Letter to the Editor

Clinical considerations for estrogen receptor-negative/progesterone receptor-positive/HER2-negative ($ER^-PR^+HER2^-$) breast cancer

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Breast cancer remains the most common cancer in women, with over 2.3 million new cases estimated in 2020 and an increasing incidence is anticipated with more than 3 million new cases/year in 2040, according to Globocan (1). $ER^-PR^+HER2^-$, one of the most controversial subtypes, makes up to 1% of all breast cancers (2).

Several theories have been proposed to explain how progesterone expression could occur irrespective of estrogen gene expression, with no consensus being reached. However, it should be highlighted that the majority of ER^-PR^+ is equivocal, given pre-analytical (e.g., tissue preparation, staining) and analytical (e.g., cutoff positivity, observer variability) (2,3). At this stage, reclassification with further immunohistochemistry (IHC) evaluation might be possible for the majority of cases as summarized on *Table 1* (4-12). On the other hand, these tumors might behave differently, affecting women younger than 50 years, sharing characteristics that resemble triple negative breast cancer such as poorly differentiated nuclear grade, high ki67 and visceral involvement as well as poor survival outcomes (2). From a treatment standpoint, pathological complete response to neoadjuvant treatment with anthracycline plus taxane-containing regimens could be up to 40% and hormonal therapy does not seem to work uniformly (2,11,13). On the other hand, recent evidence suggests that this subtype may be rare rather than equivocal (14). Therefore, given the lack of consensus and biological behavior of confirmed $ER^-PR^+HER2^-$, genomic subtyping might help clinicians in clinical practice/better characterize this subgroup.

Genomic evaluation might refine $ER^-PR^+HER2^-$ IHC subtyping. Variable levels of ESR1 could be found on ER^-PR^+ tumors, likely representing a luminal subset, favoring reclassification as ER^+, once on true ER^-PR^+, ESR1 expression should be absent or significantly lower than ER^+ tumors (11,15). Hefti and cols in 2013 demonstrated that PR expression in ER^- tumors is exceedingly rare but confirmed in 1% (45/4,111). On the same study, although a poor concordance was found between medical records (MR) and messenger-RNA (mRNA) expression or IHC by tissue microarray (TMA) on two datasets, the ER^-PR^+ subtype remained on the Gene Expression Microarray [MR 62/1,752 (4%) *vs.* mRNA 36/1,742 (2%)] and Nurses Health Study [MR 26/2,011 (1%) *vs.* IHC/TMA 71/2,011 (4%)] datasets. Gene expression might also contribute to reclassify other subtypes into ER^-PR^+ and vice-versa, once a few ER^-PR^- cases could be reclassified ER^-PR^+ (14).

Intrinsic subtyping could offer some guidance for systemic treatment in $ER^-PR^+HER2^-$ confirmed cases. Yu *et al.* in 2015 reported similar rates of basal like phenotype (most frequent, followed by luminal A) amongst ER^-PR^+ tumors, between two cohorts using PAM50 subtyping.

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Table 1 Examples of studies using revaluation techniques in ER^-PR^+ breast cancer

Author/ year	Assays	Sample size	Pre revaluation	After revaluation					
			ER^-PR^+ (%)	ER^-PR^- (%)	ER^+ (%)	ER^+PR^- (%)	ER^+PR^+ (%)	$HER2^+$ (%)	Unchanged ER^-PR^+ (%)	Revisited ER^-PR^+ (%)
Sarrif, 1981, (4)	Dextran coated charcoal	500	28 (5.60)	–	18 (64.29)	–	–	–	6 (21.42)	6 (1.2)
De Maeyer, 2008, (5)	IHC	2,013	32 (1.59)	5 (15.62)	27 (84.37)	–	27 (84.38)	7[&] (21.87)	0 (0)	0 (0)
Viale, 2007, (6)	Extraction assays; IHC	8,010/ 6,291	101 (1.26)	–	–	–	–	–	8 (7.92)	8 (0.13)
Cserni, 2011, (7)	IHC	6,587	182* (2.76)	31 (17.03)	126 (69.23)	2 (1.10)	124 (68.13)	–	1 (0.55)	1 (0.02)
Maleki, 2012, (8)	IHC	2,432	43 (1.77)	15 (34.88)	28 (65.12)	4. (9.30)	24 (55.81)	–	1 (2.33)	1 (0.04)
Ahmed, 2016, (9)	IHC	8,315	267* (3.21)	114 (42.70)	61 (22.85)	6 (2.25)	55 (20.60)	172 (64.41)	33 (12.36)	33 (0.40)
Kuroda, 2019, (10)	IHC	9,844	27 (0.27)	8 (29.63)	12 (44.44)	–	12 (44.44)	–	7 (25.93)	7 (0.07)
Kunc, 2022, (11)	IHC	135	135 (100.00)	–	47 (34.81)	–	–	21 (7.87)	55 (40.74)	55 (40.74)
Nardi, 2021, (12)	IHC	1,188	30 (2.53)	27 (90.00)	3.00 (10.00)	–	–	–	0 (0)	0 (0)
Total	–	31,014	845 (2.15)	195 (23.07)	300 (35.50)	12 (1.42)	242 (28.63)	200 (23.66)	111 (13.13)	111 (0.35)

