

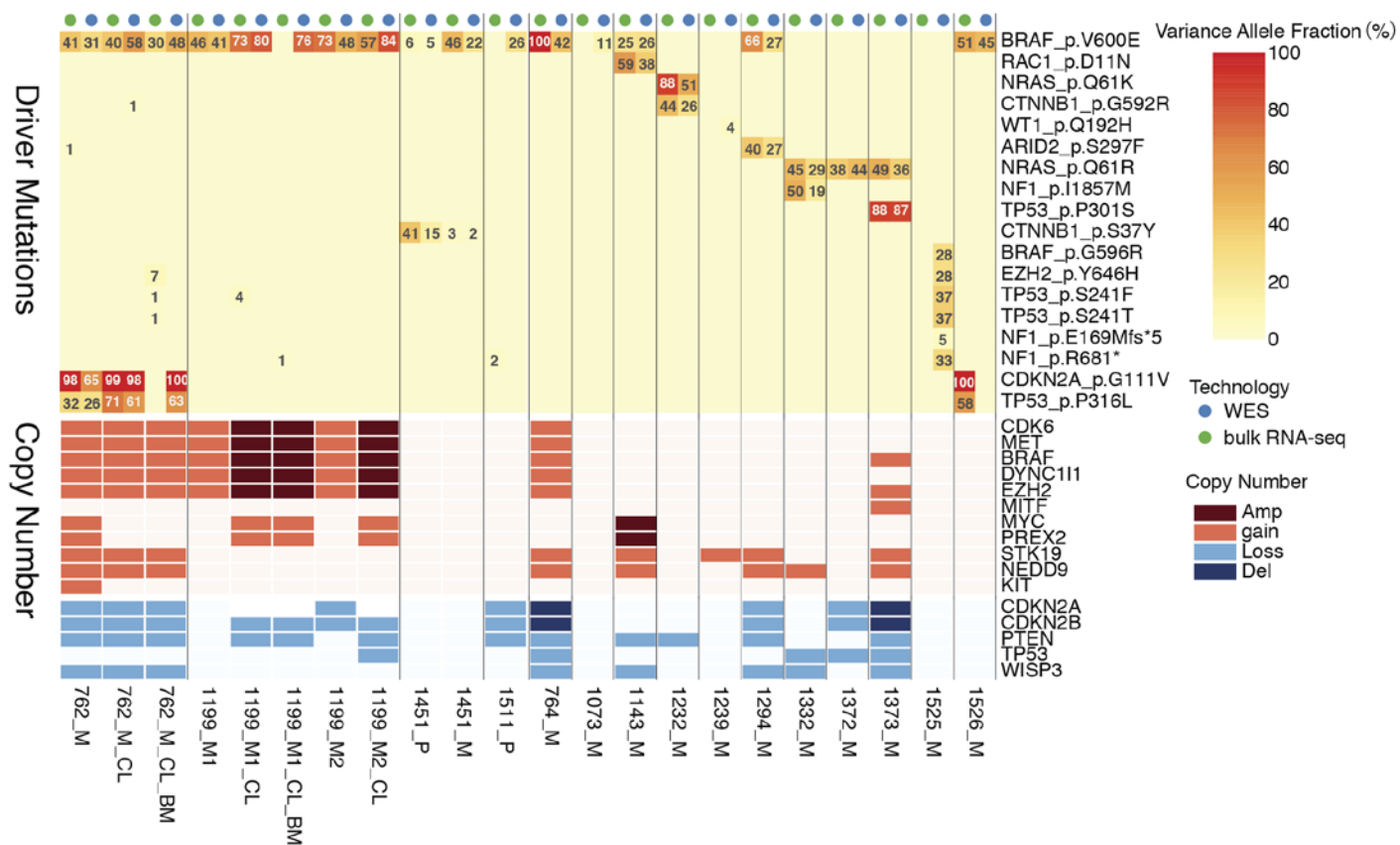
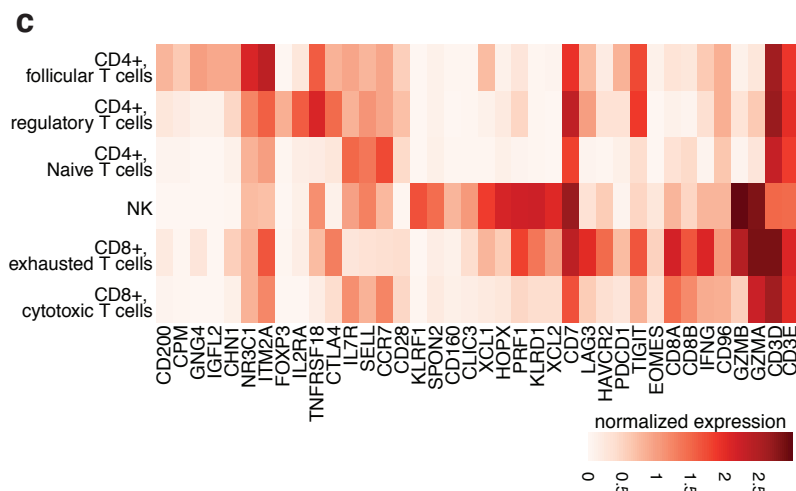
