

**Supplementary Table S1.** List of the variants detected in single circulating tumor cells (CTCs) of patients in the different timepoints. Time A: baseline; time B: 6-8 weeks after the beginning of treatment; time C: 2-4 weeks after the last dose of therapy.

Patient CH29	Time A										
	1	4	5	6	8	12	14	15	17	18	
	APC c.4451A>G p.D1484G	ATM c.998C>T p.S333F	ATM c.998C>T p.S333F	ATM c.998C>T p.S333F	ATM c.998C>T p.S333F	ATM c.998C>T p.S333F	ATM c.998C>T p.S333F	ATM c.998C>T p.S333F	ATM c.998C>T p.S333F	ATM c.998C>T p.S333F	
		AKT1 c.63delC p.T21fs	NOTCH1 c.7327G>T p.V2443L		TP53 c.628C>T p.R210X	TP53 c.628C>T p.R210X	EGFR c.872G>A p.C291Y		EGFR c.2092G>A p.A698T		
						PTEN c.900C>T p.I300I			SMAD4 c.1275delT p.A425fs		
									PDGFRA c.2558G>A p.G853D		
									SMAD4 c.529C>A p.H177N		
	Time B										
	2	8	9								
	ATM c.998C>T p.S333F	ATM c.998C>T p.S333F	TP53 c.628C>T p.R210X								
PTEN c.860C>G p.S287X	PTEN c.860C>G p.S287X	CDKN2A c.346G>T p.D116Y									
Time C											
4	20										
ATM c.998C>T p.S333F	FLT3 c.1361C>A p.S454X										
FGFR1 c.545G>A p.S182N	APC c.3067C>A p.Q1023K										
RB1 c.2264T>C p.F755S											
Patient CH30	Time A										
	1	5	8	4bis	5bis	8bis	15	16	17	15bis	18bis
	MET c.2947C>A p.L983I	GNA11 c.694C>A p.L232I	TP53 c.678G>T p.E226D	RET c.2342A>C p.Q781P	VHL c.407delG p.R136fs	NRAS c.196G>T p.A66S	ABL c.1057G>T p.E353X	TSC1 c.1444C>T p.P482S	JAK3 c.418C>T p.Q140X	ABL1 c.772C>A p.R258S	PIK3CA c.1033A>G p.N345D
	ALK c.3778C>T p.P1260S								ERBB2 c.935C>T p.T312I		VHL c.411delG p.L137fs
	MLH1 c.380C>T p.S127L										BRAF c.1372A>G p.T458A
	Time C										
1	2										

	<i>HNFI1A</i> c.851A>G p.D284G	<i>JAK3</i> c.406C>T p.H136Y	
	<i>PIK3CA</i> c.2699C>G p.S900X	<i>FBXW7</i> c.1122G>T c.G1122T	
	Time A		
	1	2	5
	<i>HNFI1A</i> c.893C>T p.A298V	<i>AKT1</i> c.49G>A p.E17K	<i>AKT1</i> c.49G>A p.E17K
	<i>TP53</i> c.518A>G p.K173R	<i>TP53</i> c.384delC p.S128fs	<i>TP53</i> c.73G>T p.V25F
		<i>TP53</i> c.384delC p.S128fs	<i>SMO</i> c.608C>T p.P203L
		<i>RB1</i> c.1032G>T p.Q344H	