Supplementary Information

Molecular landscape of *ERBB2* alterations in 3,000 advanced NSCLC patients

Hong, et al

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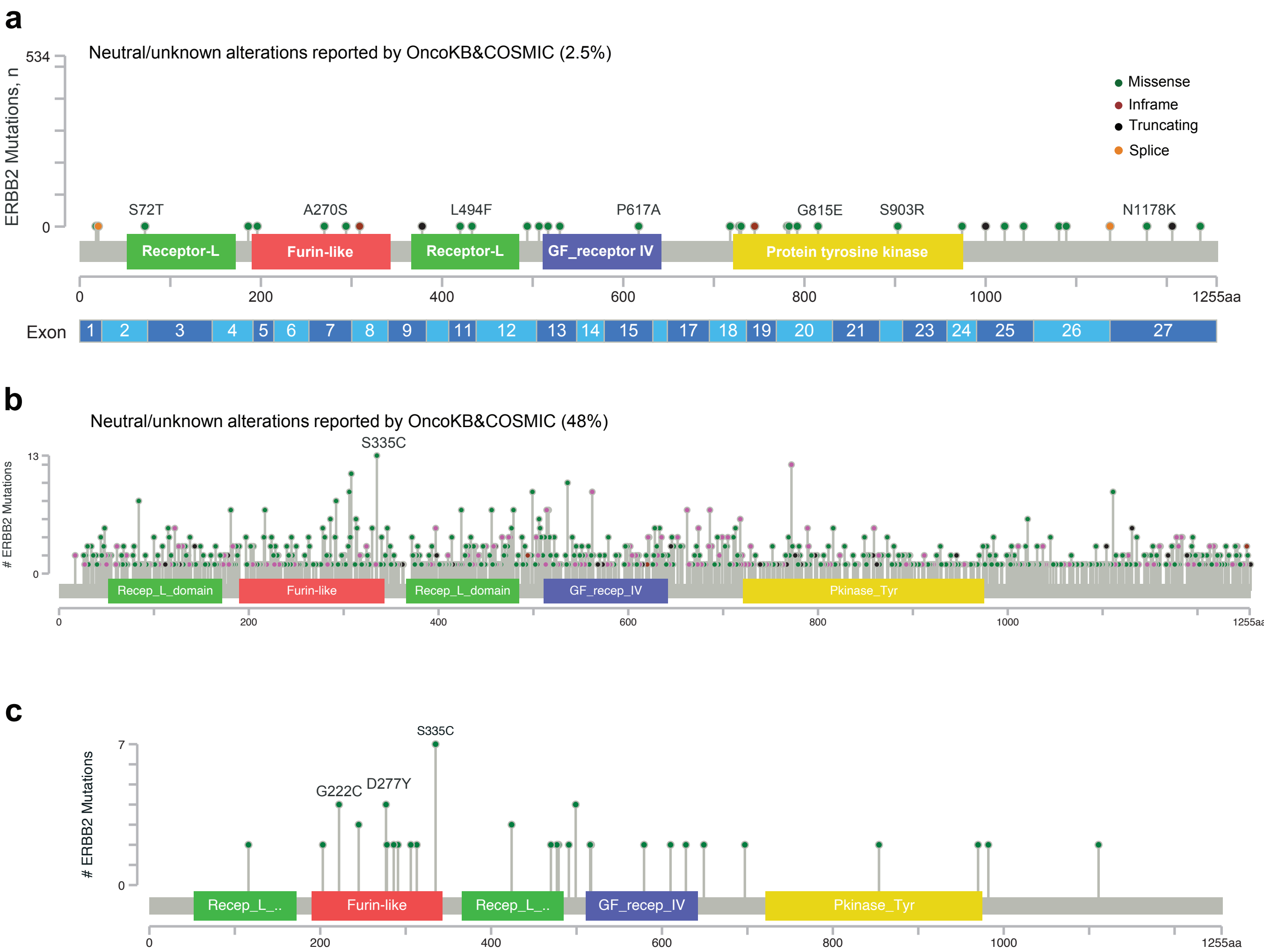
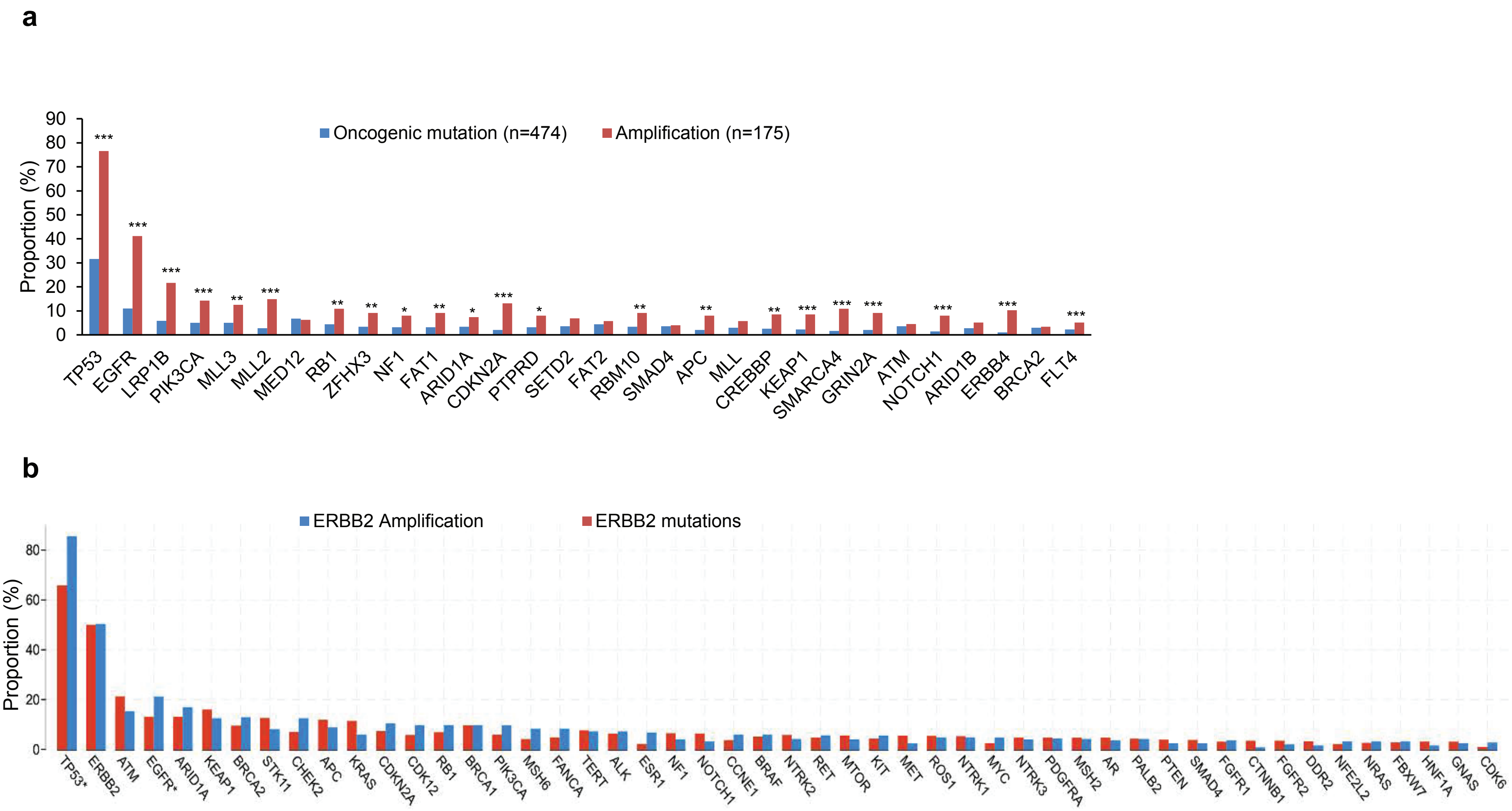
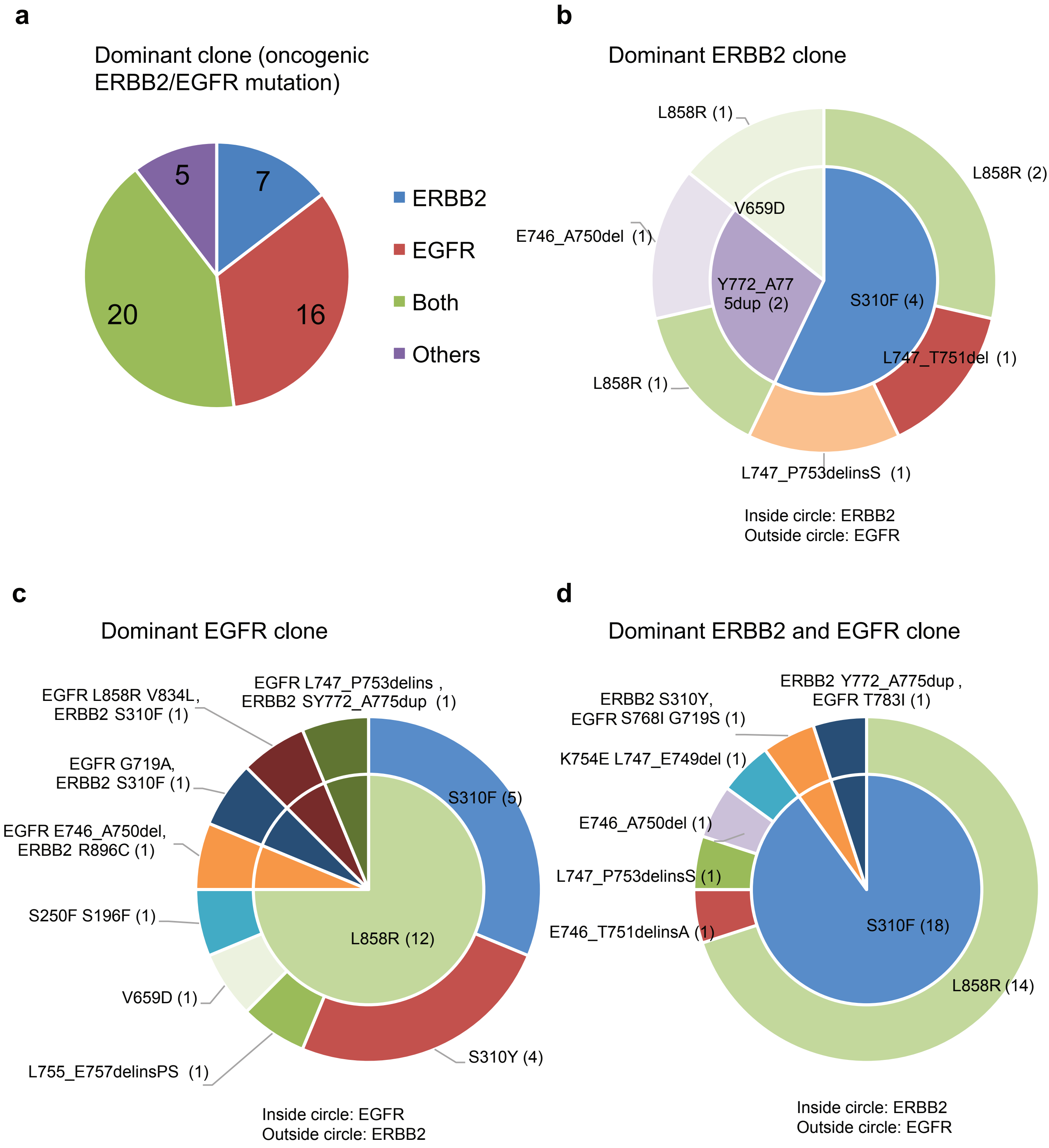