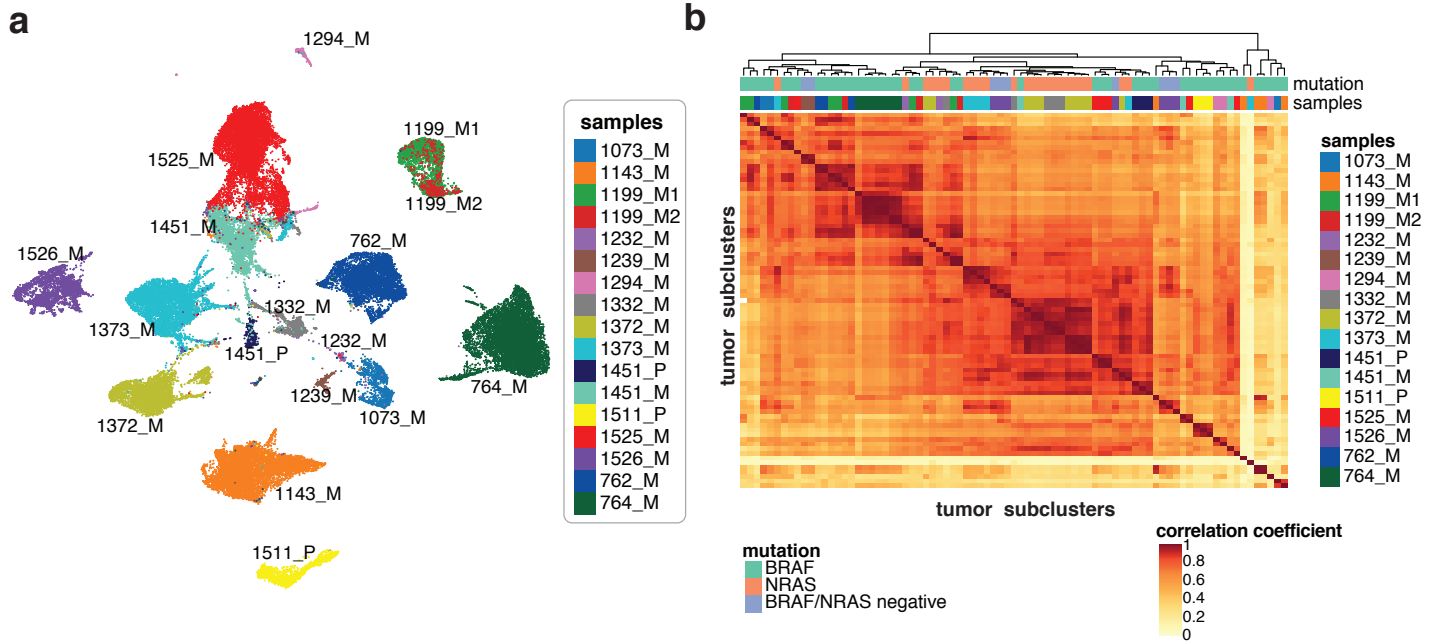
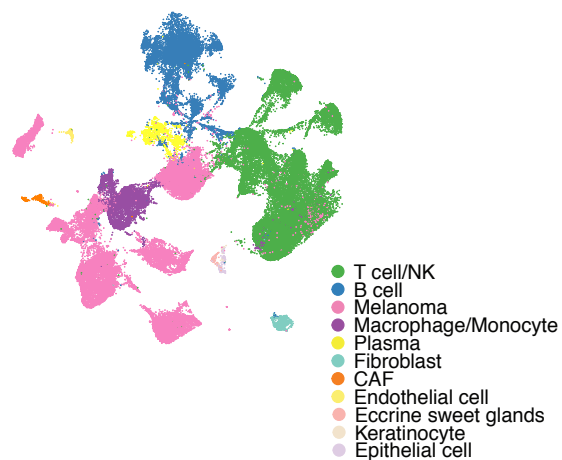


