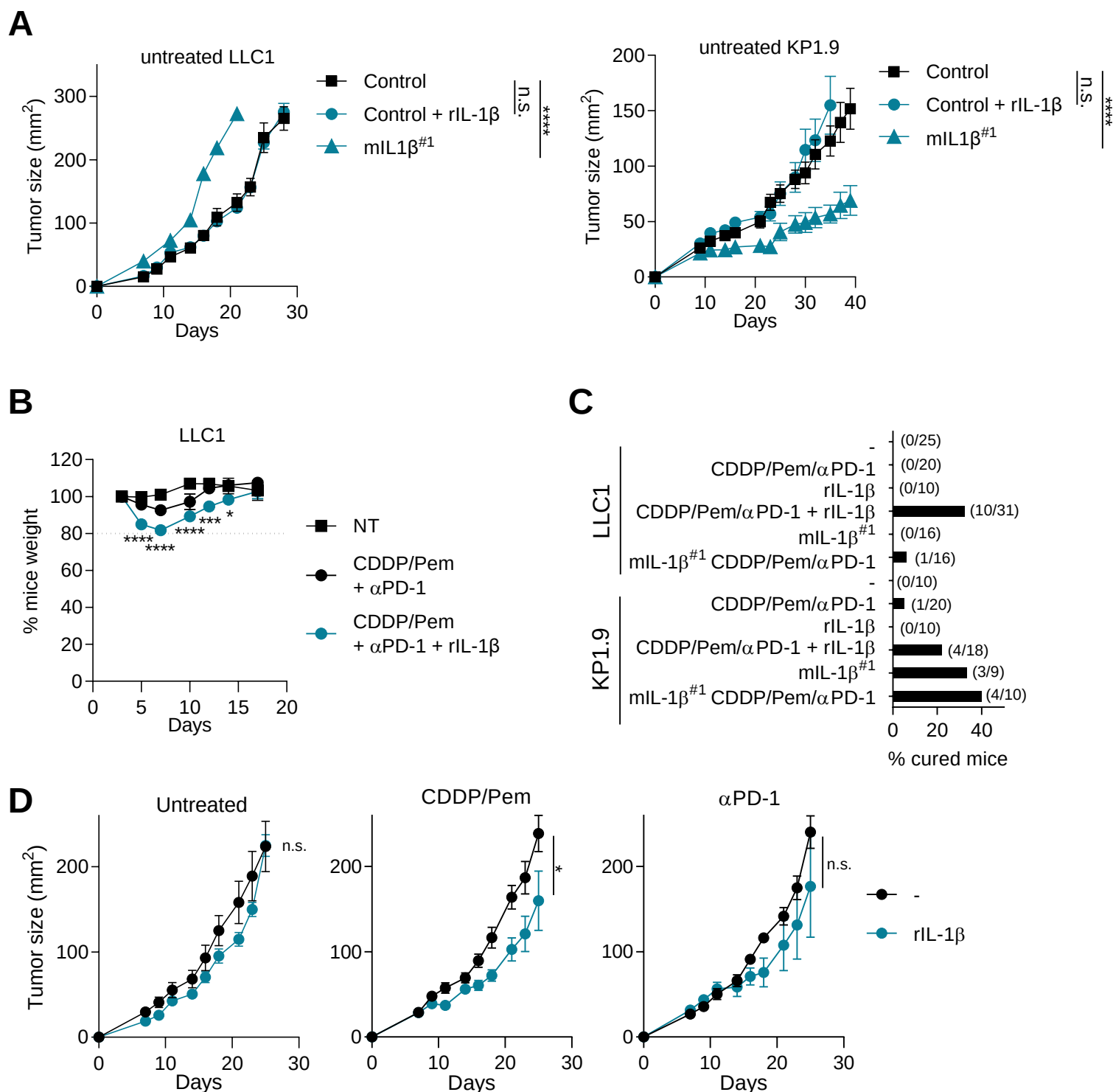


Supplementary Figure 1



A, Tumor growth curves of untreated mice from Figure 1A were represented.

B, LLC1 tumor bearing mice were treated as in Figure 1A. Mice body weight was evaluated at indicated times. Representation of percentages of initial body weights (n=9).

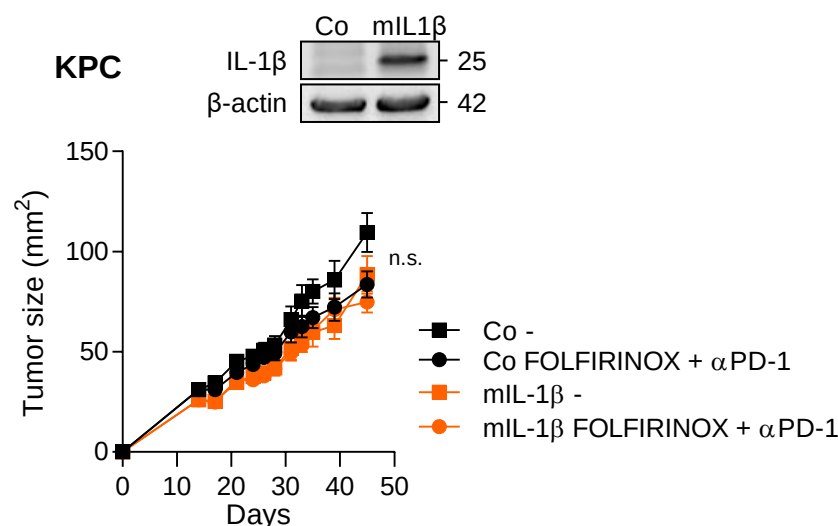
C, LLC1 and KP1.9 tumor bearing mice were treated as in Figure 1A to C. Percentages of cured mice. Numbers in brackets indicate the number of cured mice among total mice involved in several experiments.

D, LLC1 and KP1.9 tumor bearing mice were left untreated or treated with cisplatin (6mg/kg ip), pemetrexed (100mg/kg ip) at d9 (CDDP/Pem) or anti-PD-1 mAb (10mg/kg ip, 3 times a week from d9, for 3 weeks – α PD-1). Recombinant IL-1 β (rIL-1 β - 50 μ g/kg daily intra-tumor injections, from d7 to d15) was used when indicated. Tumor size was monitored (n=7).

