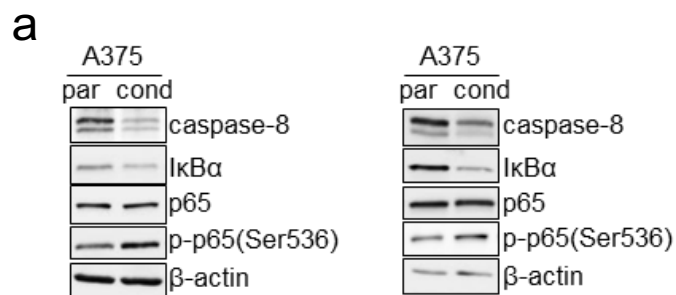


Figure S1: Clonogenic outgrowth of *mut*BRAF melanoma cells in response to dabrafenib. 8.5×10^2 A375 or 2×10^4 Malme3M cells were seeded into 6-well plates and stimulated or not with dabrafenib (Dabra, 10 μ M) for 8 days. Subsequently, cells were stained with crystal violet. Three independently performed experiments per cell lines are shown.



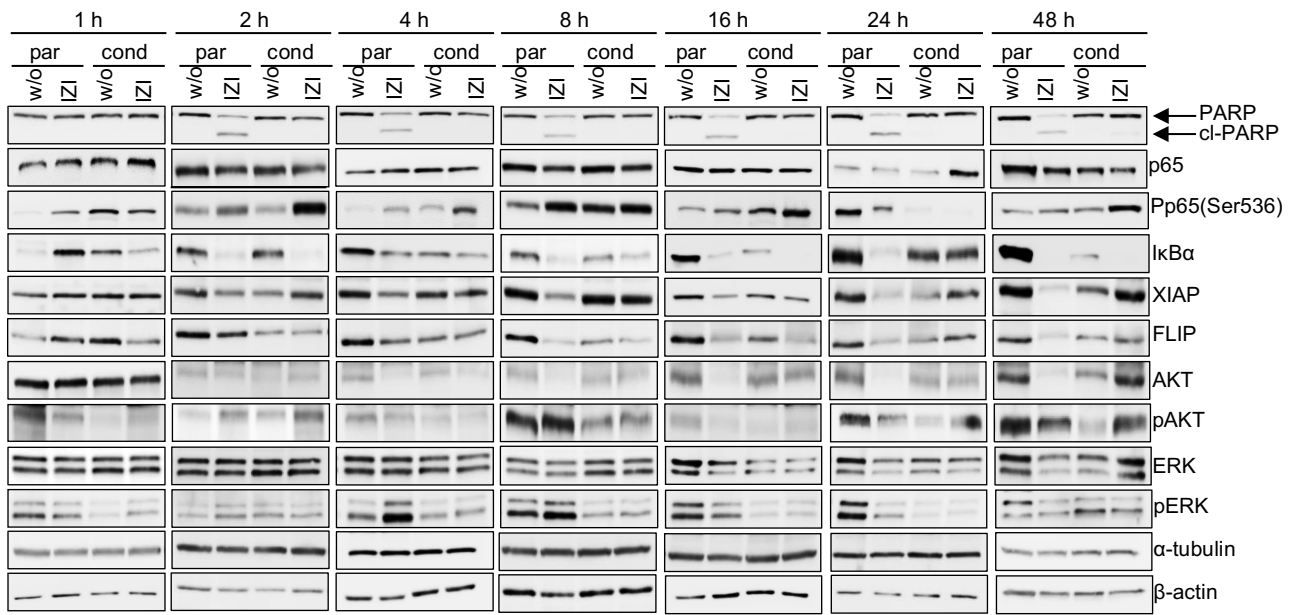
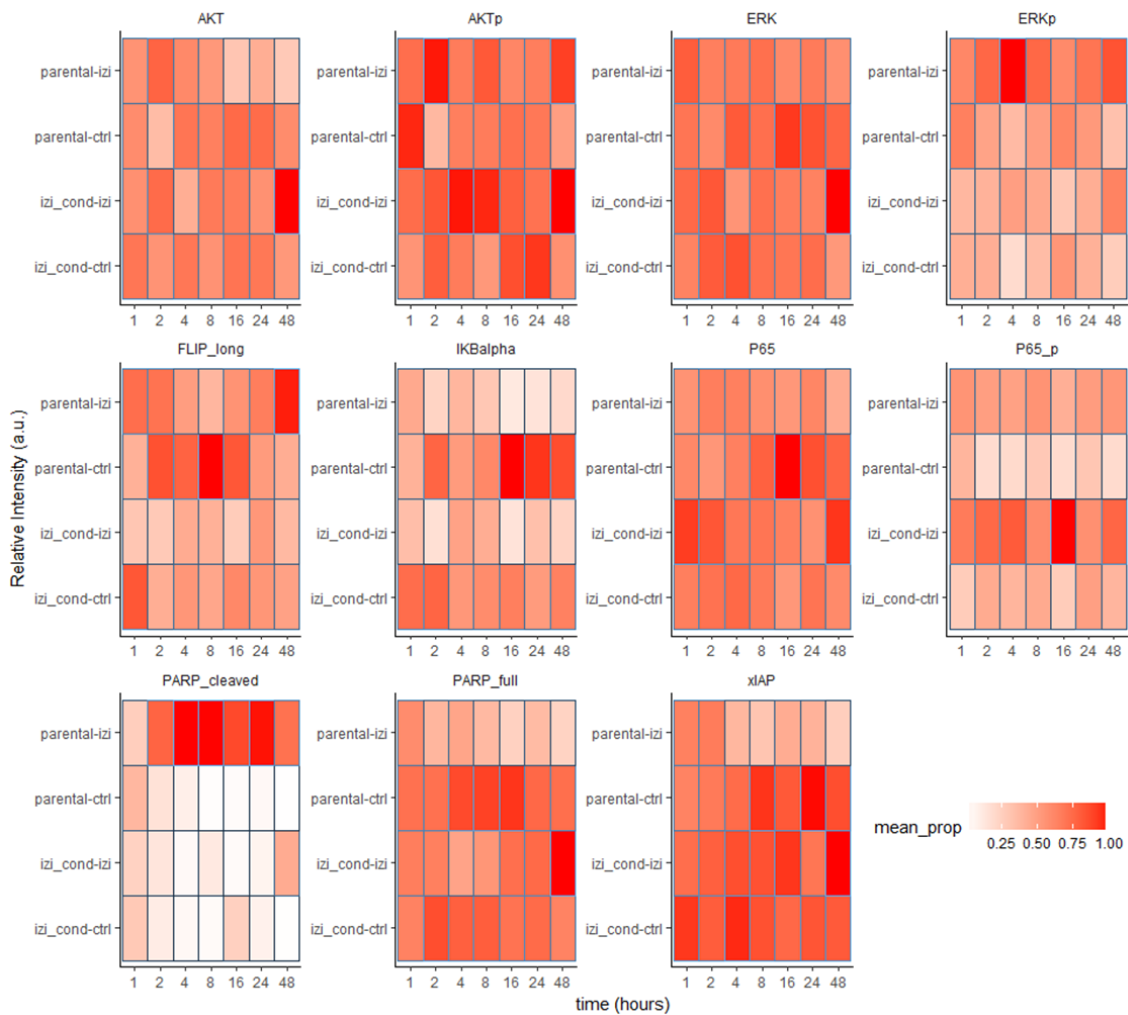
b**c**

