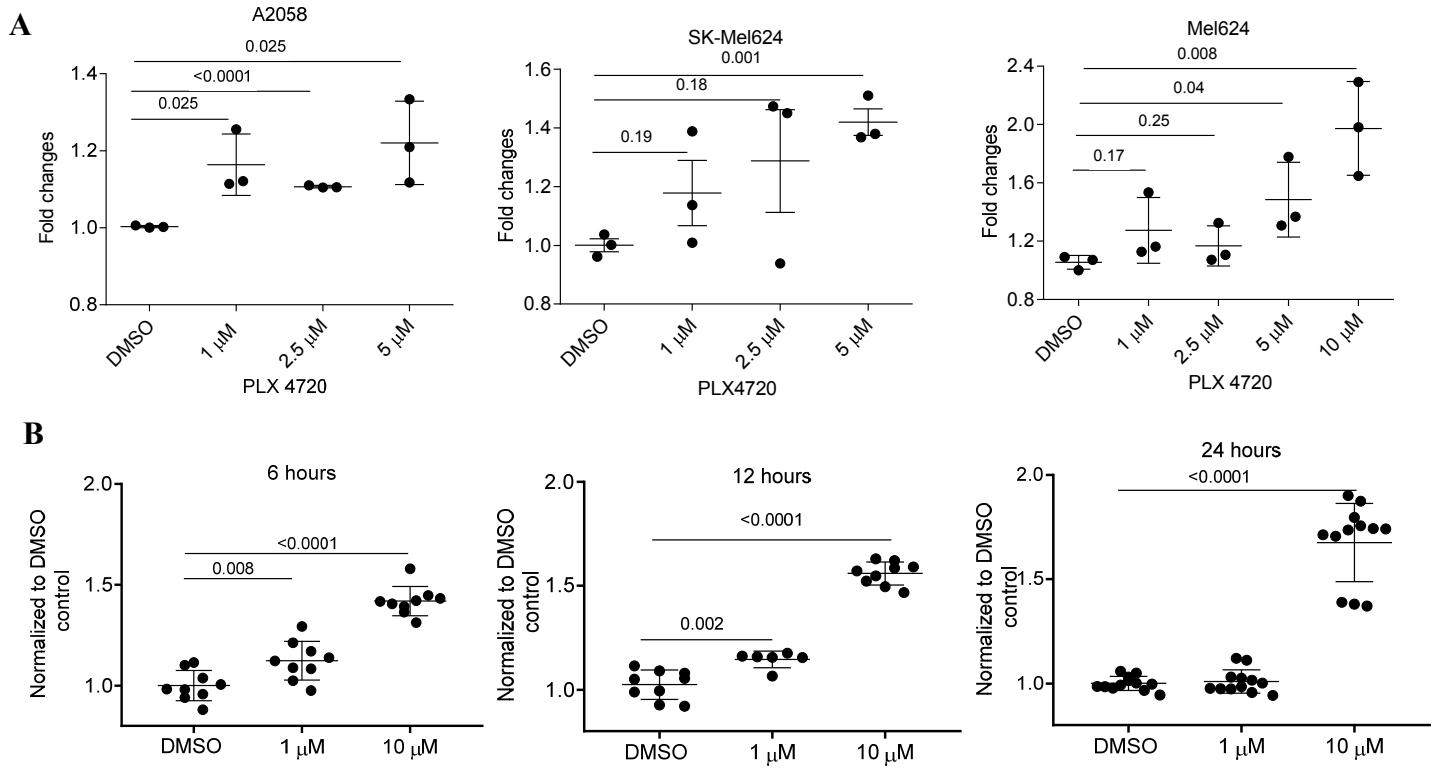
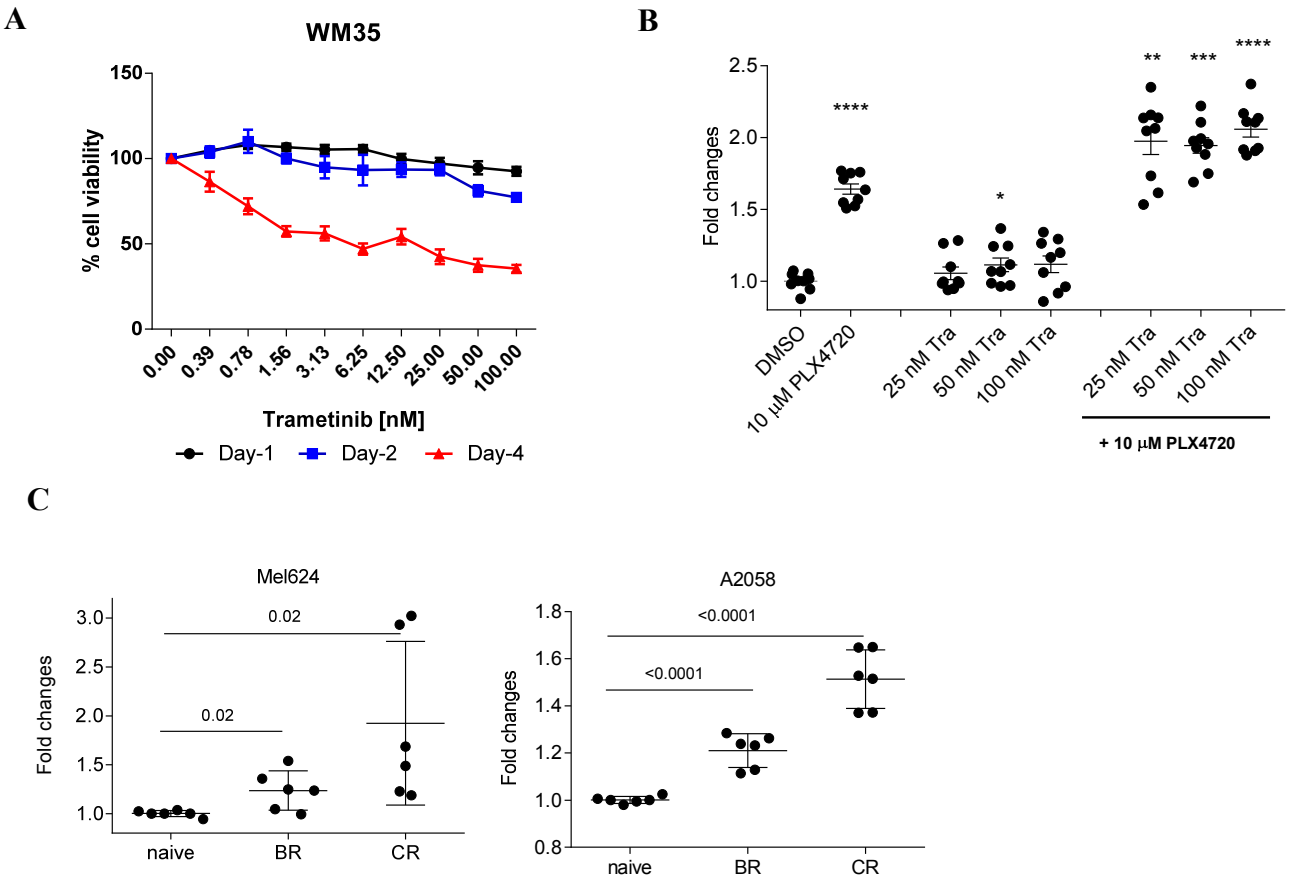