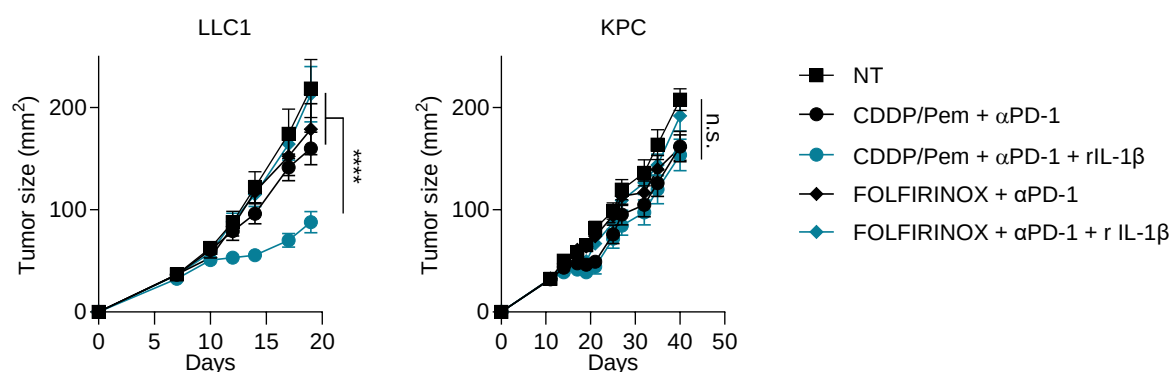
Data represent mean $\pm$ SEM (**A**, **B** and **D**). Two-way ANOVA (**B** and **D**). Unpaired t-test comparing untreated with treated conditions (**A**). *p<0.05, ***p<0.001, ****p<0.0001, n.s., not significant.

Supplementary Figure 2

A



B

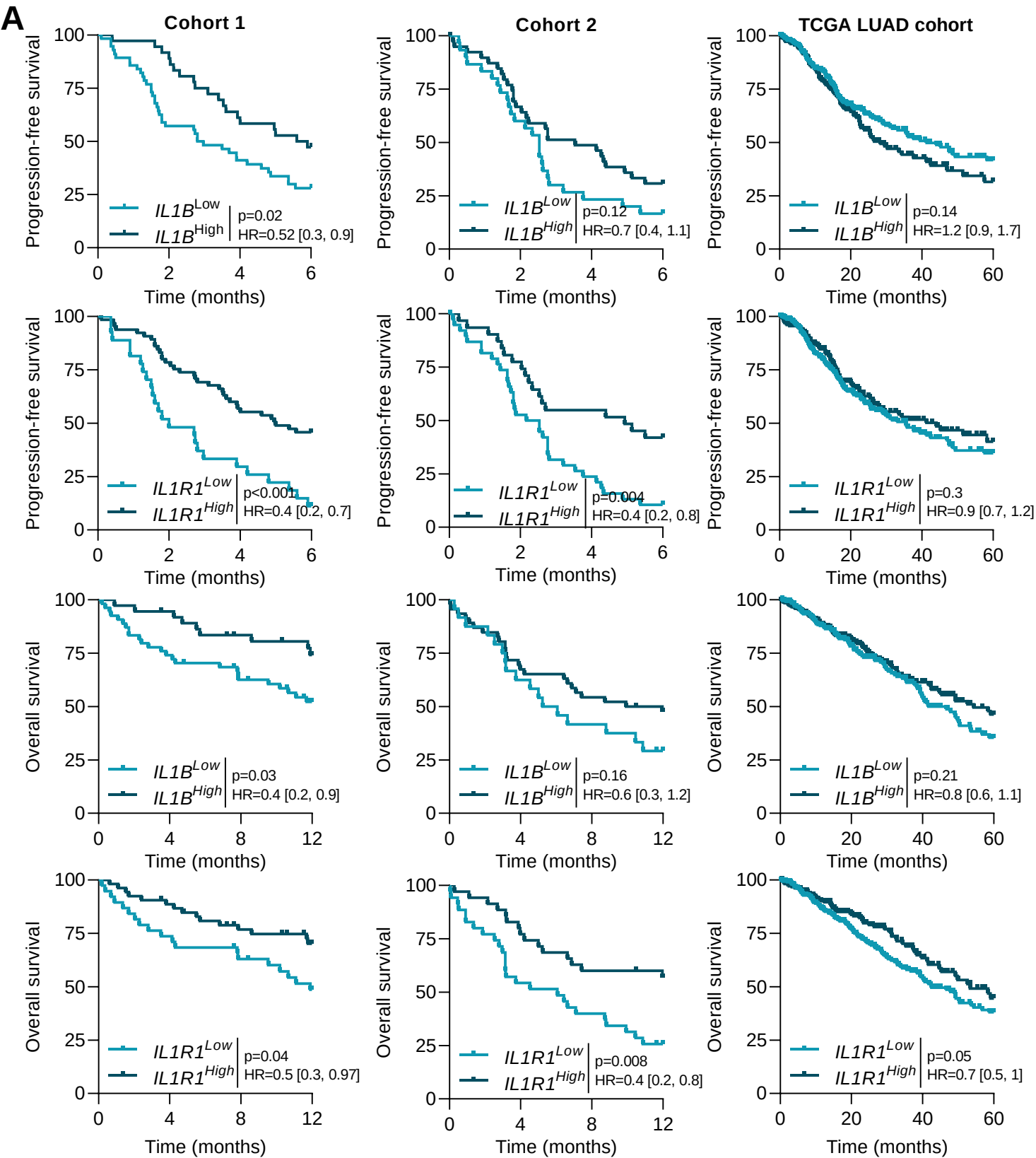


A, Control or mature IL-1 β (mIL1 β) overexpressing KPC pancreas cancer cells were s.c. injected into C57BL/6 mice. Tumor-bearing C57BL/6 mice were treated with FOLFIRINOX, 5-FU (25mg/kg ip), calcium folinate (50mg/kg ip), irinotecan (25mg/kg ip), oxaliplatin (2.5mg/kg ip) at d15 and with anti-PD-1 mAb (10mg/kg ip, 3 times a week from d15, for 3 weeks). Tumor size (n=10) was monitored. Inset: mature IL-1 β expression was analyzed by Western Blot in KPC transfected with empty vector (Co) or with a plasmid expressing the active form of IL-1 β . β -Actin was used as a loading control. Numbers indicate molecular weights in kDa.

