

Integrin beta-6 expression in Japanese patients with NSCLC

Naoyuki Oka,^{1,2} Yukihiro Yoshida,² Hitomi Okuma,³ Toru Imai,³ Christopher Thor,⁴ Polly Cronin,⁴ Kazuki Sudo,³ Yasushi Yatabe¹

¹Department of Diagnostic Pathology, National Cancer Center Hospital, Tokyo, Japan; ²Department of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan; ³Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; ⁴Department of Translational Medicine, Bothell, WA, USA

Conclusions

- Most tumor samples (90%) from Japanese patients with nonsquamous non-small cell lung cancer (NSCLC) had IB6-high expression, which was consistent with prior results from the US study (81%)¹
- Limitations of this study include a small sample size and the need for further evaluation of tumor microarray (TMA)–based screening approaches
 - However, results were consistent across TMA and tissue biopsy samples
- Prevalence of IB6-high expression status was generally consistent across disease stage, PD-L1 status, and actionable genomic alteration (AGA) status
- RNA sequencing and immunohistochemistry (IHC) for detection of IB6 showed a slight positive correlation, although possibly confounded by clustering of IHC values at 100% positivity
- Further analysis is required to definitively characterize any potential relationships between IB6 expression and AGA status



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Correspondence: Naoyuki Oka, nao2@ncc.go.jp

Background

- IB6 is a transmembrane receptor involved in wound healing and tissue remodeling; malignant cells may exploit these roles of IB6 to promote invasiveness, epithelial-mesenchymal transition, and anoikis resistance²⁻⁵
- IB6 expression is low in healthy tissues under normal conditions but upregulated in many cancers, including NSCLC²⁻⁵
- A recent retrospective study of US patients with metastatic NSCLC characterized IB6 expression by IHC and its association with patient and molecular characteristics^{1,6,7}
 - Of 227 patients, 93% had IB6 expression; IB6-high status was reported in 77% of NSCLC samples, including 81% of nonsquamous samples¹
- To explore possible regional differences, the present study evaluated IB6 expression in Japanese patients using TMA and full section biopsy specimens

Methods

- Nonsquamous NSCLC tissue specimens were obtained through the iHIPPOCRATES project at the National Cancer Center Hospital in Japan
- IB6 IHC staining and scoring were performed using TMA specimens prepared from surgically resected tissues and biopsy specimens
- IHC was conducted using the IB6 6.2A1 pharmDx assay (Dako Omnis), which was optimized to detect IB6 expression in formalin-fixed, paraffin-embedded nonsquamous NSCLC specimens⁸
 - IB6-expressing tumors had ≥1% of tumor cells with any staining intensity
 - Based on pathologist assessment, IB6-high expression was defined as staining intensity ≥2+ in ≥50% of tumor cells (**Figure 1**)
- The inherent limitations of TMA-based assessments should be considered when interpreting results

Figure 1. Examples of IB6-high and -low status in nonsquamous NSCLC

C2R1: NSCLC			C6R1: NSCLC			C2R2: NSCLC		
Lower left lung lobe, poorly differentiated adenocarcinoma			Lower left lung lobe, poorly differentiated adenocarcinoma			Lower right lung lobe, pleomorphic carcinoma		
		100% 3+ (membrane and cytoplasmic), membranous staining is not obscured by cytoplasmic staining			85% 2+ moderate membrane staining, 15% 1+ weak cytoplasmic staining			100% 0+ intensity, no staining
IB6-expressing and IB6-high			IB6-expressing and IB6-high			IB6-nonexpressing and IB6-low		

Results

- Quality criteria were met by 91 of 93 TMA specimens and 18 of 20 biopsy specimens, with no duplicates between TMA and full biopsy specimens
- In the eligible TMA specimen population (n=91), median patient age was 69 years, and 58% were male
- Stage distribution (0/I/II/III/IV/unknown) was 12/51/13/11/4/0 in patients with TMA specimens and 0/0/8/7/3/0 in patients with biopsy specimens
- IB6 expression was observed in 96% of all NSCLC specimens (n=109; **Figure 2**)
- IB6-high expression was observed in most TMA (81/91 [89%]) and biopsy (17/18 [94%]) specimens and across disease stages (**Figure 3**)

