**Supplementary Appendix**

**Supplementary Materials and Methods**

*Development of a composite score and comparison with a ratio-based metric for “molecular response”*

We developed a composite score incorporating pretreatment and on-treatment ctDNA levels, consisting of a linear combination of delta-VAF and on-treatment VAF which is described in the following equation:



The weights *w1* and *w2* were assessed by comparing their association with Response Evaluation Criteria in Solid Tumors (RECIST)-defined best overall response in Study 1108 using ROC analysis; the optimal AUC was achieved with equal contribution of each (Supplementary Figure 7A). Similar results were produced using a hazard ratio analysis (Supplementary Figure 7B). The composite score had a stronger association with RECIST response compared with on-treatment VAF alone (Supplementary Figure 7C, AUC=0.86, 95% CI 0.77, 0.95 for the composite score and AUC=0.73, 95% CI 0.61, 0.85 for on-treatment VAF). The composite score also showed a significant association with OS (p*=*4.4×10-5, unadjusted Cox analysis for the composite score), supporting the value of the composite ctDNA metric.

During optimization of the composite score, we identified instances were *n=m* (where the number of variants which emerged on-treatment were equivalent to the number pretreatment). Using a cutpoint for response of a >50% decrease in VAF, a ratio of on-treatment to pretreatment ctDNA VAF was equivalent to the composite score. The composite score also displayed similar results to the ratio when used as a definition for molecular response (Supplementary Figure 7D and 7E).