**Supplementary Figure 1.** Study design.

**Supplementary Figure 2.** Histogram showing ανβ6 histoscores for all patients with tumour blocks available (n=197) and the median histoscore (70) for this population. Histoscores were generated for each patient by integrating data relating to the intensity and frequency of ανβ6 staining, using the formula: $1 \times$ (percentage of cells staining weakly [1+]) + $2 \times$ (percentage of cells staining moderately [2+]) + $3 \times$ (percentage of cells staining strongly [3+]) [12].
Phase I safety run-in

Cohorts of 3 patients received abituzumab every 2 weeks at doses of 250 mg, 500 mg, 750 mg, and 1,000 mg, combined with SoC

1:1:1 randomization

Randomized phase II part

Abituzumab 500 mg every 2 weeks + SoC

Abituzumab 1,000 mg every 2 weeks + SoC

Cetuximab (400mg/m² [day 1, cycle 1] then 250mg/m² weekly) + irinotecan (180 mg/m² every 2 weeks)