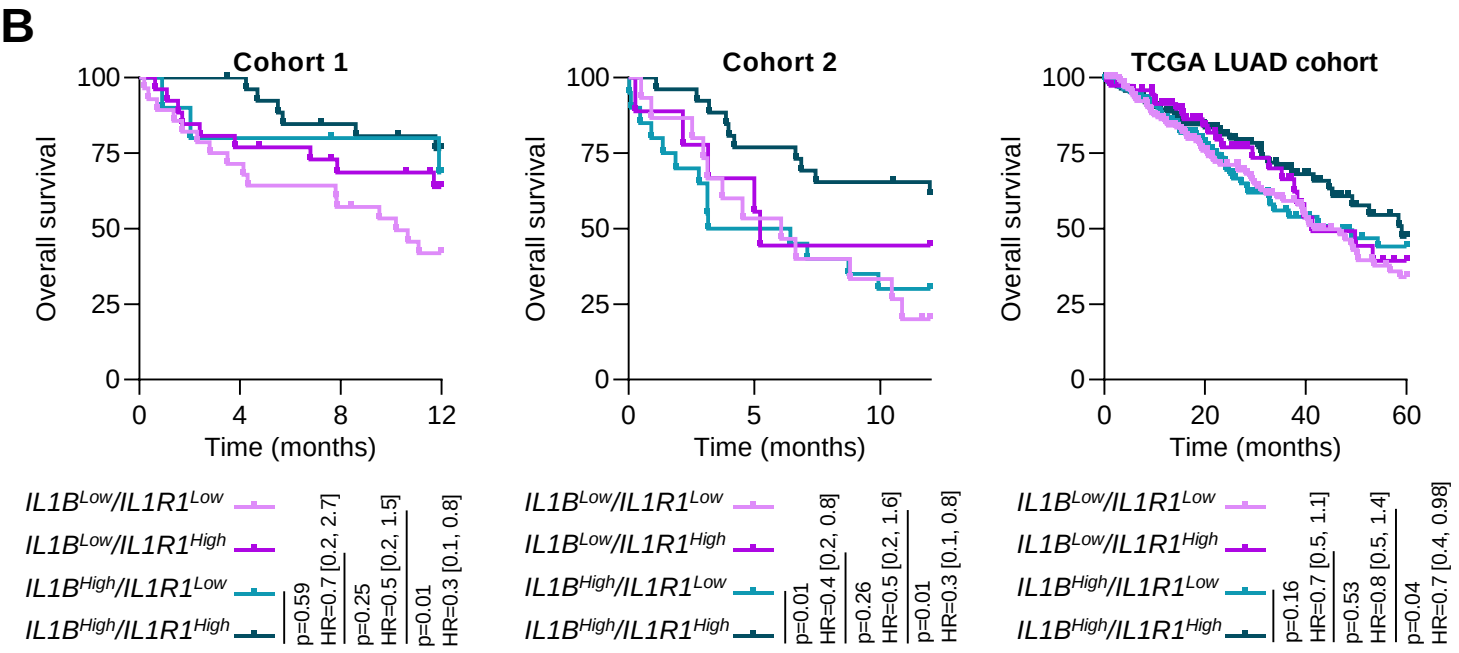
B, LLC1 or KPC cells were s.c. injected into C57BL/6 mice. Tumor-bearing C57BL/6 mice were treated with cisplatin (6mg/kg ip), pemetrexed (100mg/kg ip) (CDDP/Pem) or with FOLFIRINOX (see above) at d9 (for LLC1) and d15 (for KPC) and with anti-PD-1 mAb (10mg/kg ip, 3 times a week from chemotherapy treatment, for 3 weeks). Recombinant IL-1 β (rIL-1 β - 50 μ g/kg) was daily injected in the tumor from d7 to d15 or from d13 to d21. Tumor size (n=10) was monitored.

Data represent mean $\pm$ SEM. Two-way ANOVA. n.s., not significant.

Supplementary Figure 3 (first part)

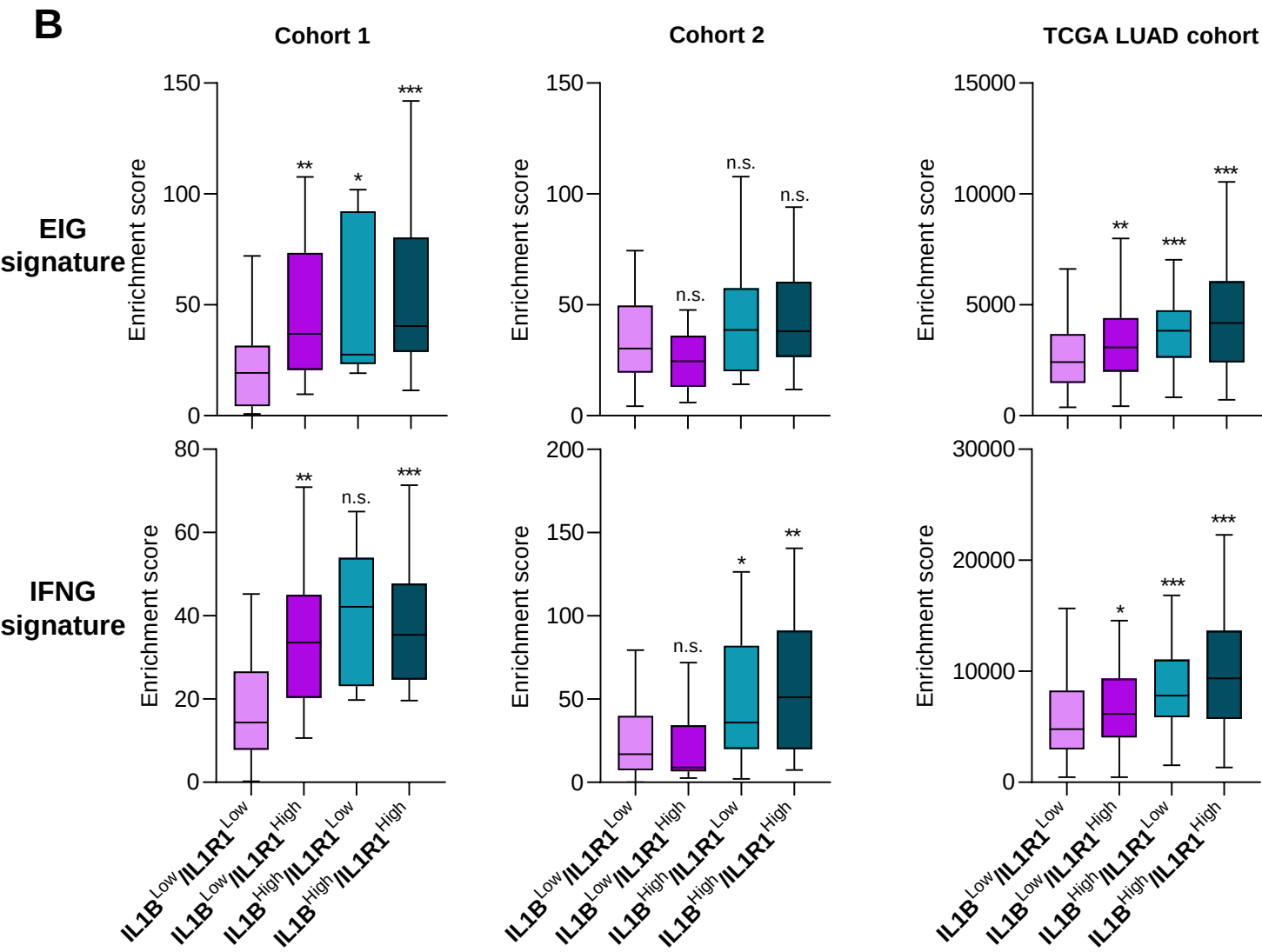
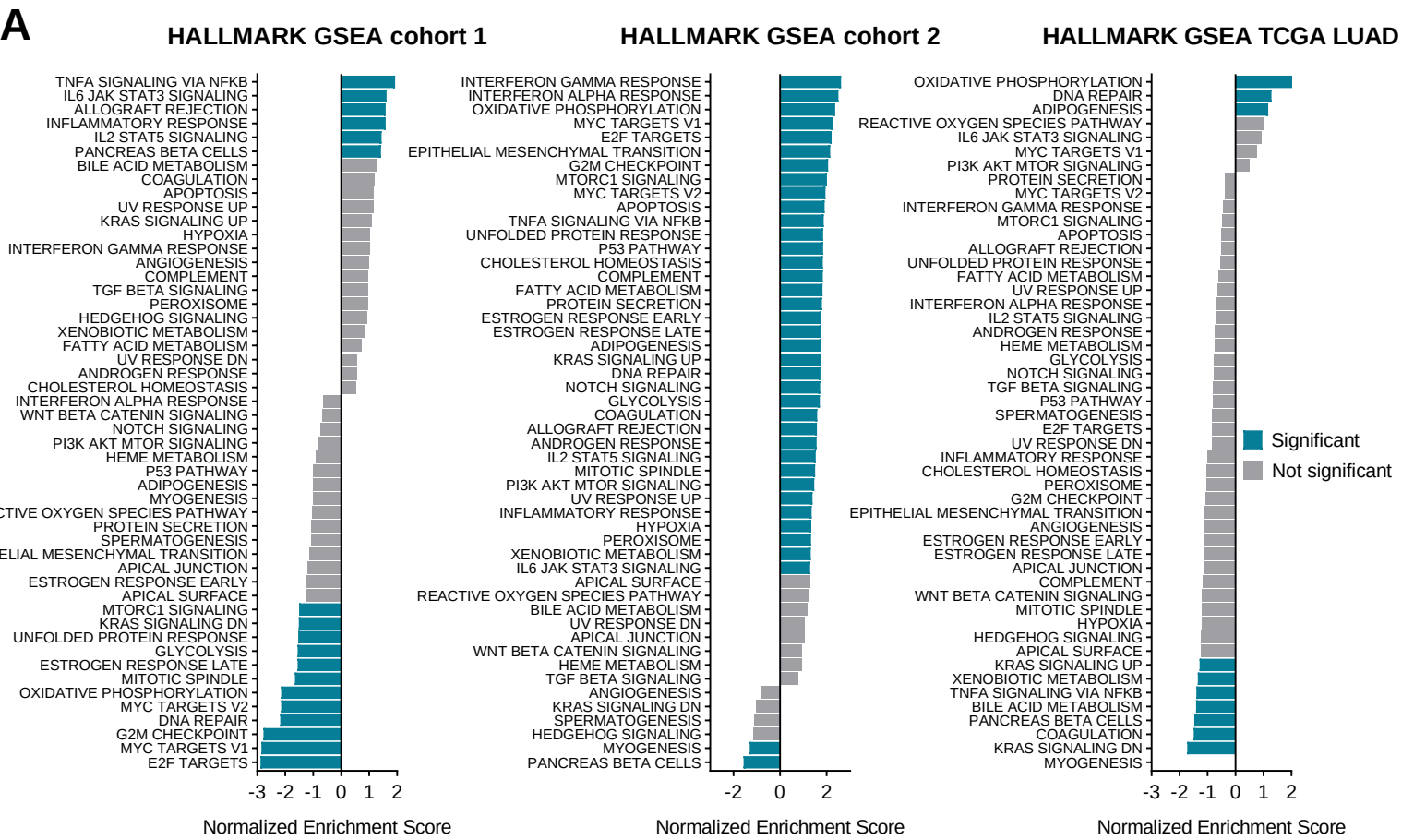