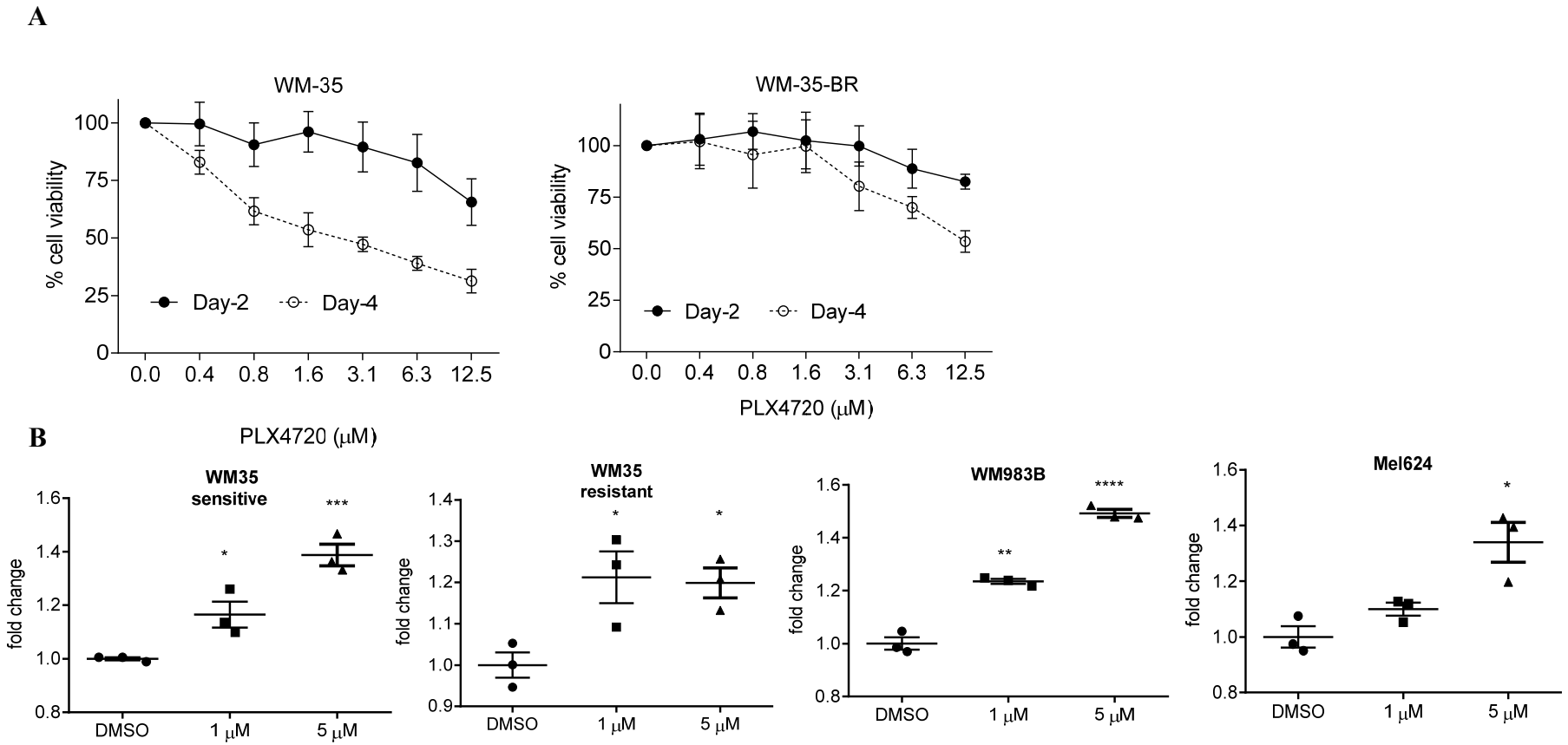


