**Supplemental Figure Legends**

**Supplemental Figure S1. Validation of anti-CD73 antibody used for IHC and analysis of cutaneous melanoma metastases.**

**(A)** Procedure of generating a polyclonal pool culture of CD73 deficient MaMel.65 and MaMel.102 melanoma cells by CRISPR-Cas9 and FACS sorting. **(B)** Immunohistochemical stain for CD73 of formalin-fixed and paraffin-embedded melanoma cell pellets with indicated genotypes. CD73 knockout (CD73ko) cultures are polyclonal and contain a low percentage of CD73+ wild-type cells for intrinsic control purposes. **(C)** Survival analyses of patients with cutaneous melanoma metastases by CD73 IHC score. p-value determined by log-rank test. **(D)** Frequency of CD73 IHC scores in primary melanomas and cutaneous melanoma metastases.

**Supplemental Figure S2. Next-generation sequencing based analysis of bisulfite conversion to assess CpG island methylation in the *NT5E* (CD73) promoter region.**

**(A)** Overview of the bisulfite conversion approach for CpG islands 1-7 in the *NT5E* (CD73) promoter region. PCR and NGS-based analysis is shown exemplary. **(B)** Summary of CpG island 1-14 methylation status (%) in the *NT5E* (CD73) promoter region.

**Supplemental Figure S3. c-Jun and FOSL1 protein expression in MaMel melanoma cell lines.**

**(A, B)** Immunoblots for MITF, IκBα, phospho-c-MET and actin in (A) MaMel.71 and (B) MaMel.15 cells stimulated with TNF-α, HGF or both. Typical MITF double-band is indicated by horizontal lines. Upper band of MITF corresponds to a ERK-phosphorylated form of MITF. n.s., non-specific band. **(C)** c-Jun and FOSL1 expression in MaMel melanoma cell line panel shown in main Figure 2D. Same lysates and loading as in main Figure 2D. Immunoblots for CD73, MITF and actin also shown in main Figure 2D are included as reference. **(D)** Immunoblots for FOSL1, phospho-ERK, ERK and actin in indicated melanoma cell lines treated with trametinib [50nM] for different time points.

**Supplemental Figure S4. Functional role of AP-1 sites in the NT5E (CD73) genomic region for the induction of CD73 by c-Jun.**

**(A)** CD73 FACS of MaMel.79b melanoma cells transiently transfected with the indicated CRISPR/Cas9-sgRNA constructs targeting different AP-1 sites (red) or a control site (grey). FACS plots for each of the biological triplicates are shown. CD73 expression in the total population of MaMel.79b cells transfected with the control sgRNA is shown as overlay (grey) in each plot. Pie charts show corresponding mutagenesis frequencies of AP-1 site or control sites in total cell populations and the respective FACS-sorted CD73 lowest 10% and CD73 highest 10% subfractions. **(B)** Histograms showing mutagenesis frequencies of AP-1 or control sites in FACS-sorted CD73 low versus high subfractions in MaMel.54a and Ma.Mel85 melanoma cell lines. Error bars indicate s.d. from technical triplicates.

**Supplemental Figure S5. IHC analysis of CD73 expression by melanoma cells in mouse ACT relapse melanomas.**

**(A)** IHC for CD73 of an ACT late relapse melanoma showing CD73 positive cells with typical histomorphological characteristics of malignant cells. **(B)** IHC for CD73 and CD45 showing frequency of CD45+ immune cells in a CD73+ area from an ACT relapse melanoma.

**Supplemental Figure S6. Comparison of the 'proliferative' melanoma phenotype gene set with the cell proliferation associated E2F and MYC gene sets.**

**(A)** GSEA plots for the HALLMARK\_EMT and VERFAILLIE\_INVASIVE gene sets in relapse versus EDT HCmel3 melanomas. NES, normalized enrichment score; FDR, false-discovery rate. **(B)** GSEA plots for the HALLMARK\_E2F/MYC versus VERFAILLIE\_PROLIFERATIVE gene sets in relapse versus EDT HCmel3 melanomas. **(C)** Core enrichment genes of the VERFAILLIE\_PROLIFERATIVE gene set. Typical pigmentation or melanocyte related genes (MITF target genes) are highlighted in brown. **(D)** Venn diagrams showing minimal overlap between the indicated gene sets used in GSEA.

**Supplemental Figure S7. Graphical abstract of CD73 expression in melanoma phenotype switching.**

The model summarizes that CD73 is regulated in the context of melanoma cell plasticity. CD73 is strongly expressed by MITFlow/AXLhigh 'invasive' melanoma expressed, but also by a subset of MITFhigh cells indicating a nascent or partial invasive phenotype switch. In that sense, CD73 is a marker of melanoma cell plasticity that is distinct from AXL or WNT5A, whose expression is more tightly associated with the fully established MITFlow invasive cell state.