Supplementary Figure 3 (second part)



Kaplan–Meier estimation of progression-free survival or overall survival in patients from cohort 1 (left panels), cohort 2 (middle panels) or the TCGA LUAD database (right panels). Patients were split into two groups with high (H) or low (L) expression of *IL1B* or *IL1R1* genes (A). Patients were split into four groups with high (H) or low (L) expression of *IL1B* and *IL1R1* genes (B). High expression was determined using the optimal cut-off estimated from maximally selected rank statistics. Log-rank t-test p-values.

Supplementary Figure 4

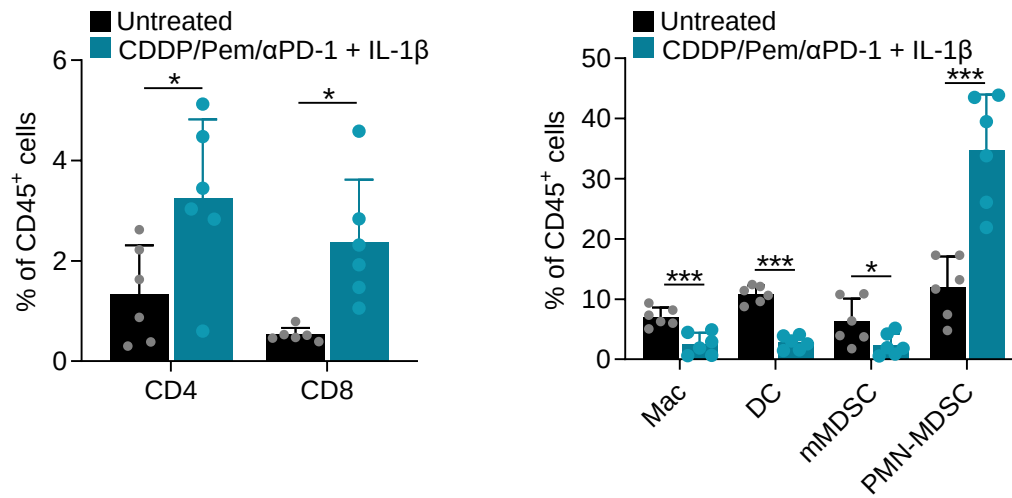


A, GSEA Hallmark analysis showing enriched gene sets in tumor samples of patients from cohort 1 (left panel), cohort 2 (middle panel) or the TCGA LUAD database (right panel) in responders vs non-responders, using median cohort PFS as a cut-off. Bars in blue indicate significant enrichment and bars in gray non-significant enrichment.

B, Enrichment score of EIG and IFNG signatures in patient tumors with high or low *IL1B* and/or *IL1R1* expression from cohorts 1 and 2 and TCGA LUAD cohort.

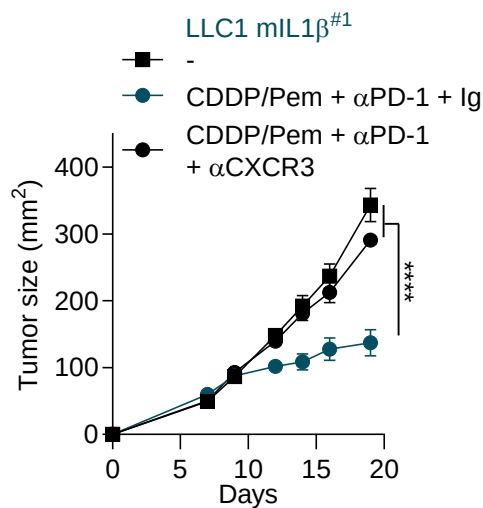
Wilcoxon test comparing Low/Low with other conditions. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, n.s., not significant.