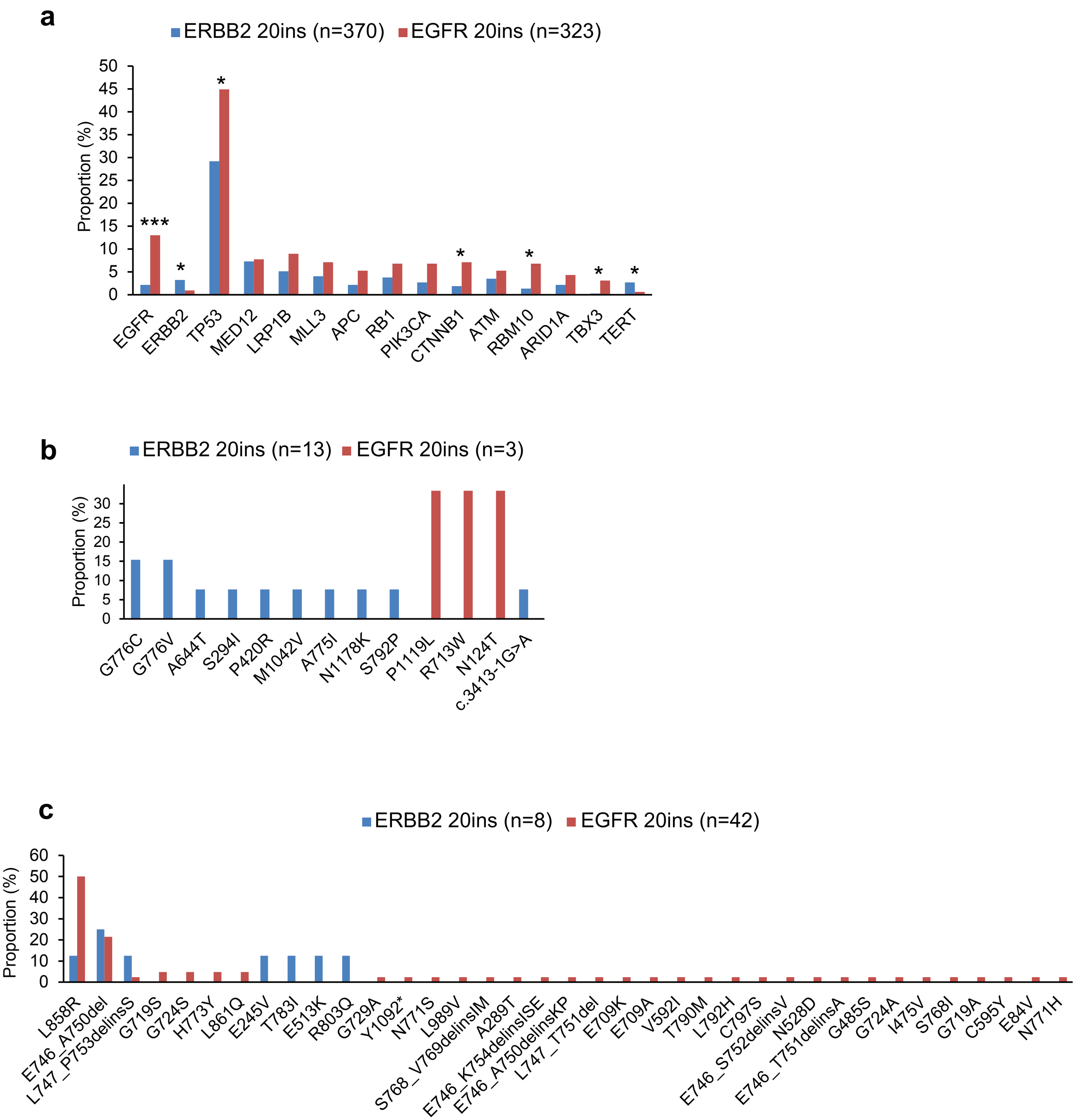
Supplementary Figure 1. **Neutral/unknown *ERBB2* alterations based on OncoKB and COSMIC. a**. Geneplus cohort. **b**. Guardant360 cohort. **c**. Variants of unknown significance (VUS) having repeated occurrence and functioning as dominant clone in Guardant360 cohort.