*, revaluated cases; [&], fish not informed. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factors receptor; IHC, immunohistochemistry; IHC, immunohistochemistry; mRNA, messenger-RNA.

Additionally, a significant association of trefoil factor 1 (TFF1) and growth regulation by estrogen in breast cancer 1 with luminal subtype and cytokeratin 5 (CK5) and endothelial growth factor receptor (EGFR) with basal like was found. When this proposed IHC was validated on 64 cases of $ER^-PR^+HER2^-$ from the Fudan University Shanghai Cancer Center, more than 60% were basal like and associated with the worst prognosis, followed by 23% luminal subtype with a better prognosis. This "three-marker" was also proven to be an independent prognostic for recurrence and predicted endocrine sensitivity as PAM50 (16). Similar rates of basal-like and luminal subtypes were reported by other authors using PAM50 and other subtypes includes HER2 enriched (~5–10%) and normal (~5%) (13,14,16,17). The studies that evaluated intrinsic subtypes are summarized on *Table 2*. Moreover, unique genes were reported to be associated with this subtype, some related to regulation of estrogen signaling and other to amino acid and fatty acid degradation, but with currently unknown clinical implication (13). On the other hand, specific genomic signatures are associated with chemotherapy and hormonal sensitivity on this tumor subtype, favoring the consideration in selected cases (3,16).

For this tumour subtype, chemotherapy seems to be the preferred treatment, once the limited available evidence from a metanalysis published in 2011 reported absence of benefit from tamoxifen in those tumours (15). It is still important to search the best definition, not only prognostic but also predictive of response, mainly due to the emergence of new generations of systemic treatment (hormonal, target, and immuno-therapies).

Therefore, we propose a prospective study of adjuvant hormone therapy involving a two-step assessment as shown in *Figure 1* could be considered to answer the adjuvant questions. During screening the tumours would be evaluated in two steps evaluation, in (I) the subtype must be confirmed by standard IHC, followed by (II) intrinsic subtyping and by IHC assessment of specific markers;

Table 2 Summary of studies that reported intrinsic subtyping of ER⁻PR⁺ breast cancer

Author/year	Assays	Sample size	ER⁻PR⁺ subjects (%)	Revaluated						
				TNBC/ basal	Luminal	Luminal A	Luminal B	Normal	HER2	ER+
Itoh, 2014, (3)	Molecular subtyping, PAM 50 classifier	501	20 (3.99)	13 (65.00)	4 (20.0)	3 (15.00)	1 (5.00)	1 (5.00)	2 (10.00)	5 (25.00)
Yu, cohort 3, 2015, (16)	PAM50 classifier	837	36 (4.30)	20 (55.56)	12 (33.33)	6 (16.67)	6 (16.67)	1 (2.78)	3 (8.33)	–
Yu, cohort 4, 2015, (16)	PAM50 classifier	483	17 (3.52)	11 (64.71)	4 (23.53)	3 (17.65)	1 (5.88)	1 (5.88)	1 (5.88)	–
Schroth, 2016, (13)	PAM50; TCGS	989	15 (1.52)	8 (53.33)	5 (33.33)	4 (26.67)	1 (6.67)	1 (6.67)	1 (6.67)	–
Li, 2020, (17)	PAM50	1,412	15 (1.06)	9 (60.00)	0 (0)	0 (0)	0 (0)	4 (26.67)	2 (13.33)	0 (0)
Kunc, 2022, (11)	IHC, mRNA	135	135 (100.00)	–	–	–	–	–	42 (31.11)	47 (34.81)
Total	–	4,357	238 (5.46)	61 (25.63)	25 (10.50)	16 (6.72)	9 (3.78)	8 (3.36)	51 (21.42)	52 (21.84)

ER, estrogen receptor; PR, progesterone receptor; TNBC, triple negative breast cancer; HER2, human epidermal growth factors receptor.