Supplementary Figure 5



LLC1 tumor-bearing C57BL/6 mice were treated with cisplatin/pemetrexed/anti-PD-1/rIL-1 β as in Figure 2B. Tumors were recovered 8 days after treatment by chemotherapy (d17). Immunophenotyping of indicated immune populations by flow cytometry. Mean of percentages among CD45⁺ cells (n=5).

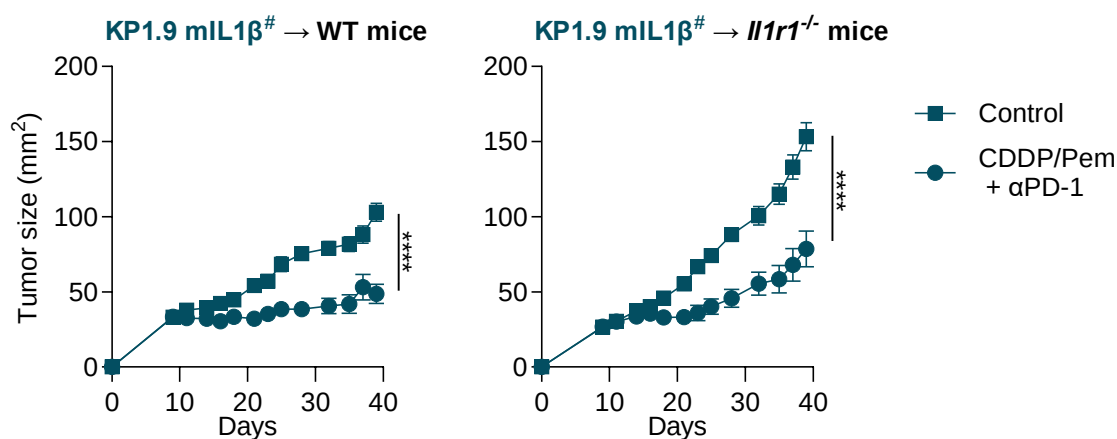
Supplementary Figure 6



mIL1 β overexpressing LLC1 tumor-bearing C57BL/6 mice were treated or not with cisplatin (6mg/kg ip), pemetrexed (100mg/kg ip) at d9 and anti-PD-1 mAb (10mg/kg ip, 3 times a week from d9, for 3 weeks) in the presence of anti-CXCR3 mAb or control Ig (5mg/kg ip, 3 times a week from d9). Tumor size was monitored (n=8).

Data represent mean $\pm$ SEM. Two-way ANOVA. ****p<0.0001.

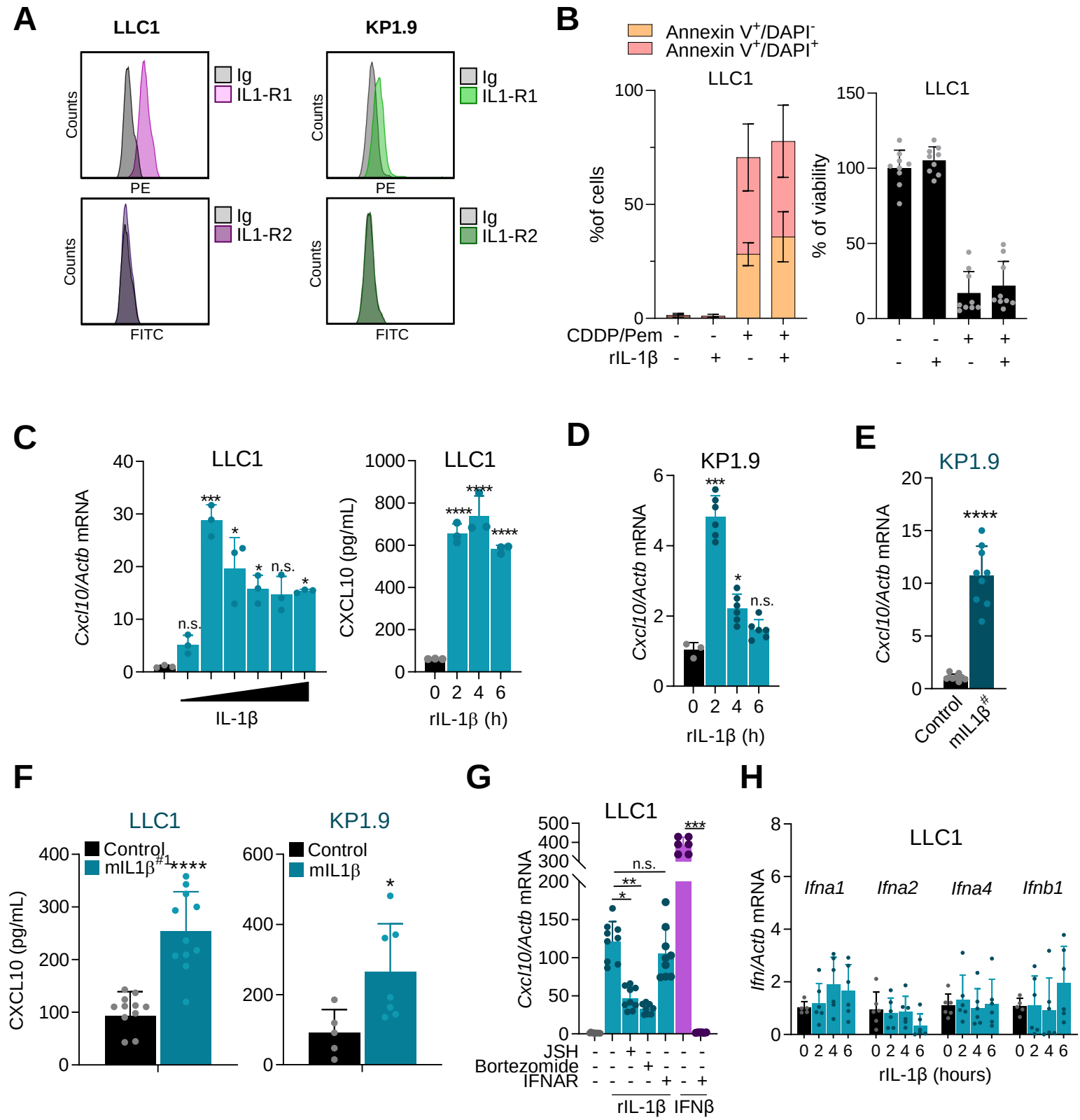
Supplementary Figure 7



mIL1 β overexpressing KP1.9 cells were s.c. injected into the flank of WT or *Il1r1*^{-/-} C57BL/6 mice. Mice were treated as in Figure 1C. Tumor size was monitored (n=10).

Data represent mean $\pm$ SEM. Two-way ANOVA. ****p<0.0001.

