## Supplementary methods

## Interpretation of ddPCR results

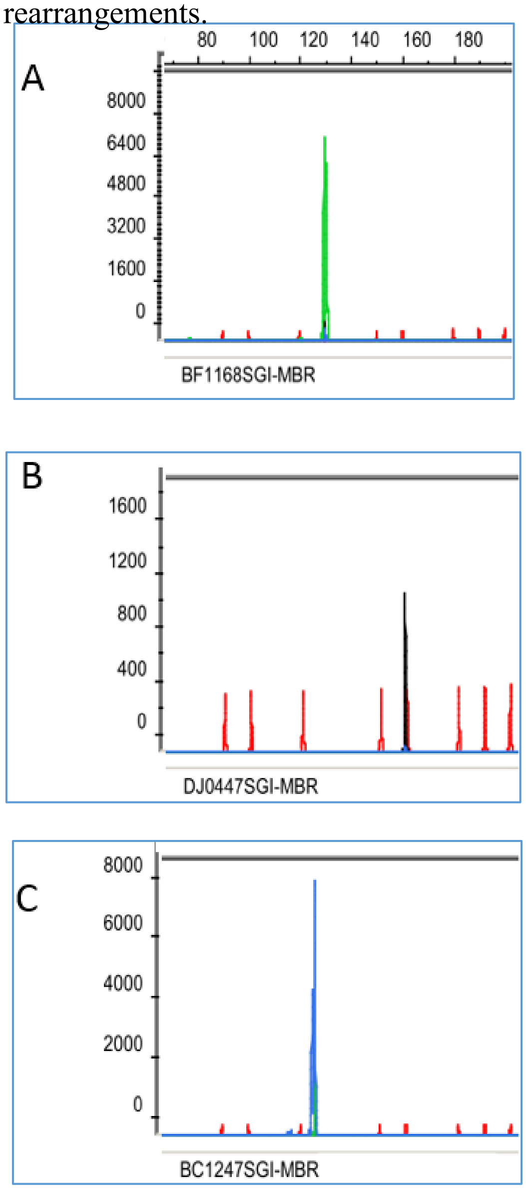
Samples of gDNA (250 ng) were analyzed in triplicate. Each experiment included a positive control (RL cell line for MBR JH6 rearrangement or selected positive primary samples for other combinations) and negative controls consisting of a non-t(14;18) translocated cell line (triplicate), and no-template controls (NTC) (water, ProAMP, Lyon, France) (triplicate). Results were interpreted according to current international guidelines:

(i) Only replicates with more than 9000 generated droplets were considered for the analysis. (ii) A sample was considered positive and quantifiable if the three replicates were positive and three or more events were detected on merged analysis. (iii) A sample was considered as positive non-quantifiable (PNQ) if less than three positive replicates and more than two events were observed on merged analysis. (iiii) A sample was considered negative if all three replicates were negative or if two events or less were detected on merged analysis.

# SUPPLEMENTARY FIGURES

**Figure S1: identification of JH segments involved in bcl2-Jh rearrangement**.

DNA was amplified using a modified Biomed-2 PCR protocol in which the consensus JH primer was substituted by a mix of JH4, JH5, JH6 primers labeled with HEX, FAM and AT550 fluorescent dye respectively. PCR products were loaded onto 3130 Genetic Analyzers. JH segments involved in translocation were revealed by the color of the bcl2-JH amplified fragment. Representative results are shown for bcl2-JH 5 (A), bcl JH6 (B) and bcl2- JH4 (C) rearrangements.



## Figure S2: ddPCR quantification of cfDNA and ctDNA at diagnosis

7.5 µl of cfDNA (10% of extracted DNA) was amplified by ddPCR, with the *ANKRD30B* reference gene (A) or bcl2-JH PCR (B)

1-2: TPH cell line as positive control

3-5: No-template control (NCT=water)

