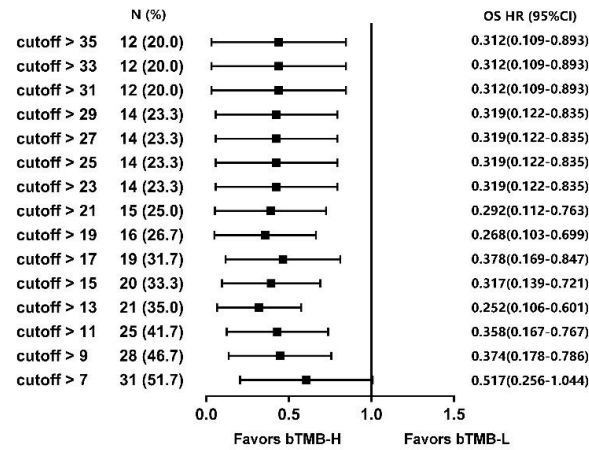
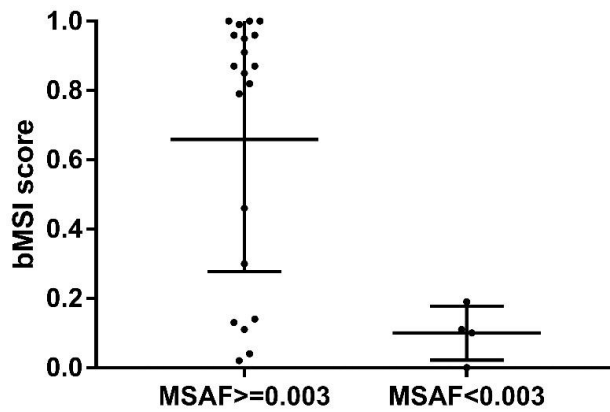


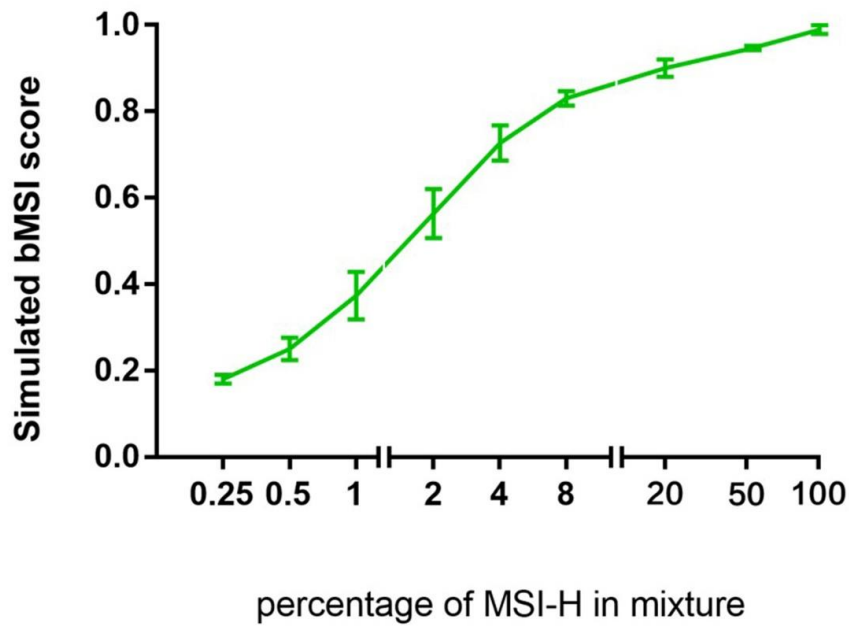
Supplemental Figure S1. Forest plots of hazard ratios for the association between overall survivals (OS) and bTMB in the clinical validation cohort.



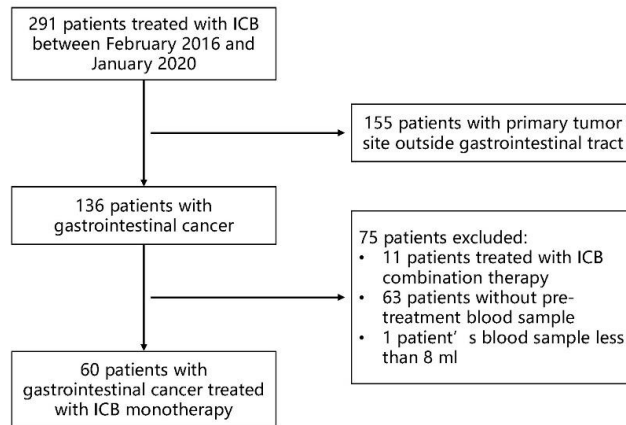
Supplemental Figure S2. The impact of maximum somatic allele frequency (MSAF) on MSI detection from the blood. Tissue MSI-H patients with an MSAF of $<0.3\%$ had a median bMSI score well below 0.2.