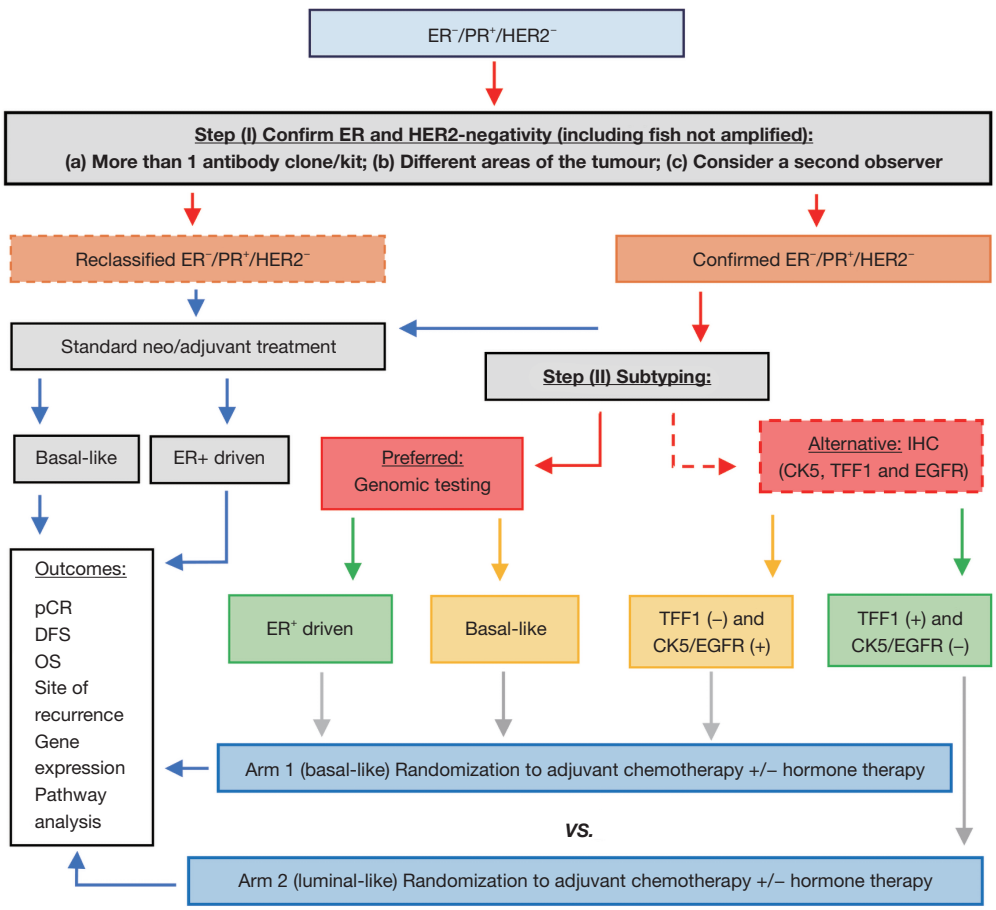

Figure 1 Clinical trial approach consideration for (ER⁻PR⁺HER2⁻) breast cancer in clinical practice. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factors receptor; IHC, immunohistochemistry; CK, cytokeratin; TFF, trefoil factor; EGFR, endothelial growth factor receptor; pCR, pathological complete response; DFS, disease-free survival; OS, overall survival.

CK5, TFF1 and EGFR, being than assigned to receive chemotherapy +/– hormonal therapy controlled by the phenotype as shown on *Figure 1*. Although this proposal suggests a potential approach to answer a challenging question, further refinement might be required to this clinical trial design once limitations could be expected, such as potentially slow accrual.

Finally, given the lack of consensus, we would encourage decisions regarding systemic treatment to be taken with the support of a multidisciplinary team discussion with patient centred decisions (18).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved.

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