**SUPPLEMENTAL FIGURES: LEGEND**

**Figure S1: Expression of immune modulators among the 4 molecular subgroups and normal samples**

Red means : higher relative expression, white : average expression, green : lower relative expression. Genes are functionally classified. Notable protein aliases are *PD-1 (PCD1), PD-L1 (CD274), PD-L2 (PDCD1LG2), TIM3 (HAVCR2)*

**Figure S2**: **Expression of cell-type specific metagenes among the different subgroups and normal samples.**

ANOVA p-values (excluding normal samples) : n.s. ≥ 0.05, \* < 0.05, \*\* < 0.01, \*\*\* < 0.001

**Figure S3: CD8+ cell infiltration according to the molecular ccRCC subtype classification.**

Representative pictures of CD8 staining (cells in red) on primary clear cells renal cell carcinomas from the analyzed cohort. One patient of each molecular sub-type (ccrcc1 (A), ccrcc2 (B), ccrcc3 (C) and ccrcc4 (D)) is depicted. Original magnification 10X.

**Figure S4: Characterisation of the ccRCC molecular subtypes: methylation status and Benporath polycomb signature**

**(A)** Rate of hypermethymated (black) and hypomethylated probes located on CpG islands for each unsupervised subgroup ccrcc1 to ccrcc4 (anova p-value <0.05). **(B)** Representation of the mean expression level of the Benporath polycomb signatures. For a given pathway, samples are sorted by mean expression value. **(C)** Plot of beta-values of the probes located on CpG islands for each unsupervised subtype compared to normal samples (NL). Warm colors = high density points, cold colors = low density points.

**Figure S5:** **Cytogenetic characterization of the ccRCC molecular subtypes**

**(A)** Rate of chromosomal instability (CIN) among the four unsupervised subgroups. **(B)** Loss and gain frequencies in the four groups. **(C)** Boxplot of the rate of normal cell between ccrcc subtypes.

**Figure S6: Characterization of the ccRCC molecular subtypes: *Myc* methylation and (target) amplification**

**Top:** Plot of the frequencies of the four ccrcc subtypes according to both status (Amplification of the *MYC* upstream region x hypomethylation of a *MYC* CpG island). The threshold discretizing hypomethylated tumors from hypermethylated tumors was given according the normal samples. **Middle:** Boxplot of the expression level of *MYC* according to both statuses. **Bottom:** Boxplot of the expression level of *MYC* according to both statuses.

**Figure S7: Summary of the results obtained on the TCGA data.**

**(A)** Gene expression profile heatmap of the 1% most variant probe sets. Samples are sorted according to the predicted subtype ccrcc1 to ccrcc4. Blue = low expression level and red = high expression level. **(B)** Barplot of the mutations associated to the four predicted subtypes (ccrcc1 to ccrcc4) . **(C)** Rate of hypermethylated (black) and hypomethylated probes located on CpG islands for each predicted subtype ccrcc1 to ccrcc4 (anova p-value<0.05). **(D)** Representation of the mean expression level of differentially regulated pathways between the four predicted subtypes. Pathways are sorted by the difference between the ccrcc4 subgroup and the normal sample (NL). For a given pathway, samples are sorted by mean expression value. **(E)** Representation of the rate of up-regulated genes within hypomethylated genes (black) and of the rate of down-regulated genes within hypermethylated genes (gray), for each pathway. Pathways are sorted by the difference between the rates of up and down-regulated genes in the ccrcc4 subtype. **(F)** Barplot of the chromosomal aberrations identified by the GISTIC algorithm and close to the aberrations identified in our cohort.

**Figure S8:** **Survival analysis of the patients included in the TCGA according to our classification ccrcc 1 to 4.**

**Figure S9:** **Illustration of the gradient assumption defined by subtype order**

Illustration of the gradient assumption defined by the subtype order: ccrcc3, ccrcc2, ccrcc1 and ccrcc4 using the pathways and genes involved in the pluripotency acquisition and described in Apostolou *et al*.

**SUPPLEMENTAL TABLES: LEGEND**

**Table S1:** **Clinical and pathological characteristics of patients.**

**Table S2: List of the 70 genes used for quantitative Real-Time PCR, their Applied Biosystems Assay ID number and the subgroups in which the genes are up- or down-regulated in the Affymetrix data.**

**Table S3: (A) Diagram showing the different analyses that have been done on the samples and (B) sample list according to the different technologies.**

**Table S4: Detail for each sample of the *PBRM1* and *VHL*-mutation status. NA stands for Not Available.**

**Table S5: For each data type, clinical, transcriptome, methylome or SNP array, sensitity and specificity of the two predictors: PD vs (PR+SD) and PR vs (PD+SD) in the training and validation sets. The ‘N()’ columns indicate the numbers of each responder type.**

**Table S6: List of the 27 genes firstly used by the classifier to predict the subtypes ccrcc2, ccrcc3 and the joint subtype ccrcc14 and list of the 8 genes used by the second classifier to assign the ccrcc14 samples to the two subtypes ccrcc1 and ccrcc4.**

**Table S7:** **Area under the ROC curve or c-index for the predictive and prognostic markers presented in Table 1 and Figures 3A, 3B and 3C.**

**Table S8:** **P-values of the pathway enrichment analysis for the genes differentially expressed, the genes differentially methylated and the genes differentially methylated and anti-correlated to expression data in the four unsupervised subgroups.**

Analyses were performed on the genes up-regulated (resp. hypermethylated), down-regulated (resp. hypomethylated) and on all differentially regulated (resp. methylated) genes. Selected pathways correspond to a non-exhaustive list of the top pathways.

**Table S9: List of the recurrent chromosomal aberrations characterizing ccrcc4-samples with a sensitivity and a specificity greater than 0.65.**

**Table S10: Correlation of the centroids of our classification in four subtypes with the Brannon classification in three subgroups *ccA*,  *ccB* and *cluster\_3* and the subtypes predicted in the TCGA cohort**