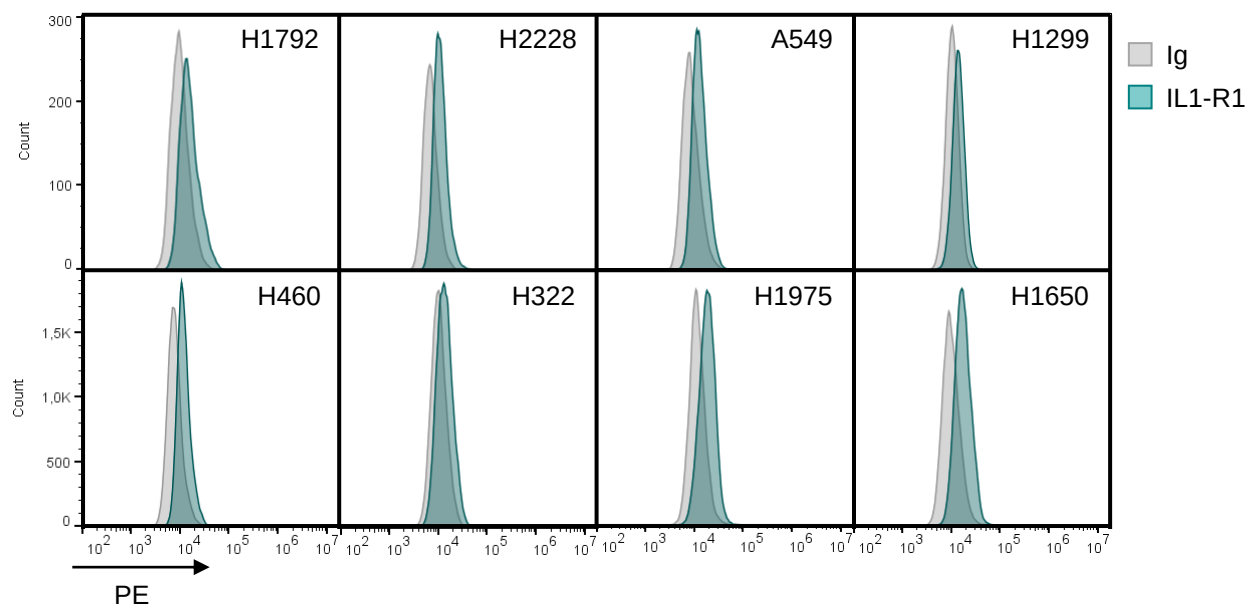
Supplementary Figure 8



- A**, IL-1R1 and IL-1R2 membrane expression was analyzed by flow cytometry on LLC1 or KP1.9 cells. Ig: control immunoglobulin.
- B**, LLC1 cells were treated with 3.7 μ M cisplatin (CDDP) and 33 μ M pemetrexed (Pem) in the presence or not of recombinant IL-1 β (100ng/mL) for 48 hours. Left panel: cells were recovered, stained with Annexin V and 7-AAD and analyzed by flow cytometry (n=9). Right panel: adherent cells were stained with crystal violet to determine cell viability (n=9).
- C**, LLC1 cells were treated with increasing concentrations (0.01ng/mL – 1 μ g/mL) for 2 hours (left panel) or with 100ng/mL for indicated times (right panel) of recombinant IL-1 β . *Cxcl10* mRNA expression was analyzed by RT-qPCR (left panel) and CXCL10 amounts in cell supernatants by ELISA (right panel) (n=3).
- D**, KP1.9 cells were treated with 100ng/mL for indicated times of recombinant IL-1 β . *Cxcl10* mRNA expression was analyzed by RT-qPCR (n=6).
- E**, Control or mIL1 β overexpressing KP1.9 cells were seeded in plates. After 24 hours, *Cxcl10* mRNA expression was analyzed by RT-qPCR (n=9).
- F**, Control or mIL1 β overexpressing LLC1 cells (left panel, n=12), control or mIL1 β overexpressing KP1.9 cells (right panel, n=6) were incubated for 24 hours and CXCL10 amounts were analyzed by ELISA in cell supernatants.
- G**, LLC1 cells were pre-treated or not with bortezomide (0,1 μ M), JSH (30 μ M) or anti-IFNAR Ab (10 μ g/mL) for 2 hours and treated or not with 100ng/mL of recombinant IL-1 β (n=9) or 10 ng/mL of IFN β (n=6) for 2 hours. *Cxcl10* mRNA expression was analyzed by RT-qPCR.
- H**, LLC1 cells were treated or not with 100ng/mL of recombinant IL-1 β for indicated times. mRNA expression of indicated genes was analyzed by RT-qPCR (n=6).

Data represent one representative experiment of three independent experiment (**A**). Data represent mean $\pm$ SD (**B to H**). Unpaired t-test comparing untreated with treated conditions (**C and D**); or control with mIL-1 β condition (**E and F**); or indicated conditions (**G**). *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, n.s., not significant.