Figure S1. Genomic landscape of 15 melanoma patients.

Heatmap shows the landscape of driver mutations and CNVs across 15 patients with vertical black lines separating patients. Copy number amplification/gain, copy number deletion/loss are shown in dark red/red, dark blue/blue respectively. The color of driver mutations indicates VAF, measured by both WES and bulk RNA-seq, shown as blue and green dots on the top, respectively.



d Integration of all cells colored by cell types



e Integration of immune cells and CAFs

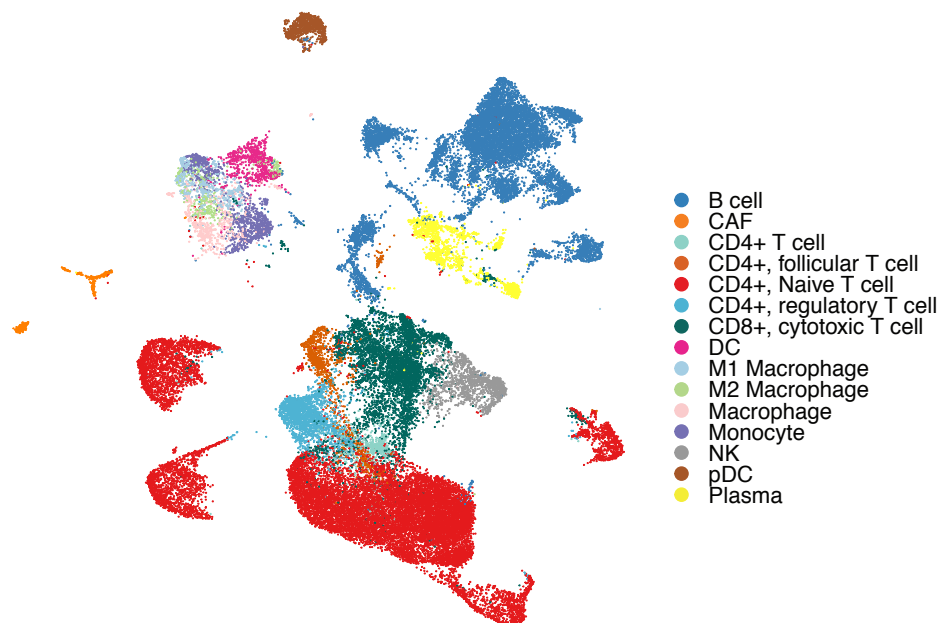


Figure S2. Inter and Intra tumor heterogeneity and cell populations characterized by scRNA-seq.

a. UMAP plot shows integrated melanoma cells from 17 tumors, colored by samples. **b.** Heatmap shows pairwise correlation of tumor subclusters from all melanoma tumor samples, with color indicating pearson correlation coefficient. Tumor subclusters are clustered by transcriptional similarity of top variable genes among subclusters. X-axis and Y-axis are the tumor subclusters. **c.** Heatmap shows average normalized expression of top differentially expressed genes of selected immune cell subtypes in 8 samples shown in Fig. 1c. **d.** UMAP plot shows integrated all cell types from 10 melanoma samples processed by Chromium Single Cell 5' Reagent Kits, colored by main cell types. **e.** UMAP plot shows integrated immune cells and CAFs from 10 samples as in panel d, colored by immune cell subtypes.