Supplemental Figure S3. Limit of detection (LOD) determination for the bMSI detection assay. The genomic DNA of the MSI-H cell line SW48 was diluted in that of the MSS cell line HT55 to create a titration series consisting of 100%, 50%, 20%, 8%, 4%, 2%, 1%, 0.5%, and 0.25%. Simulated bMSI score was plotted against titration gradient at a DNA input of 30 ng.



Supplemental Figure S4. A CONSORT flow diagram showing patient flow of the clinical validation cohort.



Supplemental Table S1. The prevalence of bMSI-H in pan-cancer.

| Tumor type | Sample size | Incidence of bMSI-H |
|-------------------|--------------------|----------------------------|
| Endometrium | 35 | 5.71% |
| Prostate | 150 | 4.00% |
| Colorectum | 452 | 3.32% |
| Stomach | 455 | 3.08% |
| Small bowel | 35 | 2.86% |
| Cervix | 112 | 2.68% |
| Sarcoma | 66 | 1.52% |
| Liver | 660 | 1.36% |
| NSCLC | 1803 | 1.22% |
| Nasopharynx | 99 | 1.01% |
| Pancreas | 316 | 0.95% |
| Ovary | 119 | 0.84% |
| Biliary tract | 270 | 0.74% |
| Esophagus | 180 | 0.00% |
| Kidney | 107 | 0.00% |
| Breast | 184 | 0.00% |
| GIST | 21 | 0.00% |
| Urothelium | 74 | 0.00% |
| Total | 5138 | 1.56% |

Supplemental Table S2. Baseline characteristics of the clinical validation cohort.

| Characteristics | Overall (n=60) | bMSI-H (n=31) | bMSS (n=29) | P value |
|---------------------------------|----------------|---------------|-------------|---------|
| Age, median (range) | 57 (15-82) | 61 (28-82) | 55 (15-76) | 0.383 |
| Sex, n (%) | | | | 0.124 |
| Male | 35 (58.3) | 15 (48.4) | 20 (69.0) | |
| Female | 25 (41.7) | 16 (51.6) | 9 (31.0) | |
| Primary tumor site, n (%) | | | | 0.429 |
| Gastric | 22 (36.7) | 10 (32.3) | 12 (41.4) | |
| Duodenum | 1 (1.7) | 1 (3.2) | 0 | |
| Small bowel | 1 (1.7) | 0 | 1 (3.4) | |
| Appendix | 1 (1.7) | 0 | 1 (3.4) | |
| Colorectal | 35 (58.3) | 20 (64.5) | 15 (51.7) | |
| ECOG performance status, n (%) | | | | 0.266 |
| 0 | 19 (31.7) | 12 (38.7) | 7 (24.1) | |
| 1 | 40 (66.7) | 18 (58.1) | 22 (75.9) | |
| 2 | 1 (1.7) | 1 (3.2) | 0 | |
| Prior lines of treatment, n (%) | | | | 0.141 |
| 0 | 4 (6.7) | 4 (12.9) | 0 | |
| 1 | 21 (35.0) | 8 (25.8) | 13 (44.8) | |
| 2 | 21 (35.0) | 11 (35.5) | 10 (34.5) | |
| >=3 | 14 (23.3) | 8 (25.8) | 6 (20.7) | |
| Immunotherapy type, n (%) | | | | 0.312 |
| Anti-PD-L1 | 27 (45.0) | 16 (51.6) | 11 (37.9) | |
| Anti-PD-1 | 33 (55.0) | 15 (48.4) | 18 (62.1) | |
| Organs with metastases, n (%) | | | | >0.999 |
| <3 | 36 (60.0) | 19 (61.3) | 17 (58.6) | |
| ≥3 | 24 (40.0) | 12 (38.7) | 12 (41.4) | |
| Liver metastasis, n (%) | 19 (31.7) | 12 (38.7) | 7 (24.1) | 0.247 |
| Peritoneal metastasis, n (%) | 21 (35.0) | 10 (32.3) | 11 (37.9) | 0.788 |
| Lung metastasis, n (%) | 20 (33.3) | 9 (29.0) | 11 (37.9) | 0.586 |
| Lymph node metastasis, n (%) | 37 (61.7) | 20 (64.5) | 17 (58.6) | 0.791 |
| bTMB | | | | 0.001 |
| bTMB-H | 21 (35.0) | 17 (54.8) | 4 (13.8) | |
| bTMB-L | 39 (65.0) | 14 (45.2) | 25 (86.2) | |
| Elevated baseline CA 19-9 | 33 (55.0) | 17 (54.8) | 16 (55.2) | >0.999 |
| Elevated baseline LDH | 22 (36.7) | 16 (51.6) | 6 (20.7) | 0.017 |
| Elevated baseline CEA | 35 (58.3) | 18 (58.1) | 17 (58.6) | >0.999 |