Figure S2: Protein expression pattern of TRAIL-sensitive parental versus TRAIL-resistant conditioned melanoma cells. (a) The expression level of caspase-8, I κ B α , NF κ B(p65) and phosphorylated-p65(Ser536) in untreated parental and IZI-conditioned A375 cells was monitored by Western-blot analysis. β -actin served as loading control (b) Expression and/or activation of PARP, NF κ B(p65), pp65(Ser536), I κ B α , XIAP, FLIP, AKT, pAKT, ERK, pERK was assessed in *mutBRAF* A375 melanoma cell lines at the indicated time points by Western-blot analysis. α -tubulin and β -actin served as loading control. One representative out of 5 independently performed experiments is shown. (c) Normalized time course Western-blot data comparing parental and IZI conditioned A375 cells upon IZI1551 treatment. The represented heatmaps show the mean expression of 5 replicates with the highest intensity scaled to 1.

	target	dose [ng/ml]	treatment	scaled_mean (%apoptosis)	scaled_error
1	apoptosis	0	ctrl	5.0	0
2	apoptosis	0.5	IZI	17.0	2.2
3	apoptosis	2	IZI	25.6	1.1
4	apoptosis	4	IZI	33.9	3.4
5	apoptosis	6	IZI	40.3	1.6
6	apoptosis	8	IZI	41.6	6.6
7	apoptosis	10	IZI	58.6	8.6
8	apoptosis	25	IZI	61.1	5.13
9	apoptosis	50	IZI	64.5	6.8

Table S1: IZI dose response data used for the EC50 calculation.

parameter values			
reaction	parental	conditioned	interpretation
BCL2- Casp3cl	0.013	0.013	equal
Casp3cl->Apoptosis	0.500	0.501	equal
Casp3cl- XIAP	0.379	0.004	different
Casp8cl- cFLIP	0.354	0.365	equal
cFLIP->pAKT	0.981	0.984	equal
cFLIP->pIKK	0.071	0.192	different
cFLIP->pERK	0.736	0.736	equal
cFLIP- Casp8cl	0.006	0.005	equal to 0
FADD->pIKK	0.921	0.795	different
housekeeper->cFLIP	0.679	0.680	equal
housekeeper->pp65	0.004	0.008	equal to 0
housekeeper->XIAP	0.731	0.730	equal
housekeeper_BRAF->BRAF	0.022	0.021	equal
IKBalph- pp65	0.006	0.006	equal to 0
NRAS->pAKT	0.019	0.016	equal
NRAS->BRAF	0.978	0.979	equal
pAKT->pIKK	0.008	0.013	equal
pAKT->Survival	0.012	0.020	equal
pAKT- BRAF	0.005	0.005	equal to 0
PARPcl->Apoptosis	0.500	0.499	equal
pERK->pp65	0.473	0.118	different
pERK->Survival	0.963	0.954	equal
pIKK- IKBalph	0.850	0.859	equal
pIKK->pp65	0.523	0.874	different
pMEK->pERK	0.264	0.264	equal
pp65->cFLIP	0.321	0.320	equal
pp65->Survival	0.025	0.026	equal
pp65->XIAP	0.269	0.270	equal
XIAP- Casp3cl	0.013	0.871	different

Table S2: Table comparing the optimal parameter values used for model predictions after L1/2 and L1 groups regularization.