Supplementary Figure 2. **Differential upregulated genes in patients with *ERBB2* amplifications compared to those with *ERBB2* oncogenic mutations**. **a**. Geneplus. **b**. Guardant360. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$



Supplementary Figure 3. **Clonality relationship between *ERBB2* and *EGFR* when co-occurring in NSCLC in Geneplus cohort**. **a**. Dominant clone (oncogenic *ERBB2/EGFR* mutation); **b**. Dominant *ERBB2* clone; **c**. Dominant *EGFR* clone; **d**. Dominant clone in both *ERBB2* and *EGFR*.



Supplementary Figure 4. **Comparison of co-occurring gene mutations in patients with *ERBB2* or *EGFR* exon 20 insertion (ex20 ins) in Geneplus cohort**. **a**. Bar plot showing the proportion of co-occurring gene difference between two groups. **b**. Concomitant ERBB2 alterations with *ERBB2* ex20 ins or with *EGFR* ex20 ins. **c**. Concomitant *EGFR* alterations with *ERBB2* ex20 ins or with *EGFR* ex20 ins. * $p < 0.05$; *** $p < 0.001$

Supplementary Table 1. Clinical features of patients with *ERBB2* somatic mutations and *ERBB2* amplifications detected by the 1021 gene panel in Geneplus cohort

Characteristics	n = 663
Age, years	
Mean (SD)	56.3 (12.7)
Median (min-max)	57 (21-89)
Gender, n (%)	
Male	290 (43.7)
Female	373 (56.3)
Smoking, *n* (%)	
Never	286 (70.3)
Ever	121 (29.7)
Unknown	256 (100)
Tumor stage, *n* (%)	
I	39 (17.6)
II	14 (6.3)
III	28 (12.7)
IV	140 (63.4)
Unknown	442 (100)
Histology, *n* (%)	
Adenocarcinoma	548 (94.3)
Squamous cell carcinoma	27 (4.6)
Adenosquamous carcinoma	4 (0.7)
Sarcomatoid carcinoma	1 (0.2)
Neuroendocrine neoplasms	1 (0.2)
Unknown	82 (100)
Sample type, *n* (%)	
Tissue	606 (91.4)
Blood	45 (6.8)
Pleura effusion	10 (1.5)
Others	2 (0.3)
PD-L1 test, *n* (%)	
Yes	144 (21.7)
No	519 (78.3)
TPS<1%	88 (61.1)
TPS,1%-50%	45 (31.3)
TPS≥50%	11 (7.6)
TMB test, *n* (%)	
Yes	625 (94.3)
No	38 (5.7)
Mean (SD)	5.1 (6.9)
Median (min-max)	2.88 (0-68.0)