6-17: Plasma samples

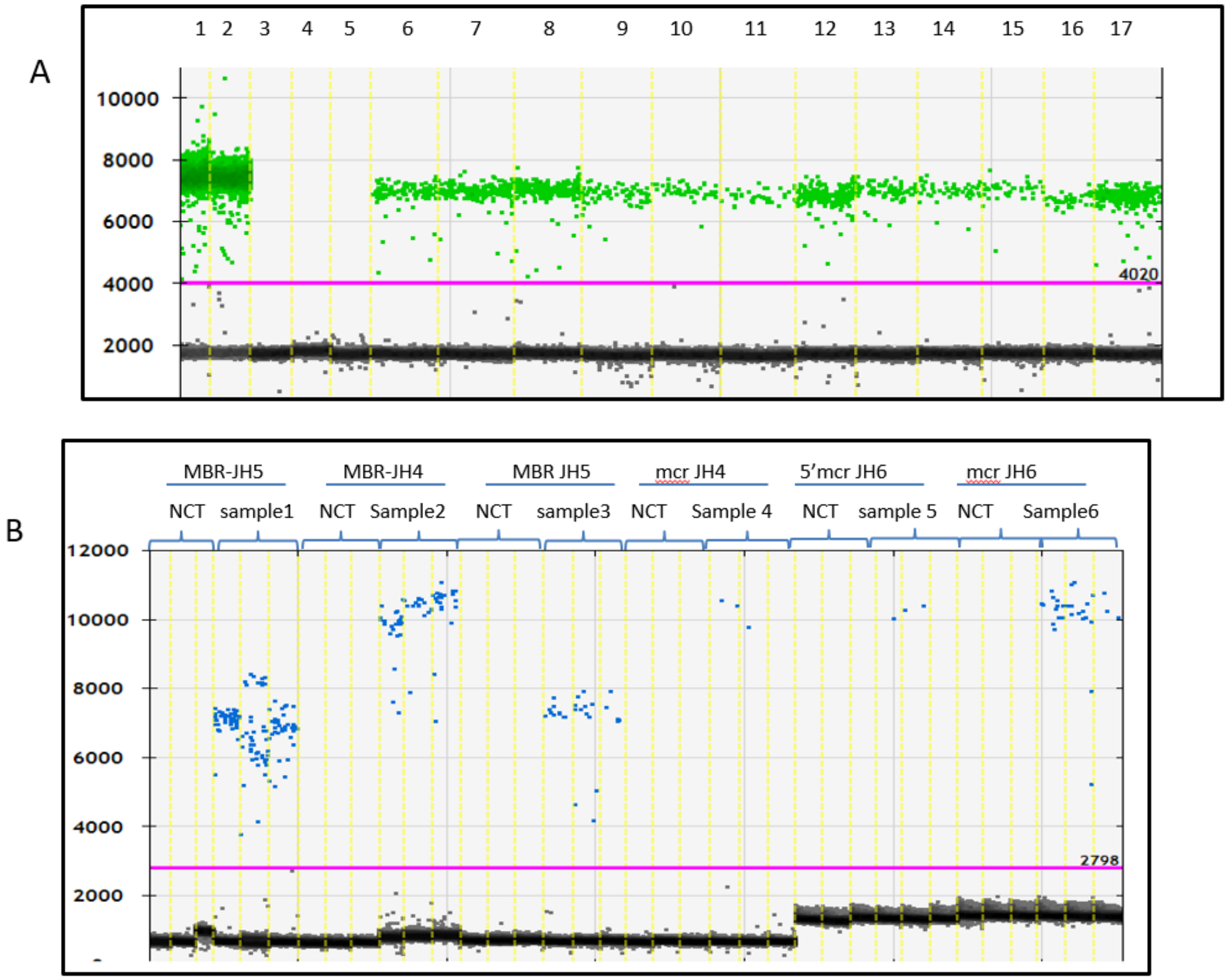
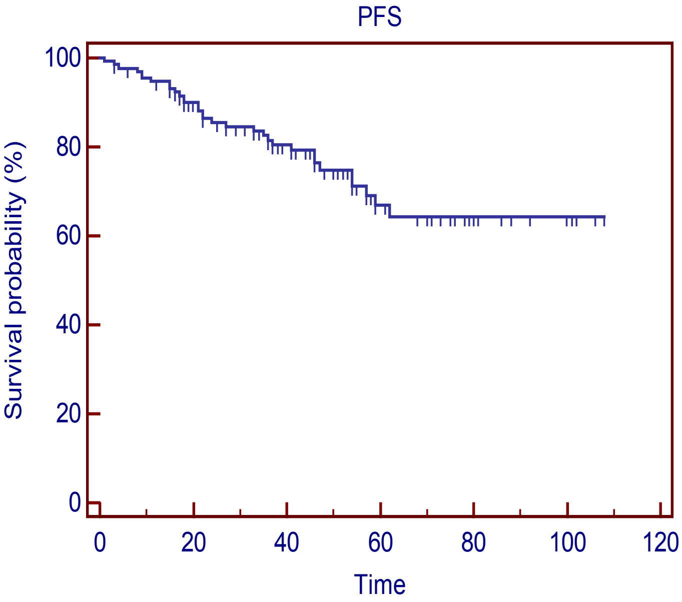