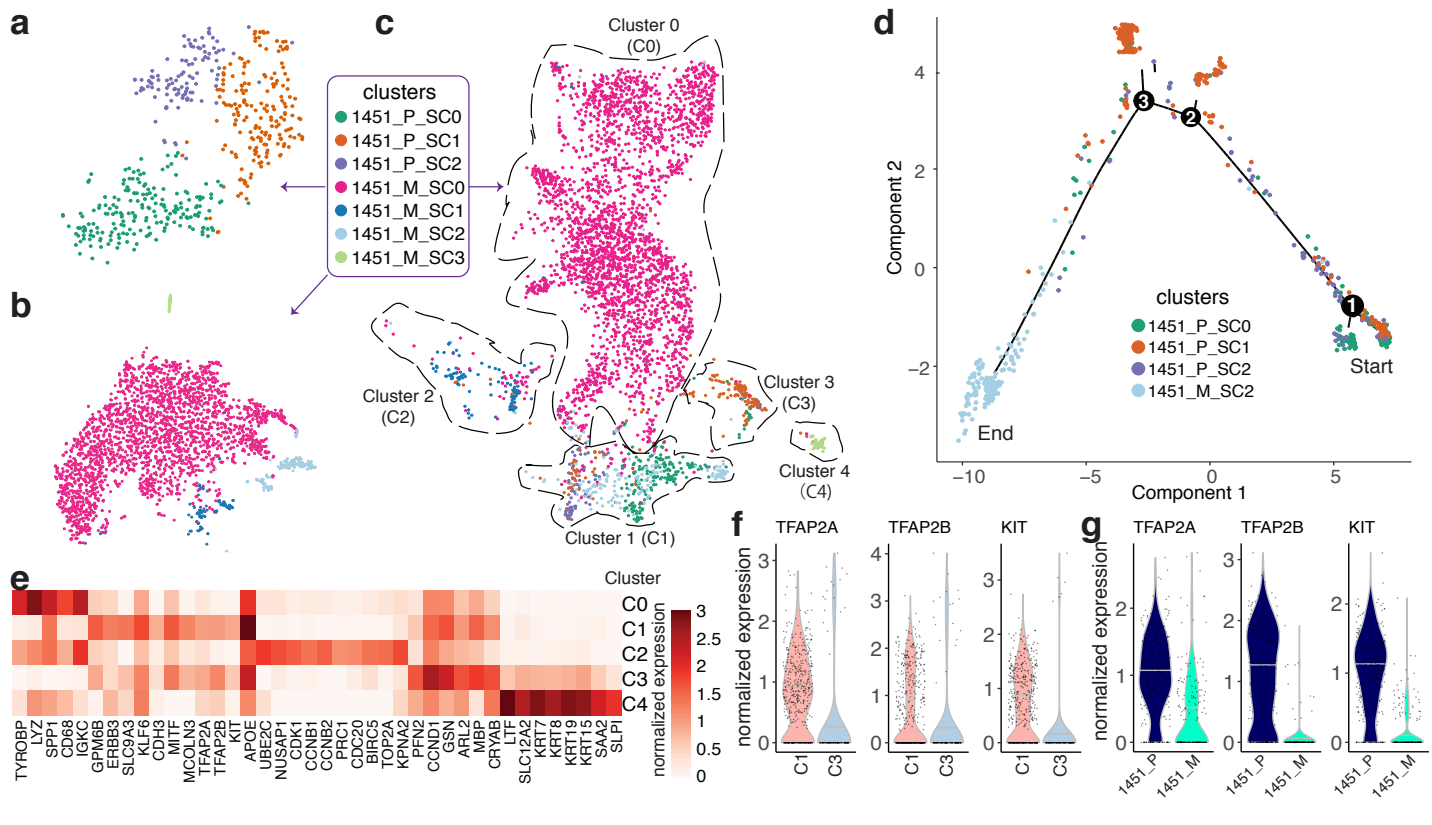


Figure S3. Clonal evolution of melanoma cells from primary to metastasis in patient 1451.

