologic complete response.

- 1.1: Pathologic complete response is evaluated on hematoxylin & eosin–stained sections from the surgical specimen after neoadjuvant therapy (immunohistochemical staining for cytokeratins can eventually be used in selected challenging cases).
- 1.2: Pathologic complete response is defined as the absence of invasive cancer in the breast and all sampled lymph nodes (ypT0/Tis, ypN0). The presence of residual in situ carcinoma does not exclude the definition of pCR.

Box 2. Consensus: information required for the evaluation of breast cancer surgical specimens after neoadjuvant therapy.

- 2.1: Surgical specimens post-neoadjuvant therapy must be sent to pathology laboratory with a form providing the clinical information that is required for an accurate sample evaluation:
  - ➢ Information about pre–neoadjuvant therapy tumour
    - Clinicoradiologic site
    - Clinicoradiologic size
    - Clinicoradiologic stage
    - Biological characteristics (hormone receptor and HER2 status)
  - ➢ Information about clinical response
    - Clinicoradiologic site and size of clinically suspected residual tumour, if any
  - ➢ Marker used for tumour bed identification (e.g. clips)
  - ➢ Type and duration of neoadjuvant therapy

trial that includes specific requirements for handling the surgical specimen[16,17] (Box 2).

How to perform gross examination and sampling of the surgical specimen after NAT

The surgical sample may be submitted fresh, vacuum-packed, or formalin-fixed. Because the ischemia time may affect the analysis of the prognostic and predictive biomarkers, it should be limited within 30 minutes according to international recommendations.[18] During the gross examination of post-NAT surgical samples, it is essential to identify the tumour bed. However, this area may be difficult to identify, especially in cases of significant clinical response and in dense breast tissue. Tumour bed usually consists of an irregular area of translucent, fibrous tissue with or without residual tumour nodules (Figure 1). Two main patterns of tumour response to therapy can be seen: concentric shrinkage and scattered pattern. Concentric shrinkage response is characterized by a progressive shrinkage of the tumour mass. This type of response mainly occurs in HER2-positive and triple-negative cancers. In this case, any potential residual tumour can usually be identified during the gross examination. Scattered pattern response is characterized by a reduction of tumour cellularity with small residual tumour foci scattered all over the tumour bed (Figure 2). This type of response is observed mainly in estrogen receptor (ER)–positive cancers. In this case, it can be more difficult to identify residual tumour foci during the gross examination.[16,17] Once the tumour bed has been identified, it is necessary to measure the surgical specimen, reporting the two largest dimensions of the tumour bed and of any residual tumours. In case of BCS, the distance between the tumour bed/residual tumour and the margins must be evaluated to guide any enlargement of margin excision.

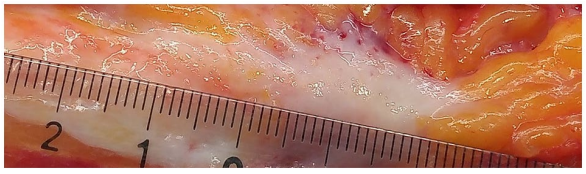

Figure 1. Tumour bed in mastectomy specimen after neoadjuvant therapy (gross photograph). Tumour bed appears as an irregular area of translucent, fibrous tissue. No residual tumour nodules can be grossly identified in this case.

Adjuvant therapy after NAT and surgery is justified, especially for HER-2–positive and triple-negative tumours, regardless of the size of the residual tumour, although the size does have an effect on the patient's prognosis.[19–22] Accurate sampling of the surgical specimen is therefore essential so as not to miss any residual tumour. For surgical resection following NAT, it is necessary to ink the margins, slice the specimen serially at 0.5 cm intervals, and sample the tumour bed, mapping the different sections with diagrams and photographs, to reconstruct the size of the residual tumour, if any, and of the tumour bed. However, there is a great variability concerning the sampling of these specimens in both clinical study protocols and clinical practice. The Breast International Group (BIG)–North American Breast Cancer Group (NABCG) guidelines recommend, for large tumours, five representative blocks for every 1–2 cm of the pretreatment tumour size, with a maximum of 25 blocks, whereas the FDA recommends a minimum of 1 block/cm of the pretreatment tumour size or at least 10 blocks, therefore a minimum of 10 blocks, and a maximum number based on the size of the primary lesion.[6,11] When available, the use of large sections allows a complete evaluation of the tumour bed,

Box 3. Consensus: Gross examination and sampling of the surgical specimen after neoadjuvant therapy.