Supplemental Figure 1. Temporal regulation and the effect of combination of B-raf inhibitor on M6PR expression. A. Cell surface M6PR levels on indicated cell lines after 24 hours treatment with PLX4720 and results were normalized to control (DMSO treated samples). Bars represent standard deviation (SD). Statistical analysis by unpaired two-tailed Student's t test. **B.** WM35 cells were treated with PLX4720 for indicated time. M6PR expression was evaluated by flow cytometry. Results of individual experiments, mean and SD are shown. P values were calculated using two-sided Student's t-test.

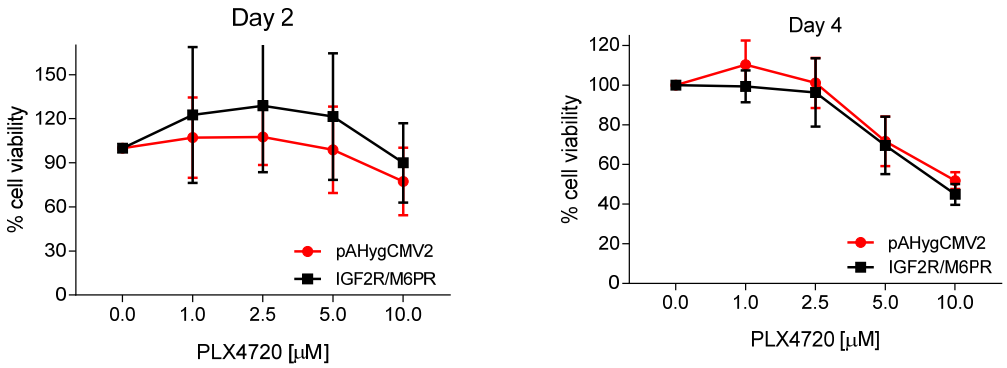


Supplemental Figure 2. Effect of combination of B-raf and MEK inhibitors on M6PR expression. A. MTT assay results showing the cell percentage of live WM35 cells after treating with vehicle (DMSO) or different doses of Trametinib for 1-4 days. **B.** Cell surface M6PR levels of WM35 cells, detected after 24 hours treatment of DMSO, PLX4720 only, Trametinib only or combination of PLX4720 and Trametinib by flow cytometry. Geometric mean was calculated and results were normalized to control (DMSO treated samples). Combined results of 3 different experiments. Bars represent standard error mean (SEM). Statistical analysis by unpaired two-tailed Student's t test with significance determined at *p <0.05, ****p < 0.0001 versus DMSO treated control group and **p < 0.01, ***p < 0.001, ****p < 0.0001 versus 10 µM PLX4720 treated group. **C.** BRAFi (BR) and combined BRAFi + MEKi resistant (CR) cell lines were established by long term exposure to PLX4720 or PLX4720 and Trametinib. M6PR expression was measured by flow cytometry in experimental replicates. Mean and SD are shown. P values in Student's t-test are shown.