**Figure S3: Clinical outcome of the 133 included patients**

**A: Progression-free survival**

**B: Overall survival**

**A**



**B**

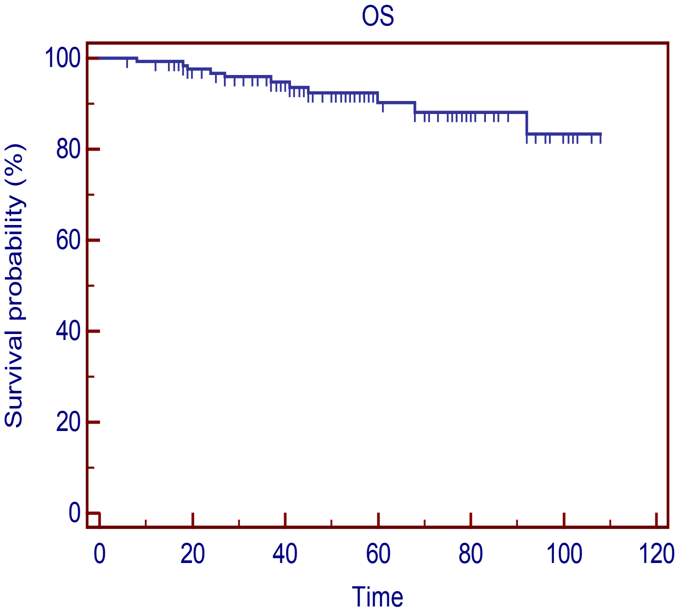
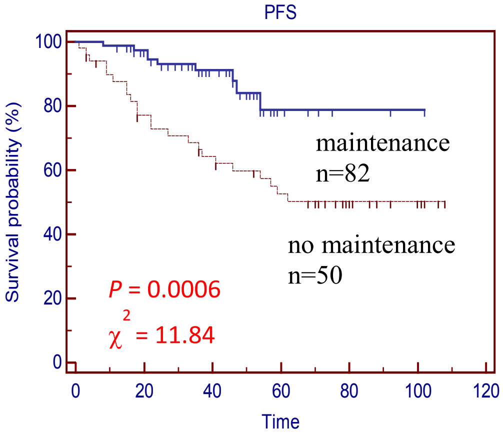


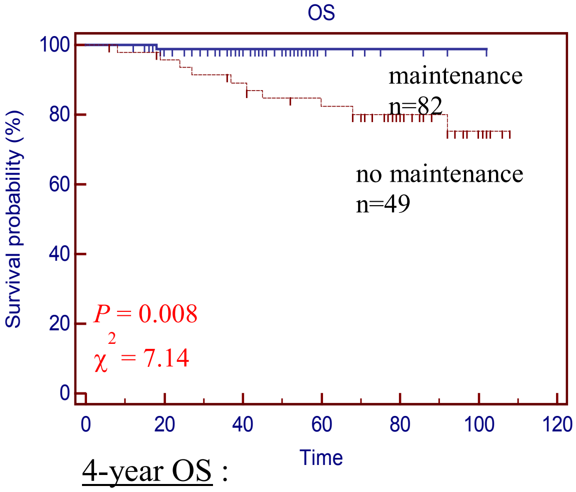
**Figure S4: Clinical outcome according to maintenance therapy.** Maintenance: patients who received maintenance therapy; no maintenance: patients who did not receive maintenance therapy. A: Progression-free survival. B: Overall survival

**A**



4-year PFS :
84% vs 60%
HR 3.40 [1.69-6.86]

**B**

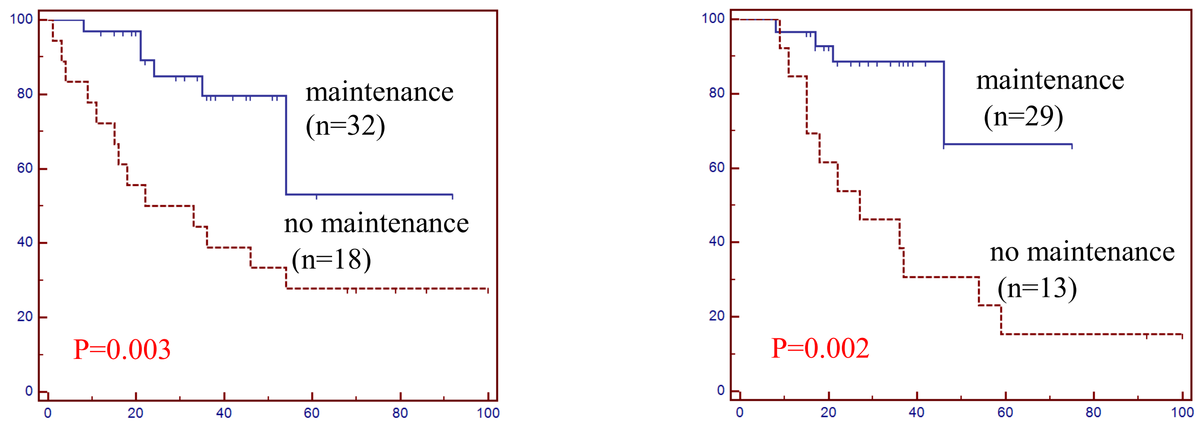


4-year OS :
99% vs 85%
HR 8.52 [2.60-27.89]

**Figure S5: Progression-free survival according to maintenance therapy in patients with high TMTV high CTC and high cfDNA.** Maintenance: patients who received maintenance therapy; no maintenance : patients who did not receive maintenance therapy

**A: Patients with TMTV >510 cm$^3$ (n=50)**

**B: Patients with CTC >1.8.10$^{-3}$ (n=42)**



<u>4-year PFS</u> :
80% vs 33%
HR 3.76

<u>4-year PFS</u> :
67% vs 31%
HR 4.75

C: **Patients with cfDNA >2550 eqg/mL (n=37)**