- 3.1: Surgical specimens after neoadjuvant therapy can be submitted to the pathology laboratory fresh, vacuum-packed, or formalin-fixed. The examination of a fresh sample may facilitate the identification of the tumour bed.
- 3.2: For an accurate evaluation of the prognostic and predictive factors, the ischemia time should be noted and kept within 30 minutes.
- 3.3: In the case of surgical resection after neoadjuvant therapy, it is necessary to identify and examine the tumour bed, reporting the largest two dimensions and any residual tumour.
- 3.4: In the case of breast-conserving surgery, it is also necessary to measure the distance between the tumour bed/residual tumour and the resection margins. This assessment should be performed also during the microscopic examination, using different inks during sampling to allow correct histologic identification of the margins.
- 3.5: Tumour bed sampling must include five representative blocks for every 1–2 cm of the pretreatment tumour size, with a maximum of 25 blocks. In those centers where macro embedding cassettes are used, they may allow the sampling of the entire tumour bed. However, for small surgical resections, it is reasonable to sample the entire tumour bed.
- 3.6: It is necessary to map the tissue sections using photographs and diagrams to reconstruct the size of any residual tumour and of the tumour bed.
- 3.7: After the first sampling, in case of apparent pCR and especially for hormone-positive tumours, it is recommended to take additional samples, if the tumour bed has not been entirely sampled, or to perform additional cuts of available tissue blocks.

using the macroembedding cassettes that are typically employed for prostate cancer evaluation.[23] Any additional stainings can be performed by dissecting the area of interest on the block, thus embedding the area of interest in a conventional block, which allows stardard sectioning on a conventional slide (Box 3).

How to perform the microscopic examination of the surgical specimen after NAT

In residual breast cancers after NAT, evaluation of the histologic type and grade of the tumour using standard classifications and systems is not always feasible.[14,24] Indeed, the therapy itself can change the morphologic characteristics of the tumour cells, which usually show major cytologic modification and lower proliferative and mitotic activity (Figure 2). However, it may be useful to report tumour grade in some cases, particularly if a residual tumour is clearly identifiable as poorly responsive to treatment based on mitotic activity or proliferation index (Ki-67). More specifically, after NAT, a high Ki-67 index and the presence of lymphovascular invasion are important markers of aggressive biological behavior.[25,26] Moreover, when the standard grading system cannot be applied because the residual tumour is very small and no 10 high-power fields can be evaluated for the mitotic count, it may be useful to report the nuclear grade. Tumour cellularity provides valuable information for the staging of the residual tumour and it should be evaluated as a percentage of the fibrous tissue area on each section of the tumour bed, or compared to the cellularity of diagnostic biopsy, where available[16,27] (Box 4).

The ER and progesterone receptor (PgR) status, the HER2 status, and the Ki-67 of the residual tumour can be different from those observed in the pretherapy biopsy.[28–32] Indeed, only moderate agreement has been reported considering tumour (surrogate) molecular subtypes.[33] These discordances may be related to technical factors, to the biological heterogeneity of the tumour, or to the therapy itself. There is no unanimous consensus and uniform practice regarding biomarkers retesting on residual tumour after NAT.[34] Reassessment is recommended in pretreatment triple-negative carcinoma.[11,35] The conversion to hormone receptor– and/or HER2-positive status in this tumour subtype can affect adjuvant therapy decision (i.e. switch to targeted therapy) and has been associated with improved survival.[34,36,37] Moreover, changes in the expression of PgR and Ki-67 after NAT have been shown to provide no predictive but prognostic information that may aid in recurrence risk stratification.[19,29] Although it may not be necessary for triple-positive tumours, reassessment of these biological characteristics after NAT can be useful to better