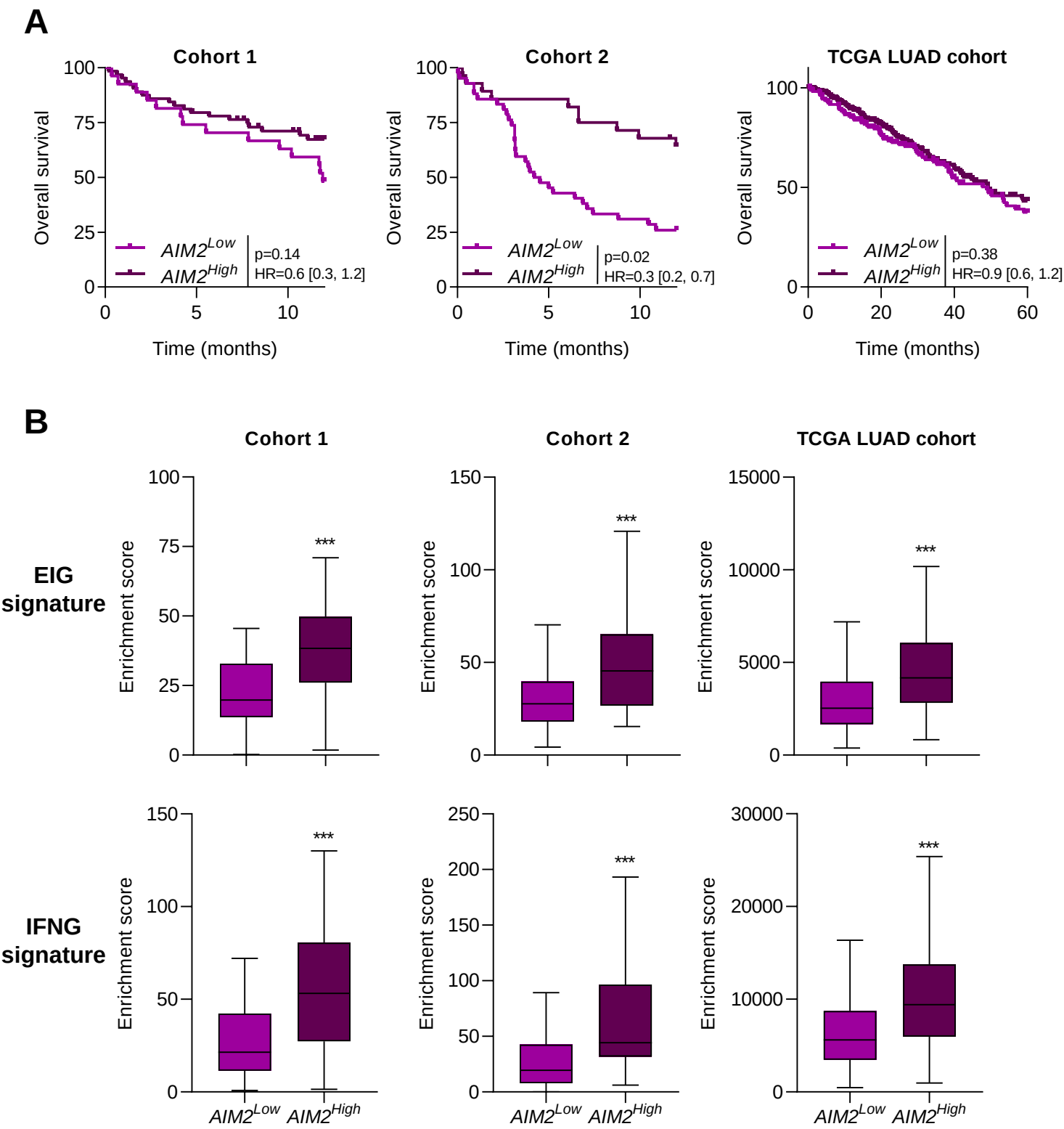
Supplementary Figure 9



IL-1R1 membrane expression was analyzed by flow cytometry on indicated human lung cancer cell lines. Ig: control immunoglobulin.

Data represent one representative experiment of two independent experiments.

Supplementary Figure 10

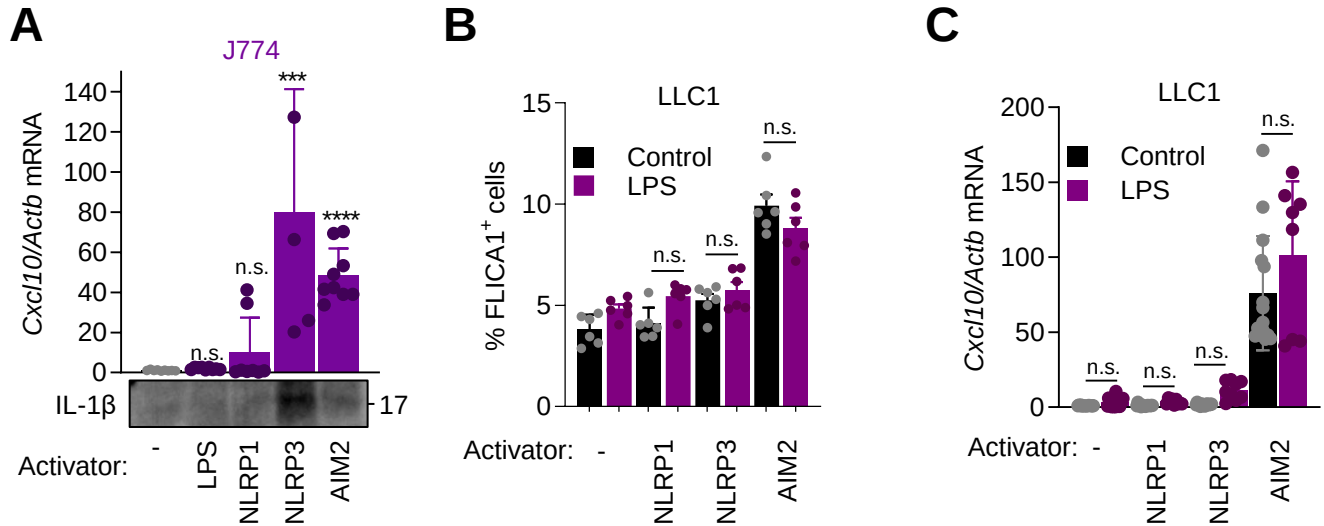


A, Kaplan–Meier estimation of overall survival in patients from cohort 1 (left panel), cohort 2 (middle panel) or the TCGA LUAD database (right panel). Patients were split into two groups with high (H) or low (L) expression of *AIM2*. High expression was determined using the optimal cut-off estimated from maximally selected rank statistics.

B, Enrichment score of EIG and IFNG signatures in tumors with high or low *AIM2* expression of patients from cohorts 1 and 2 and TCGA LUAD cohort.

Data represented as boxplots of median $\pm$ interquartile range; whiskers correspond to min and max (**B**). Log-rank t-test p-values (**A**). Wilcoxon test comparing Low with High condition (**B**). *** $p<0.001$.