a. UMAP shows subclones of melanoma cells from patient 1451 primary tumor (1451_P). SC=sub-cluster. **b.** UMAP shows subclones of melanoma cells from patient 1451 metastatic tumor (1451_M). **c.** UMAP shows integrated melanoma cells from both primary and metastatic tumors of patient 1451, colored by subclones indicated in panels a and b. Dashed lines indicate the clustering structure based on transcriptional profiles of merged samples. **d.** Monocle trajectory analysis of cells in 1451 primary tumor and subcluster 2 (SC2) in metastatic tumor (1451_M). **e.** Heatmap shows the average normalized expression of top differentially expressed genes (DEGs) of each cluster in merged samples. **f.** Violin plots show the normalized expression of TFAP2A, TFAP2B, KIT in cluster 1 (C1) and cluster 3 (C3) respectively. **g.** Violin plots show the normalized expression of TFAP2A, TFAP2B, KIT in cluster 1 from primary tumor (P) and metastatic tumor (M) respectively.

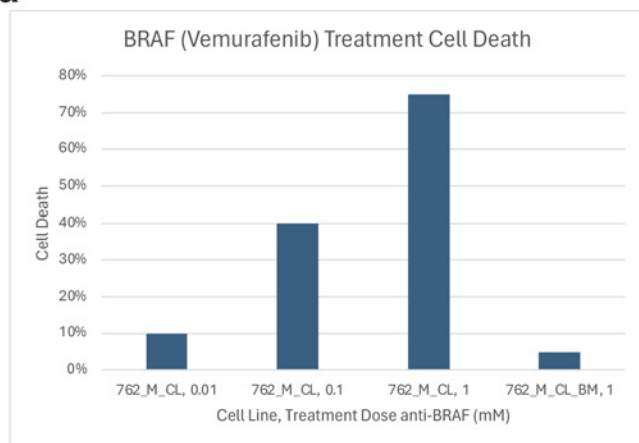
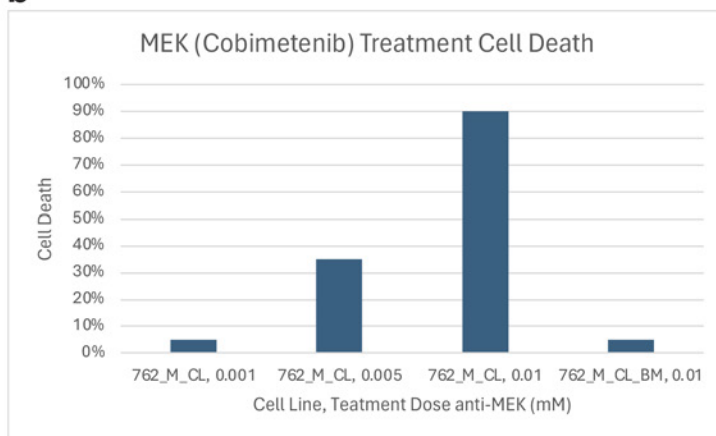
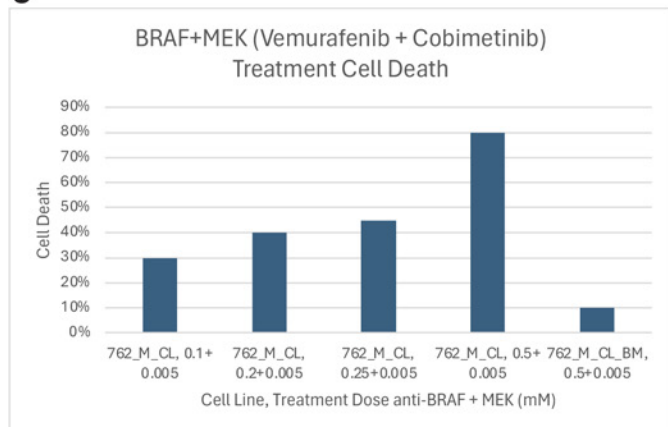
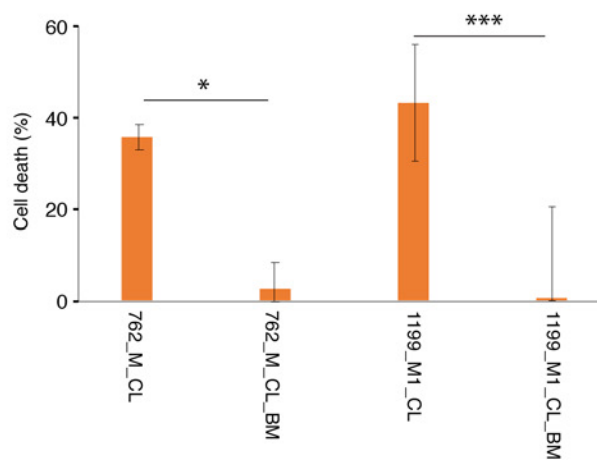
a**b****c****d**