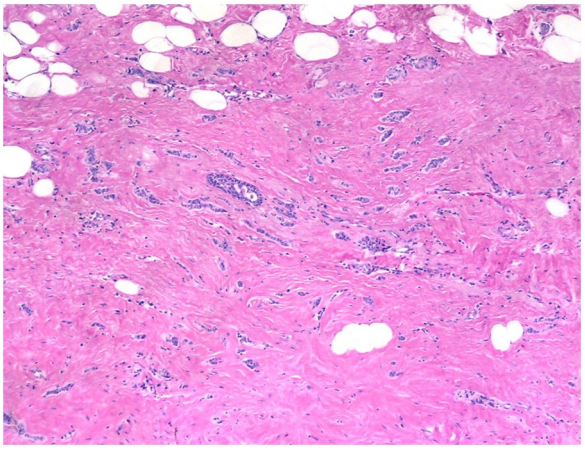

Figure 2. Hematoxylin & eosin–stained slide of tumour bed from mastectomy specimen after neoadjuvant therapy (micrograph; original magnification 100×). Small residual foci of tumour can be seen scattered in the fibrous tissue of tumour bed. In this case, tumour shows a partial response characterized by reduced cellularity (scattered pattern).

Box 4. Consensus: Microscopic examination of the surgical specimen after neoadjuvant therapy.

- 4.1: The microscopic analysis of specimens after neoadjuvant therapy must include the evaluation of:
  - ➢ residual tumour size
  - ➢ residual tumour cellularity
  - ➢ margins in breast-conserving surgery
  - ➢ the presence of lymphovascular invasion
- 4.2: It is mandatory to reassess the biological parameters (ER, PgR, HER2, Ki-67) in non-triple-positive tumours; this evaluation is also appropriate in all cases.
- 4.3: Assessment of tumour grade may be performed whenever possible.

understand the evolution of the disease, whether and how the tumour responds to the therapies, and consequently, to guide adjuvant therapy decision-making (Box 4).

How to evaluate lymph node status after NAT

The pathologic assessment of lymph nodes after NAT is similar to that performed for non–post-neoadjuvant surgical specimens, though their identification may be more difficult due to their generally smaller size. The presence of fibrosis could make more difficult the macroscopic and histologic identification of metastases and consequently all lymph nodes must be thoroughly evaluated (Figure 3). The most recent guidelines suggest that axillary dissection can be avoided in patients with clinically positive lymph nodes at diagnosis (cN1/2) reverting to cN0 after NAT and achieving a negative sentinel lymph node (SLN) status.[38,39] In the neoadjuvant setting, multiple (possibly 3 or more) SLNs should be removed and examined, together with any clipped lymph node in cases when a clip has been placed in the pretreatment metastatic node.[38,39] It is necessary to perform an extensive evaluation of these lymph nodes after fixation and embedding or on frozen sections during the intraoperative examination, according to the procedures for non–post-NAT SLNs. Also for non-SLNs, it is recommended to sample the entire lymph node, with slices cut at 2-mm intervals to ensure detection of all macrometastases. The report should indicate the number of positive lymph nodes, the size of the largest metastasis, and the presence of micrometastases and isolated tumour cells (ITC), as they represent negative prognostic factors.[40,41] Furthermore, in the neoadjuvant setting, the presence of micrometastases or ITC excludes the diagnosis of pCR.[42] Consequently, the recommendations are (1) to not use molecular assay (e.g. one-step nucleic acid amplification) to analyze lymph nodes in the neoadjuvant setting, especially for SLNs, as these methods are unable to detect ITCs[43]; and (2) to restrict the intraoperative analysis of SLNs to centers with established expertise in this diagnostic approach or to specific cases where clinical and surgical management is difficult (Box 5).[16] Studies are ongoing to establish the possibility of de-escalating axillary treatment also for patients with micrometastases or ITC after NAT, and for whom axillary dissection or radiotherapy is still performed.[44,45]