Figure 2. Classification of IB6 expression status

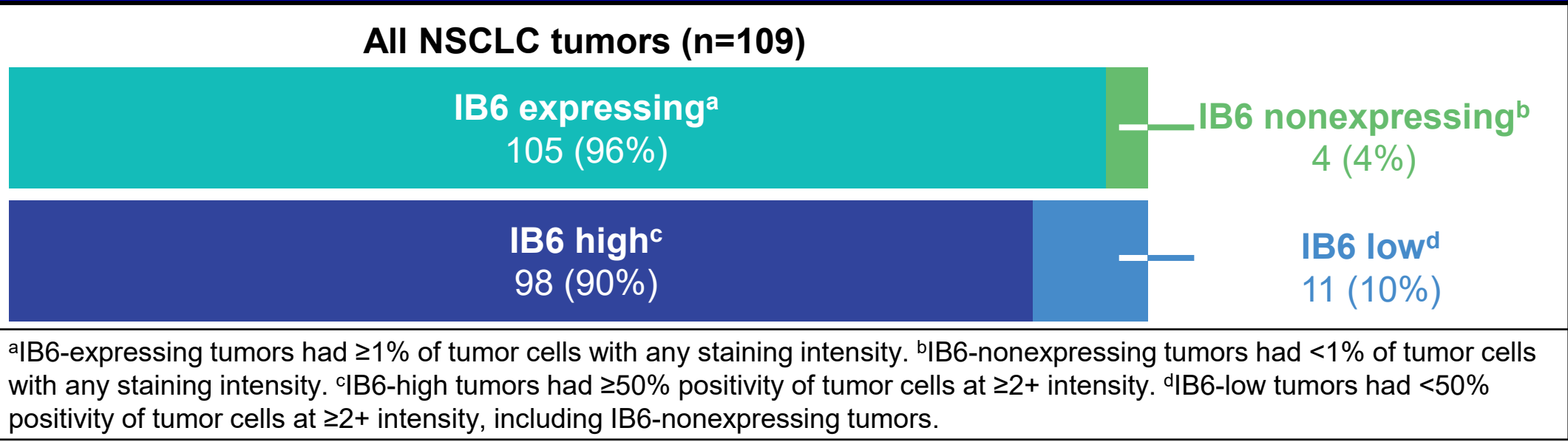