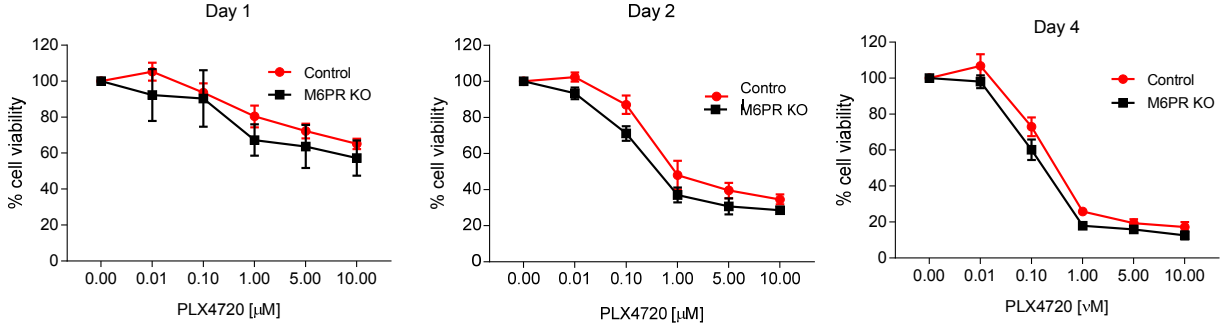


Supplemental Figure 3. WM35 cells resistant to PLX4720. BRAFi resistant WM35 cell line (WM-35BR) was established by long term exposure to PLX4720. Cell viability was measured in experimental replicates in MTT test after 2 and 4 days of treatment. Mean and SD are shown. **B.** Effect of Dabrafenib on the expression of M6PR. Indicated cells were treated with dabrafenib for 16 hr (1 μM or 5 μM) and M6PR expression was evaluated by flow cytometry. Mean and SD are shown. P values were calculated using two-sided Student's t-test; * - $p<0.05$; ** $p<0.01$; *** - $p<0.001$; ****- $p<0.0001$ from DMSO treated controls.