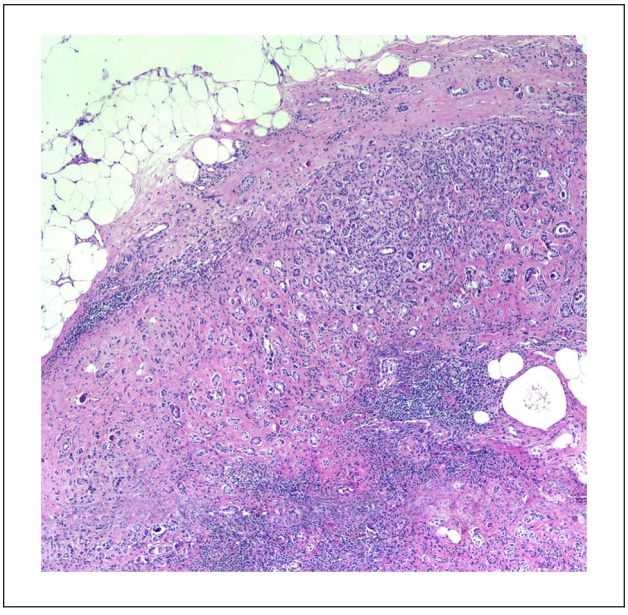

Figure 3. Hematoxylin & eosin–stained slide of metastatic axillary lymph node after neoadjuvant therapy (micrograph; original magnification 100×). Lymph node tissue is almost entirely replaced by metastatic breast cancer with extracapsular extension, calcifications, and focal fibrosis.

How to stage residual tumour after NAT and what information has to be included in the final report

After NAT, it is possible to achieve a pCR, i.e. absence of residual tumour in the surgical specimen. In the case of partial response, the residual tumour may show a reduced size as compared to the pretreatment tumour or reduced cellularity with multiple tumour foci scattered throughout the tumour bed.[16] Different systems have been proposed for staging residual tumour after NAT.[17] In the TNM staging system, the size of the largest continuous focus is used and, if multiple residual foci are observed, the suffix "m" is added to indicate the presence of a multifocal tumour.[42] This system, however, does not provide precise information on the amount of residual tumour, and therefore does not allow to evaluate the tumour response to therapy. The BIG-NABCG guidelines recommend adding to TNM staging data regarding the extent of the tumour bed still

Box 5. Consensus: evaluation of lymph node status after neoadjuvant therapy.

- 5.1: In the neoadjuvant setting, multiple sentinel nodes must be removed.
- 5.2: All removed lymph nodes must be submitted for histologic analysis.
- 5.3: All sentinel lymph nodes (and any clipped lymph nodes) must be extensively examined; the analysis should preferably be performed after formalin fixation and paraffin embedding of the sample. Intraoperative analysis on frozen sections should be considered based on the center experience or restricted to cases of difficult clinical and surgical management.
- 5.4: During the gross examination, all sentinel lymph nodes should be sliced perpendicularly to the longest axis, with 2-mm-thick sections. After paraffin embedding, each section of the lymph node will be serially sliced according to the standard procedure for the analysis of sentinel lymph nodes.
- 5.5: Non-sentinel nodes must be entirely submitted for histological analysis sectioned at 2-mm intervals.
- 5.6: Microscopic examination of the lymph nodes after neoadjuvant therapy must include:
  - ➢ The number of positive lymph nodes
  - ➢ The size of the largest metastasis
  - ➢ The presence of micrometastases and ITC
  - ➢ Any extracapsular extension of the metastases
  - ➢ It is useful to report the presence of fibrosis in the examined lymph nodes.
- 5.7: Molecular assays are not recommended for the analysis of sentinel lymph nodes in the post-neoadjuvant setting.
- 5.8: The presence of ITC (pN0i+) in the lymph nodes after neoadjuvant therapy excludes the diagnosis of pCR.

Box 6. Consensus: staging of a residual tumour after neoadjuvant therapy.