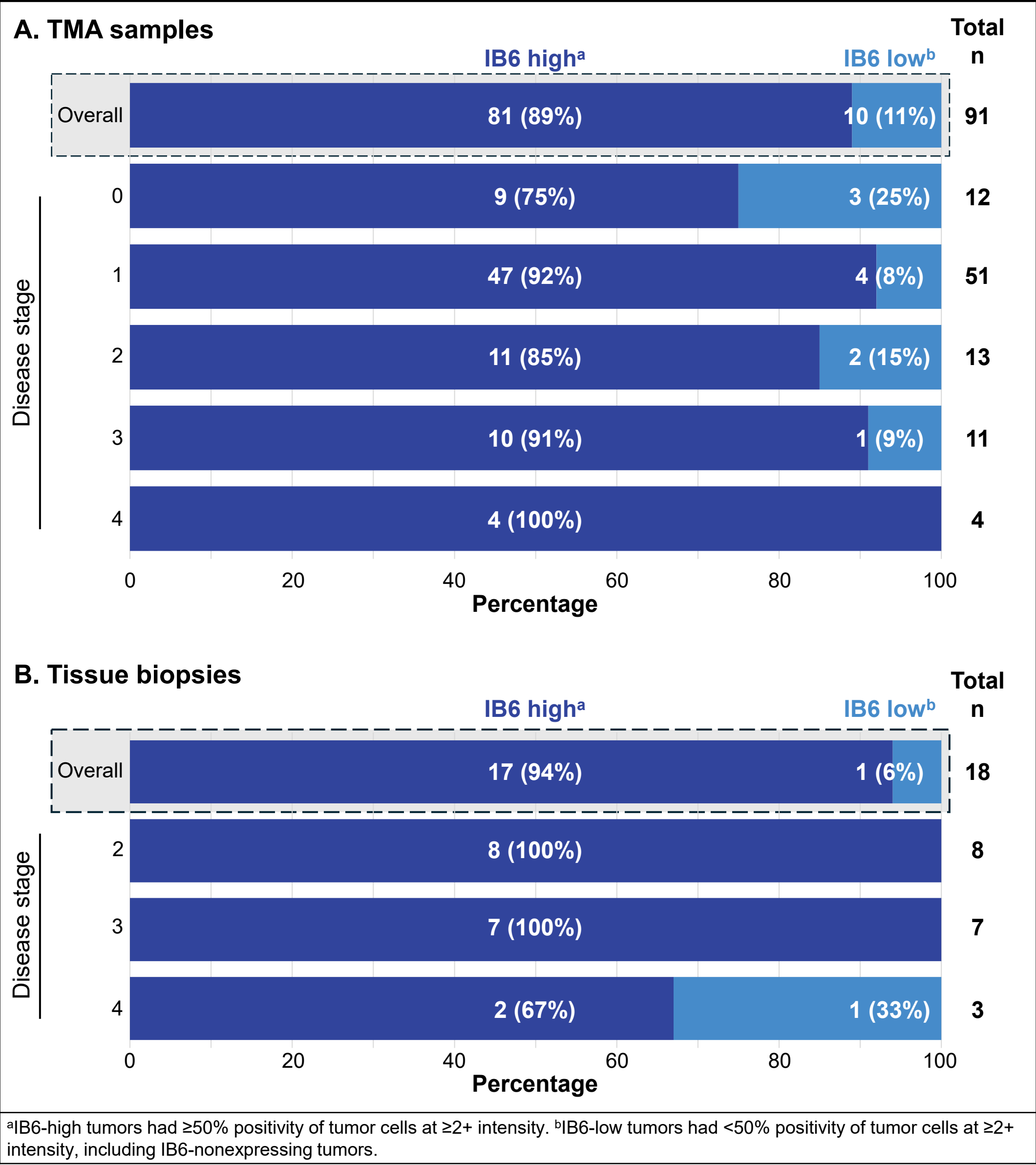
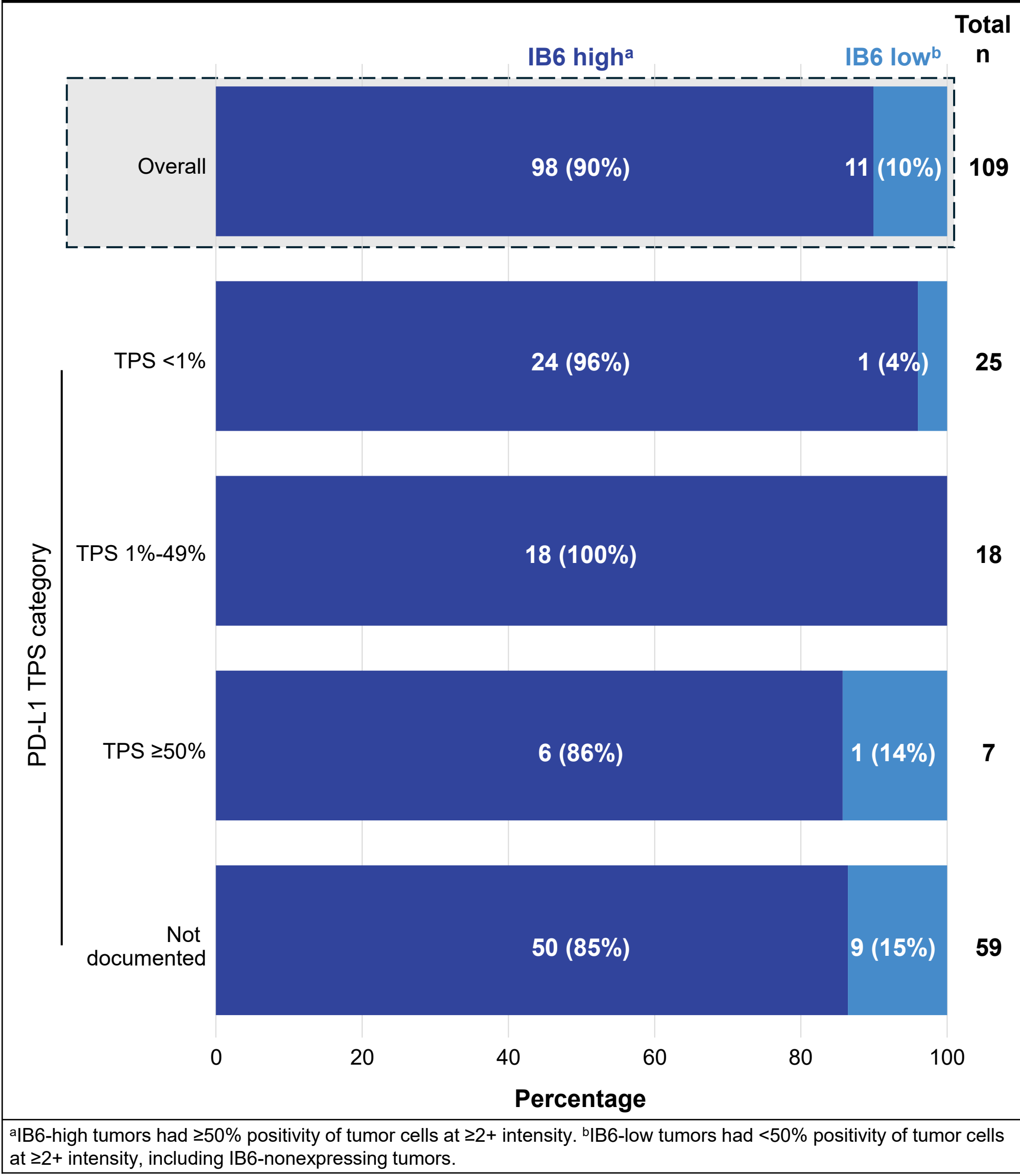