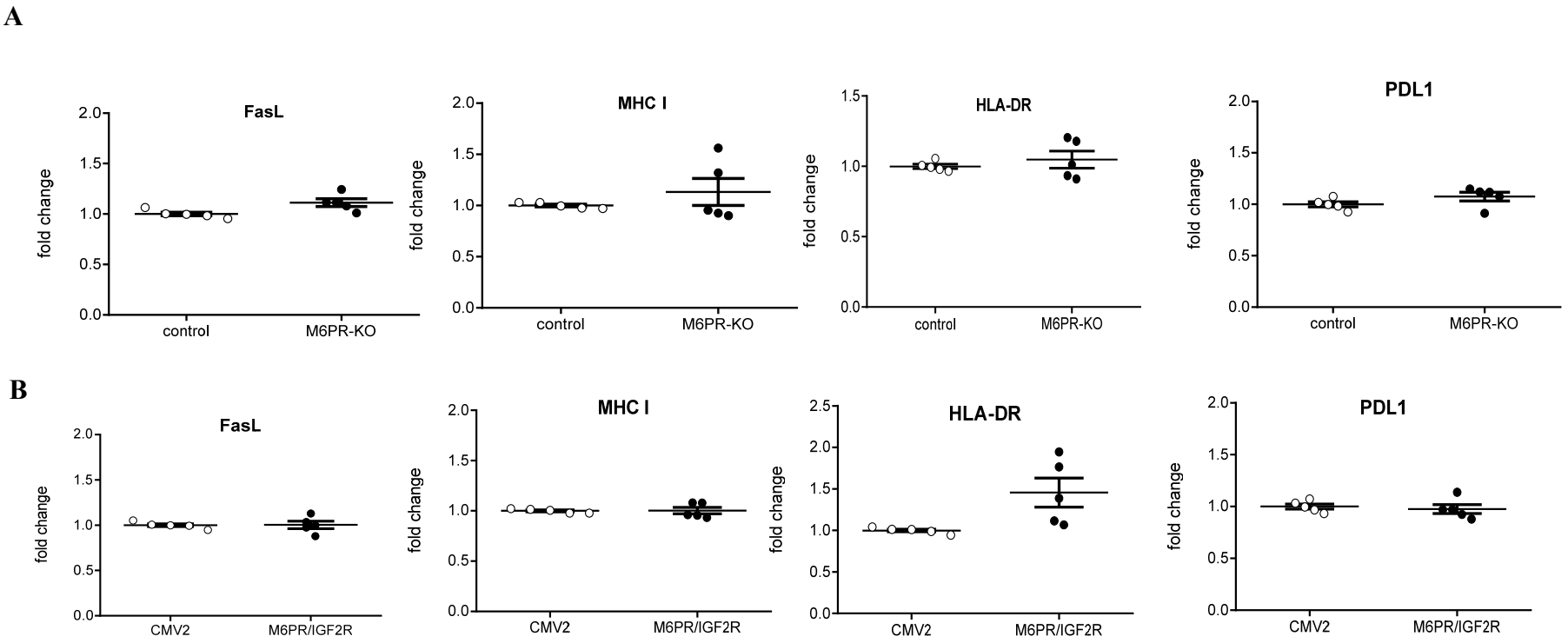
A



B



Supplemental Figure 4. Effect of M6PR overexpression and deletion on melanoma cell sensitivity to PLX4720 in MTT test. A. M6PR overexpressing cells. Ten experimental replicates were performed 2 and 4 days after start of the treatment. Mean and SD are shown. **B.** MTT assay results showing the cell percentage of live WM983B and WM983B-M6PR KO cells after treating with vehicle or different doses of PLX4720 for 1-4 days. Five independent replicates with the same results were performed..



Supplemental Figure 5. Expression of surface molecules on melanoma cells with manipulated expression of M6PR. A. M6PR-KO WM983B cells. **B.** M6PR overexpressing WM35 cells. Appropriate control was used for each cell line as described in the manuscript. Fold increase over control in independent experiments are shown. Cells were seeded in tissue culture plates and 2 day later (80~90% confluent), cells were collected for staining. Mean and SD of biological replicates (n=5) are shown.

Supplemental Table 1 Clinical characteristics of patients enrolled to the study

	Patient No.	Age	Gender	Stage	Previous Therapy	Site of Resection	Number of TIL infused	Response at 12 Weeks	Response at 12 Months	Duration of Vem treatment (months)
	1	18	F	M1c	αCTLA-4, αPD1, IL2	Soft tissue	2.0E+10	PD	PD	6
	2	31	F	M1c	none	Soft tissue	9.1E+09	PD	PD	3
	3	50	F	M1c	none	Soft tissue	8.1E+10	PR	PR	18
	4	38	M	M1c	none	Soft tissue	4.3E+10	PR	PD	8
	5	68	F	M1c	none	Inguinal node	5.2E+10	PR	PR	1
	6	55	M	M1c	None	Axillary node	8.6E+10	PR	PR	12
	7	68	F	M1c	none	Soft tissue and axillary node	3.1E+10	PR	PD	3
	8	42	M	M1c	none	Soft tissue	3.9E+10	PR	PD	9
	9	47	M	IIIC	none	Axillary node	5.0E+10	CR	CR	24
	10	41	M	IIIC	none	Axillary node	5.2E+10	SD	PD	13
	11	49	M	M1c	αCTLA-4, αPD1	axillary node	5.3E+10	PR	PR	20
	12	47	F	M1c	none	Neck node	6.5E+10	PD	PD	4
	13	53	M	M1c	adjuvant αCTLA-4 & αPD1	Axillary node	3.1E+10	PR	PR	18
	14	53	M	IIIC	none	Soft tissue	5.6E+10	SD	PD	9
	15	39	F	M1b	none	Inguinal node	7.3E+10	PR	PD	7
	16	35	M	M1c	none	Axillary node	1.1E+11	PD	PD	1

Supplemental Table 2. Grade 3+ Adverse Events in treated patients

	Adverse Event[1]	Grade 3	Grade 4
	Neutropenia	0	16
	Lymphopenia	0	16
	Thrombocytopenia	2	12
	Febrile neutropenia	11	0
	Rash	7	0
	Anemia	6	0
	Vascular catheter-related thrombosis	4	2
	Cutaneous squamous cell carcinoma	5	0
	Pulmonary edema	4	0
	Hyponatremia	3	0
	Emesis	3	0
	Hypertension	3	0
	Primary cutaneous melanoma	1	0
	Cutaneous basal cell carcinoma	1	0
	Oliguria	1	0
	Hypotension	1	0
	Diarrhea	1	0
	Anasarca	1	0
	Confusion	1	0
	Transaminitis	1	0
	Vasovagal reaction	1	0
	Hyperbilirubinemia	1	0

[1] Note that one patient was treated with vemurafenib but not with ACT