**Supplementary Table S1: Patients description from C1 and C2 cohorts with corresponding clinical data**

**Supplementary Table S2: NIPICOL and ImmunoMSI cohorts with clinical data including survival data**

**Supplementary Table S3: Listing of 22 somatic variants with a significant effect on patients' survival in both C1 and C2 cohorts at alpha=10%**

**Supplementary Table S4: Testing of association with iPFS of 99 RNA signatures of cellular component of the TME encompassing various immune and stromal phenotypes in both C1 and C2 cohorts**

**Supplementary Figure S1. Correlations between MSISensor, MSICare and different genomic instability indexes**

MSISensor score (x-axis) is shown according to the number of somatic mutations per Mb (A), indels mutations (B), missense SNVs (C) or the number of indels according to missense SNVs (D). Next, MSICare score (x-axis) is displaying according to the number of somatic mutations per Mb (E), indels mutations (F), missense SNVs (G) and MSISensor score (H).

**Supplementary Figure S2. Progression free survival (iPFS) curve according to MSICare level.**

Kaplan-Meier survival curves plotted for progression-free survival (iPFS) according to MSICare scores before exlusion of dMMR/MSS samples (left panel) and after exlusion of dMMR/MSS samples (right panel). The top 80th percentile of MSICare scores are indicate as High and the bottom 20th percentile of MSICare scores as Low.

**Supplementary Figure S3. Progression free survival (iPFS) curve according to non-repetitive Gene variant status**

Kaplan-Meier survival curves plotted for progression-free survival (iPFS) according to some Genes mutation status (Wild type are indicated in grey and mutated in dark-red).

**Supplementary Figure S4. Testing progression free survival by iRECIST (iPFS) in association with pathway activity.**

Univariate association of pathway activity estimated by GSVA in C1 NIPICOL cohort (left) and C2 ImmunoMSI cohort (right). Gene set defining pathways were taken Bioplanet collection by default, or Elsevier pathway collection and BIOCARTA when specified.

**Supplementary Figure S5. Characterization of the four RNA components defined by ICA in C1 NIPICOL.**

Four RNA components defined by ICA were significantly associated with objective response defined by iRECIST. From left to right: Pathway enrichment (NES: normalized enrichment score), C1 iRECIST objective response, univariate association with iPFS in C1, association with objective response defined by iRECIST in C2 and univariate association with iPFS in C2.

**Supplementary Figure S6. RNA signatures.**

a. Correlation of the stromal signature, defined by ICA, with tumor cellularity estimated by exome sequencing. b. Univariate association of the intra-tumorale proportion of CMS with progression-free survival by iRECIST 29.