Figure 3. Prevalence of IB6-high status by IHC across disease stage



- PD-L1 expression was available for a subset of samples (33 TMA, 17 biopsy; n=50 total; **Figure 4**)
 - 6 samples had both high IB6 and PD-L1 expression (tumor proportion score [TPS] ≥50%)
 - 24 samples had high IB6 expression and any PD-L1 expression (TPS ≥1%)
 - 24 samples had high IB6 expression and no PD-L1 expression (TPS <1%)
 - Of the 2 samples with low IB6 expression and available PD-L1 data, 1 had no PD-L1 expression, and the other was TPS ≥50%

Figure 4. Prevalence of IB6-high status by IHC across PD-L1 expression levels



- Data concerning the presence of AGAs were available for a subset of the TMA samples (n=34; **Figure 5**)
 - 57 TMA samples did not have sequencing data available at the time of analysis
- Although the sample numbers are small and biased towards IB6 high in all cases, the χ^2 test was conducted across all binned AGAs to assess a potential IB6/AGA relationship
 - A statistically insignificant association was found between IB6-high vs -low status and the presence of AGAs ($\chi^2[7]=9.06$; $n=34$; $P=0.248$)
- A slight correlation was observed between IB6 expression detected by RNA sequencing and IHC (Spearman R: $P=0.03$, Rank R=0.32, Rank R²=0.1, degrees of freedom=81; **Figure 6**)

