Deduciti that induces differentiation and apoptosis of leukemic cells, is a well-known agent. In a previous Phase 1 (dose escalation) study, we found in relapsed/refractory (r/r) AML patients who were treated with SGI-110 (36 mg/m²/125 mg/m²) subcutaneously (SQ) daily for 5 days a correlation between low LINE-1 demethylation induction, a three gene expression classifier score (low CDA, low P15 and high DNMT3B) and response to SGI-110. Here, we analyzed r/r AML patients (n=122) from Phase 2/1 studies treated at pharmacologically effective doses of SGI-110 looking for determinants of hypomethylation and response. Phase 1 patients with r/r AML (n=27) who were treated at a therapeutic dose range of SGI-110 (36 mg/m² - 125 mg/m²) by SQ daily for 5 days. Phase 2 study of AML patients received 60 mg/m² SQ daily for 5 days (n=22), 90 mg/m² SQ daily for 5 days (n=25) and 60 mg/m² SQ daily for 10 days (n=48). Global DNA demethylation at post-treatment was estimated by bisulfite-pyrosequencing for the LINE-1 repetitive sequence. We also examined expression of a panel of genes (CDA, P15, P19, DNMT3B, DNMT3A, DNMT3L, and CTCF) at baseline by quantitative RT-PCR.

We analyzed samples from 122 patients with r/r AML. Median age was 58.6 (range, 23–88); 75 were males (61.5%). Overall, peak LINE-1 demethylation generally occurred on day 8 after daily 5 treatment, or on day 8 or 15 after daily 10 treatment. In individual patients, peak LINE-1 demethylation ranged from -4.95% to -56.3%. In 122 r/r AML patients, 28 showed overall remission (23.0%, 15 CR and 13 CRi/CRp). Unsupervised clustering by expression of a panel of genes at baseline grouped the patients into two clusters: A (N=95, response rate = 28.5%) and B (N=27, response rate = 0%). Cluster B is characterized by high DNTM3 expression, low P15 expression, low CDA expression (average 2 score 1.44 ± 0.26 in cluster B compared to -1.26 ± 0.14 in cluster A, p<0.001) and reduced demethylation (demethylation average -14.2 ± 7.9% in cluster B compared to -21.1 ± 13.8% in cluster A, p=0.0001)(Fig. 2). Peak LINE-1 demethylation was significantly higher in responders than non-responders (average demethylation -32.3 ± 11.0% in responders compared to -21.5 ± 1.42 % in non-responders, p<0.0001). Fig. 2A Three gene classifier score (low CDA, low P15 and high DNMT3B) was associated with low RFI demethylation (p<0.001, Fig. 2B) as well as complete response to SGI-110 (mean Z-score 0.75 in non-responders compared to -1.67 in responders, p=0.0144)(Fig. 4A). In a phase 1/2 study of SGI-110, we identified in r/r AML patients a gene expression signature (High DNMT3B, low P15, and low CDA) associated with reduced demethylation and response to SGI-110 and we found strong trends for associations between demethylation and response.