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DOI: <https://doi.org/10.1016/j.pathol.2020.12.001>

Re: INSM1 is a novel prognostic neuroendocrine marker for luminal B breast cancer: author reply

Sir,

This letter is in response to the questions raised by Kawasaki *et al.* regarding our recently published paper on INSM1 as a

novel prognostic neuroendocrine (NE) marker in breast cancer.¹ We appreciate their comments on our study and thank them for sharing their experience.² One question that they raised was about the proportion and morphology of breast cancers showing INSM1+/chromogranin (CG)–/synaptophysin (SYN)–. The other point was on the morphological findings of invasive cancers showing CD56 reactivity exclusively.

In our INSM1 study, in total there were 1375 cases with complete staining results on INSM1, CG and SYN. Among them, 1159 (84.3%) cases expressed neither markers, 72 (5.2%) cases showed co-expression of INSM1 with either CG and/or SYN, and 121 (8.8%) cases expressed only CG and/or SYN with no INSM1. There were 23 (1.7%) cases showing INSM1 expression exclusively (CG–/SYN–/INSM1+, INSM only positive). In our report, the INSM1+ cases with NE morphology in the illustration also expressed CG and SYN, thus were classical neuroendocrine tumors (NET). For the 23 INSM1 only positive cases, the majority belonged to the luminal subtypes (11 luminal A and 10 luminal B cases; 91.3%). A high proportion of them were of low grade and invasive breast carcinoma of no special type (IBC-NST). Despite being mostly IBC-NST, NE morphology (clear cell, spindle and carcinoid morphology) was observed in four INSM1 positive only cases. Two of these were low grade with predominant NE morphology which were categorised as NET. The other two showed 50–70% NE morphology and were classified as mixed IBC-NST with NET. Details of the INSM1 only positive cases are shown in Table 1. We agreed with Kawasaki *et al.* as reported in their recent study³ that INSM1 expression indeed highlighted additional NE cases. Given its similar clinicopathological association as CG and SYN, it could be a potential useful diagnostic marker for NE features in breast cancer.

Regarding CD56, 54 (4.0%) of 1351 cases showed exclusive expression of this marker. Among them, NE morphology was found in eight cases. Of these, five cases showed predominant NE morphology and were classified as NET; the remaining three cases were mixed IBC-NST with NET. However, a lower proportion of them (35 cases, 64.8%) were of luminal subtypes. Although CD56 could also

Table 1 Detailed features on cases showing INSM1+/SYN–/CG– (n=23)

Features	n (%)	Remarks
Diagnosis		
IBC-NST	17 (73.9)	
IDC/ILC	2 (8.7)	
Mixed IBC-NST and NET	2 (8.7)	
NET	2 (8.7)	<ul style="list-style-type: none"> • Grade 2 case with 20% spindle and 30% carcinoid morphology • Grade 1 case with 70% carcinoid morphology • Grade 1 case with 50% clear cell and 50% carcinoid morphology • Grade 1 case with 100% carcinoid morphology
Grade		
1	10 (43.5)	
2	5 (21.7)	
3	8 (34.8)	
Luminal		
Luminal	21 (91.3)	<ul style="list-style-type: none"> • 11 luminal A and 10 luminal B
Non-luminal	2 (8.7)	<ul style="list-style-type: none"> • 1 triple negative breast cancer and 1 HER2-overexpressing

IBC-NST, invasive breast carcinoma of no special type; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

highlight additional NE cases, these CD56 only positive cases appeared to have distinct features from typical NE cases. We have recently compared the clinicopathological features and outcome of breast cancer based on the level of CD56, CG and SYN.⁴ CD56 showed a positive correlation with CK14 but not CG and SYN. Further comparison was carried out between cases with SYN/CG+ CD56+/- and CG-/SYN-/CD56+ (CD56 only positive) cases. We found that CD56 only positive cases did not show typical NE associations; conversely, they were associated with younger patient ages, non-luminal subtypes and high levels of expression of basal markers (EGFR, p63, CK5/6 and CK14). In addition, CD56 only positive cases showed more similar disease free survival to IBC without any NE features, than cases with SYN/CG+ CD56+/- expression. It appeared that CD56 only positive cases behaved more like IBC without any NE features, differing from the typical NE cases. Further studies are required to confirm the relevance of CD56 as a NE marker in breast cancer.

NE differentiation in breast cancer has been under-diagnosed in routine clinical settings. Apart from not being routinely tested, some cases can still be missed by the common NE markers, namely SYN and CG. There is an unmet need for NE marker development in breast cancers. On the basis of current data, as a NE marker, INSM1 appears to hold better promise than CD56.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

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