SUPPLEMENTARY METHODS SM3

Survival analyses

1. End points

The main end-point was disease-free survival (DFS). Association between clinicopathological features and apoptosis-based signatures with overall survival (OS) was also assessed in the discovery cohort. DFS was calculated as the time between the date of study entry and the date of first recurrence or last tumor-free follow-up. OS was calculated as the time between the date of study entry and the date of death from any cause or last follow-up. The study entry date was the date of surgery or date of diagnosis for the discovery and validation cohorts, respectively. DFS and OS were already compiled by the original authors for the expansion dataset.

2. Kaplan-Meier analyses

As primary analyses, we compared OS and DFS curves by the following groups in the discovery cohort: APOPTO-CELL (SC>25% *vs.* SC≤25%; **Fig. 2E-F**), APOPTO-CELL-PC3 (low-, medium- *vs.* high-risk; **Fig. 4B-C**), RF signatures (probability of recurrence <20%, 20-50% *vs.* >50%; **Fig. 5F**), and single proteins (low- *vs.* high-expression using the median as cut-off point for Procaspase-9, XIAP, SMAC and Procaspase-3; **Suppl. Fig. S1**). In exploratory analyses, we compared DFS and OS curves when patients were categorized based on the bootstrap robustness group (robust low-risk *vs.* robust high-risk *vs.* non-robust; **Fig. 3D-E**). As additional exploratory analyses, we assessed APOPTO-CELL-PC3 in the context of clinically relevant sub-populations (TN III-A and III-B *vs.* III-C; proximal, distal *vs.* rectal; presence *vs.* absence of lymphovascular invasion; **Suppl. Fig. S2**). In the validation cohort, we compared DFS curves for APOPTO-CELL, APOPTO-CELL-PC3, and the RF

signatures (**Fig. 6A-C**). As exploratory analyses in the validation cohort, we additionally assessed these relationships when stratifying by CRC molecular subtypes (**Fig. 6D-I**).

1.3 Cox proportional hazards models

Clinical factors investigated included T stage (T2 and T3 *vs.* T4), N stage (N1 *vs.* N2), TN stage (III-A and III-B *vs.* III-C), age (categorical: under 50, 51-60, 61-70 *vs.* over 70), nodal count (continuous linear), gender (male *vs.* female), tumor location (proximal, distal *vs.* rectal), lymphovascular invasion (invasion *vs.* no invasion), and differentiation (poor *vs.* moderate to well). We included the covariates significantly associated with clinical outcomes in univariate Cox analyses (T stage and lymphovascular invasion) as precision variables in multivariate Cox analyses for the APOPTO-CELL-PC3 and RF signatures. We did not examine Cox models in the validation cohort owing to the low number of events among these patients. For the expansion cohort, we fit univariate and two exploratory multivariate Cox models (model 1 and model 2) assessing associations between APOPTO-CELL and APOPTO-CELL-PC3 and the risk of relapse. Model 1 adjusted for treatment (chemotherapy *vs.* no chemotherapy), microsatellite status (stable *vs.* unstable), and BRAF mutation (wild-type *vs.* mutated). Model 2 was additionally adjusted for sex (male *vs.* female), age (continuous linear), tumor location, and KRAS mutation.

The proportional hazards assumption was assessed for each factor using log(-log(survival)) *vs* log(time) plots and Schoenfeld residuals.