Figure 5. Prevalence of IB6-high status across AGAs in TMA samples^a

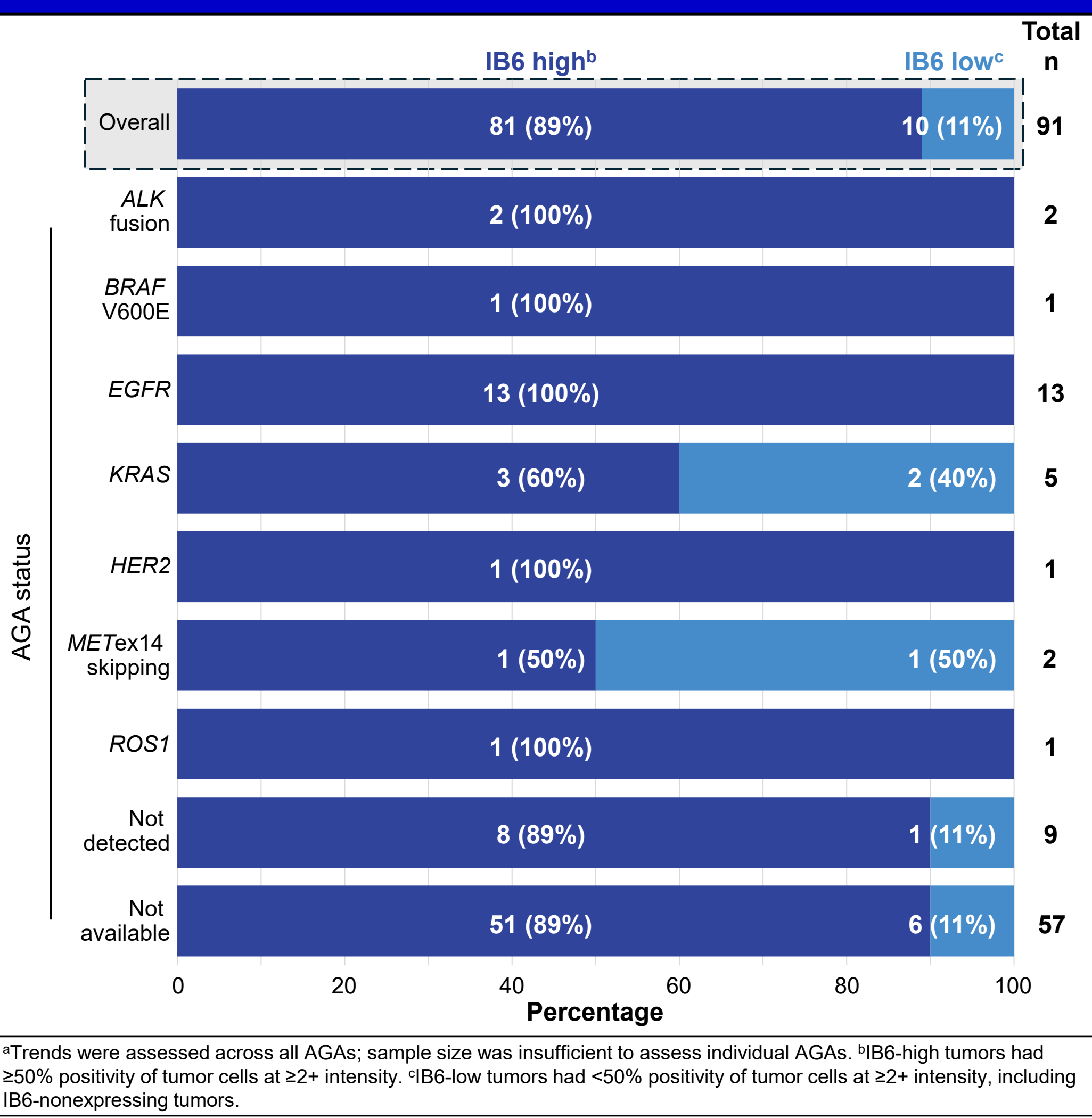


Figure 6. IB6-high RNA expression and protein correlation as measured by IHC