- 6.1: For the staging of residual breast cancer following neoadjuvant therapy, in addition to the AJCC/pTNM system, whenever possible, it is advisable to report the macro- or microscopic evaluation of the two dimensions of the area including all the residual tumour foci.
- 6.2: It is advisable to include in the pathology report all the characteristics required to calculate the RCB (the two dimensions of the tumour bed, residual tumour cellularity as a percentage of the area of the tumour bed, the percentage of in situ cancer, the number of positive lymph nodes, and the size of the largest lymph node metastasis), and, if possible, include also the RCB class and value. Other staging systems (e.g. CPS+EG, Pinder) may be considered.
- 6.3: Given the complexity and the heterogeneity of residual tumour patterns, it is advisable to share this information within a multidisciplinary team.

occupied by residual tumour.[11] Alternatively, the residual cancer burden (RCB) can be used. RCB is a prognostic tool that is also useful to inform adjuvant therapy decision-making.[27,46] RCB combines pathologic parameters, including the largest (two) dimensions of the tumour bed, the residual tumour cellularity, the percentage of in situ cancer, the number of positive lymph nodes, and the size of the largest lymph node metastasis to calculate a continuous index and identify risk classes based on different RCB thresholds (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3). The prognostic value of RCB varies for the different breast cancer subtypes and it is particularly robust for triple-negative and HER2+ tumours. Although for patients with TNBC, the difference between pCR and minimum residual disease does not appear to be particularly significant, for women with HER2+ disease, all the different RCB classes have a considerable prognostic impact.[46] There have been further attempts to improve the prognostic value of RCB by integrating it with the Ki-67 index, tumour grading, and receptor status.[47] The RCB system, however, already provides considerable prognostic information and does not require additional information that, though statistically significant, does not appear to be clinically useful. CPS+EG is another staging system used in clinical trials of adjuvant therapy in case of residual tumour after NAT.[48–50] The CPS+EG score combines pretreatment clinical and posttreatment pathologic stage (CPS), ER status (E), and grade (G) to estimate the risk of recurrence and stratify patients treated with NAT based on their outcomes, representing a valuable prognostic tool in hormone receptor- positive/HER2– tumours after NAT[51–54] (Box 6).

Conclusions

NAT has been increasingly used in the treatment of women with EBC and multidisciplinary teamwork is fundamental to reap the full benefit from this approach. In this setting, pathologists play important roles. The accurate evaluation of diagnostic core biopsies with a complete biological characterization of the tumour is important to determine patients' eligibility for NAT and the treatment regimen itself. The assessment of pCR or residual tumour (non-pCR cases) at surgery provides crucial prognostic and predictive information to guide adjuvant therapy decisions and patient management after NAT. However, the variability of pCR definitions and protocols for evaluation of surgical specimens may hamper the evaluation of NAT efficacy and ultimately of patient outcomes. This consensus reviews fundamental points of the pathologic analysis of breast cancer surgical specimens after NAT with the proposal of a

standardized and common approach amenable to be implemented in the pathology practice. This standardized procedure may improve the reproducibility of the pathology report, serving as a backbone to maximize the benefit of NAT and to refine the role of neoadjuvant strategy in the individualization of treatment for women with EBC.

Acknowledgements

The authors thank Elena Di Blasi for assistance with the figures and GIPAM–SIAPEC/IAP leadership (Isabella Castellano and Anna Sapino) and AIOM leadership (Lucia Del Mastro, Nicla La Verde, Giordano Beretta, Saverio Cinieri) for reviewing and endorsing the consensus.

Declaration of conflicting interests

E.G.-R. has received honoraria and/or advisory fees and/or research funding from AstraZeneca, Exact Sciences, Novartis, Roche, and ThermoFisher. G.V. has received honoraria for consulting, advisory role, speakers' bureau, travel, accommodation, expenses, and/or research funding from MSD Oncology, Pfizer, Dako, Roche/Genetech, Astellas Pharma, Novartis, Bayer, Daiichi Sankyo, Menarini, Ventana Medical Systems Dako/Agilent Technologies, Cepheid, and Celgene. The other authors have no conflicts of interest to declare.

Funding

This work was partially supported by the Italian Ministry of Health with Ricerca Corrente and 5x1000 funds.

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