Figure S4. Dosage titrations and BRAF/MEK inhibitor killing of naïve and resistant cell line.

a. Vemurafenib, **b.** Cobimetinib, and **c.** Vemurafenib + Cobimetinib dose titrations for BRAF-MEK naïve cell line 762_M_CL, as well as BRAF-MEK resistant cell line, 762_M_CL_BM. Cell death was determined via estimates from microscopy with trypan blue staining for non-viable cells. **d.** Bar chart shows BRAF/MEK inhibitors killing of 762_M_CL versus its corresponding BRAF/MEK resistant line 762_M_CL_BM, and 1199_M1_CL versus its corresponding BRAF/MEK resistant line 1199_M1_CL_BM. $\ast=p<0.05$ and $\ast\ast\ast=p<0.001$.

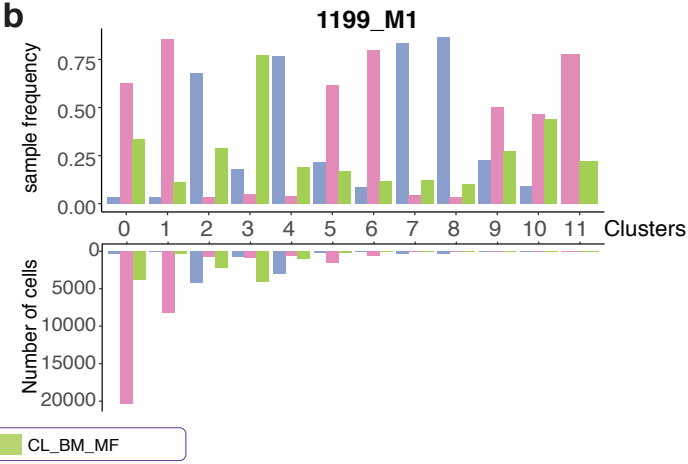
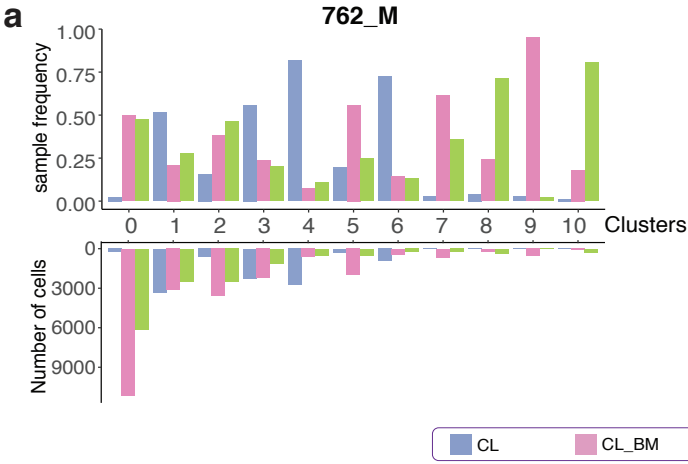


Figure S5. Numerical population breakdown for scRNA-seq data of cell lines samples for 762_M and 1199_M1.

a. Top: Bar chart shows the proportion of cells from each sample in every cluster in case 762_M. The total number of cells in each sample was normalized by the minimum number of cells among 3 samples before calculating proportion. Bottom: Bar charts shows the number of cells from each sample in every cluster in case 762_M (related to Fig. 4b and Fig. 4c). **b.** Top: Bar chart shows the proportion of cells from each sample in every cluster in case 1199_M1. The total number of cells in each sample was normalized by the minimum number of cells among 3 samples before calculating proportion. Bottom: Bar chart shows the number of cells from each sample in every cluster in case 1199_M1 (related to Fig. 4b and Fig. 4c).