Supplementary Figure 11

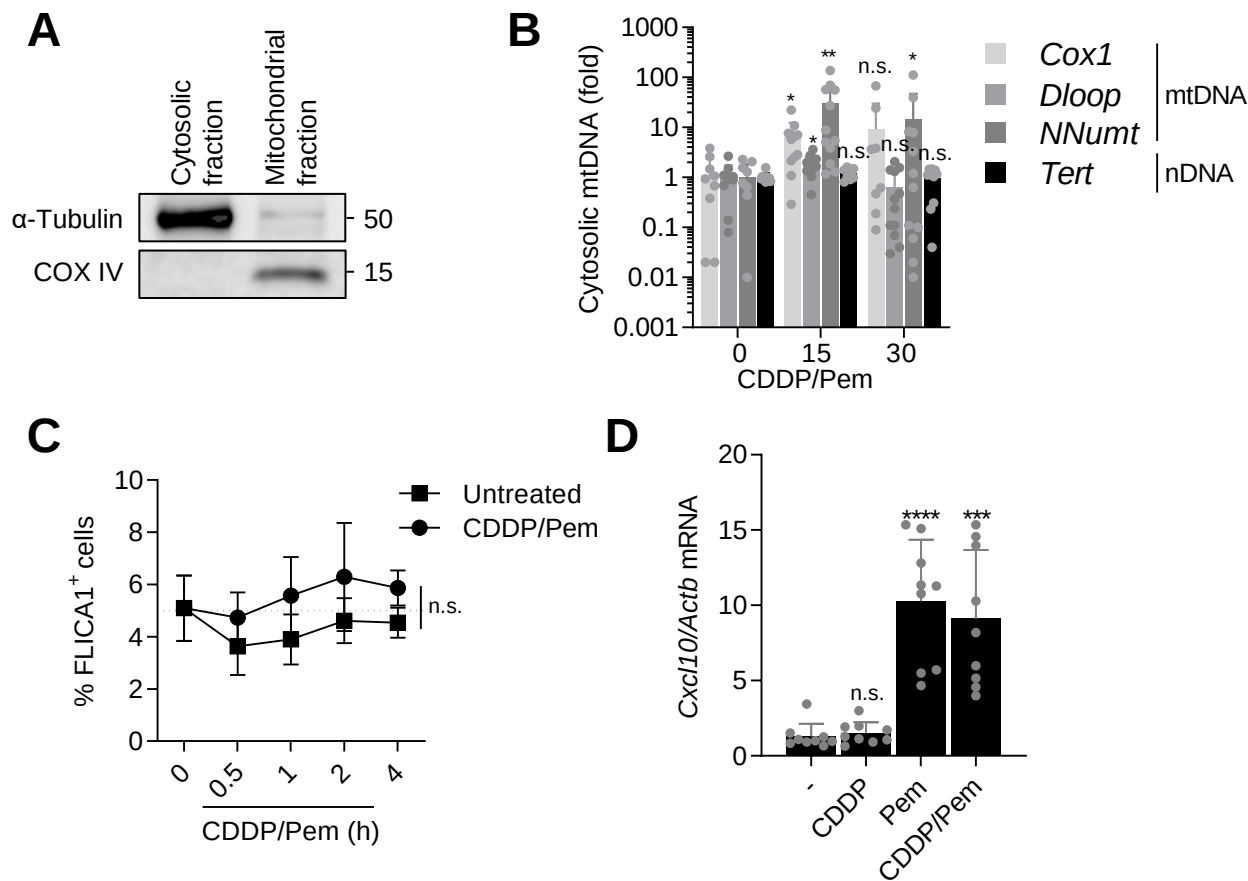


A, J774 macrophage-like cells were treated either with LPS (0.5 μ g/mL), the NLRP1 activator Val-boroPro (0.05 mM), the NLRP3 activator ATP (5mM) or the AIM2 activator poly(dA:dT) (5 μ g/mL). After 1 hour of treatment, the presence of IL-1 β was analyzed by Western Blot in cell supernatants. After 18 hours of treatment, *Cxcl10* mRNA expression was analyzed by RT-qPCR (n=9).

B and C LLC1 cells were treated or not with LPS (0.5 μ g/mL) for 2 hours, and then, with the NLRP1 activator Val-boroPro (0.05 mM), the NLRP3 activator ATP (5mM) or the AIM2 activator poly(dA:dT) (5 μ g/mL). After 1 hour of treatment, caspase-1 activity was analyzed using FLICA1 by flow cytometry (n=6) (B). After 18 hours of treatment, *Cxcl10* mRNA expression was analyzed by RT-qPCR (C, n=9).

Data represent mean $\pm$ SD. Unpaired t-test comparing untreated with treated conditions (**A**); or indicated conditions (**B and C**). ***p<0.001, n.s., not significant.

Supplementary Figure 12



A, Indicated protein expression was analyzed in mitochondrial and cytosolic fractions by Western Blot. Numbers indicate molecular weights in kDa.

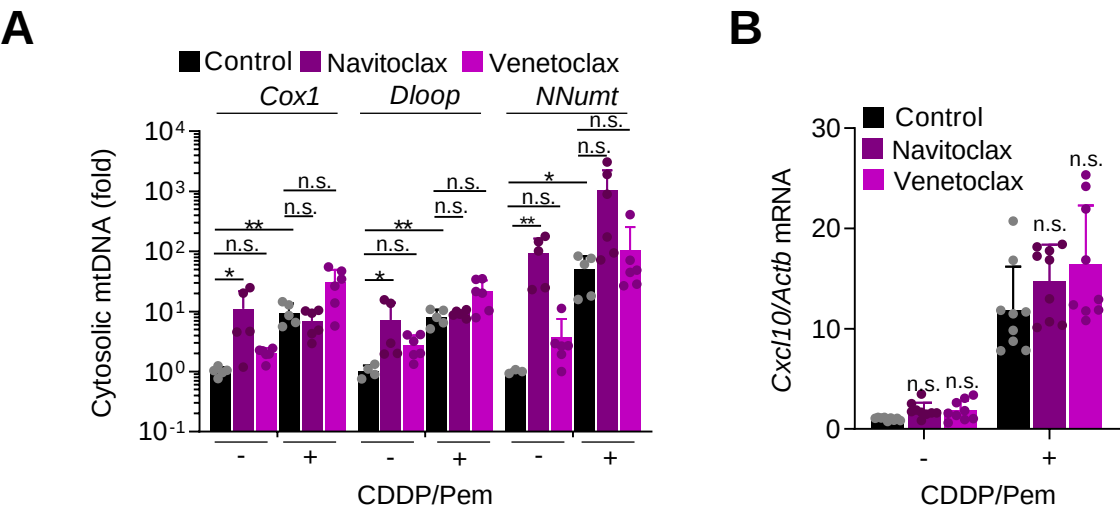
B, LLC1 cells were treated or not with 3.7 μ M cisplatin (CDDP) and 33 μ M pemetrexed (Pem) for 0, 15 or 30 minutes. RT-qPCR analysis of mitochondrial (*Cox1*, *Dloop*, *Non-Numt*) or nuclear (*Tert*) genes was performed on cytosolic fractions (n=9).

C, LLC1 cells were treated or not as in B and caspase-1 activity was measured using FLICA1 by flow cytometry at indicated times (n=6).

D, LLC1 cells were treated or not with 3.7 μ M cisplatin (CDDP) and/or 33 μ M pemetrexed (Pem) for 18 hours. *Cxcl10* mRNA expression was analyzed by RT-qPCR (n=9).

Data represent mean $\pm$ SD (**B to D**). Two-way ANOVA (**C**). Unpaired t-test comparing untreated with treated conditions (**B and D**). *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, n.s., not significant.

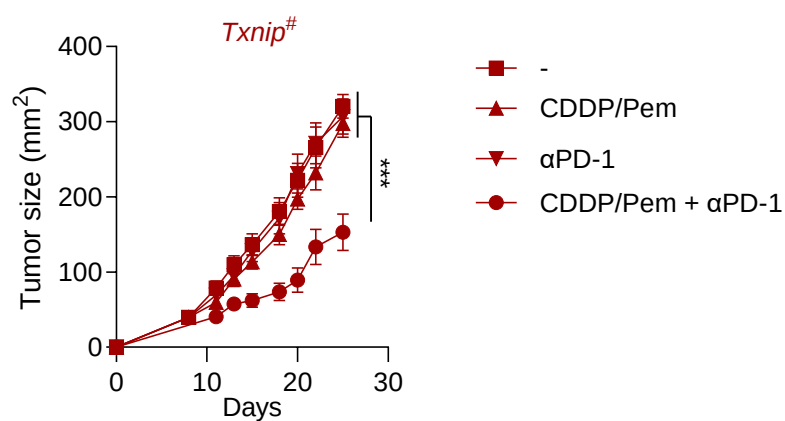
Supplementary Figure 13



A and B, LLC1 cells were pre-treated or not with Navitoclax or Venetoclax (5μM) and treated or not with 3.7μM cisplatin (CDDP) and 33μM pemetrexed (Pem). RT-qPCR analysis of indicated mitochondrial genes was performed on cytosolic fractions, after 30 minutes (A, n=6). *Cxcl10* mRNA expression was analyzed by RT-qPCR, after 18 hours of treatment (B, n=9).

Data represent mean ± SD. Unpaired t-test comparing indicated conditions (A); Navitoclax or Venetoclax with corresponding control condition (B). *p<0.05, **p<0.01, n.s., not significant.

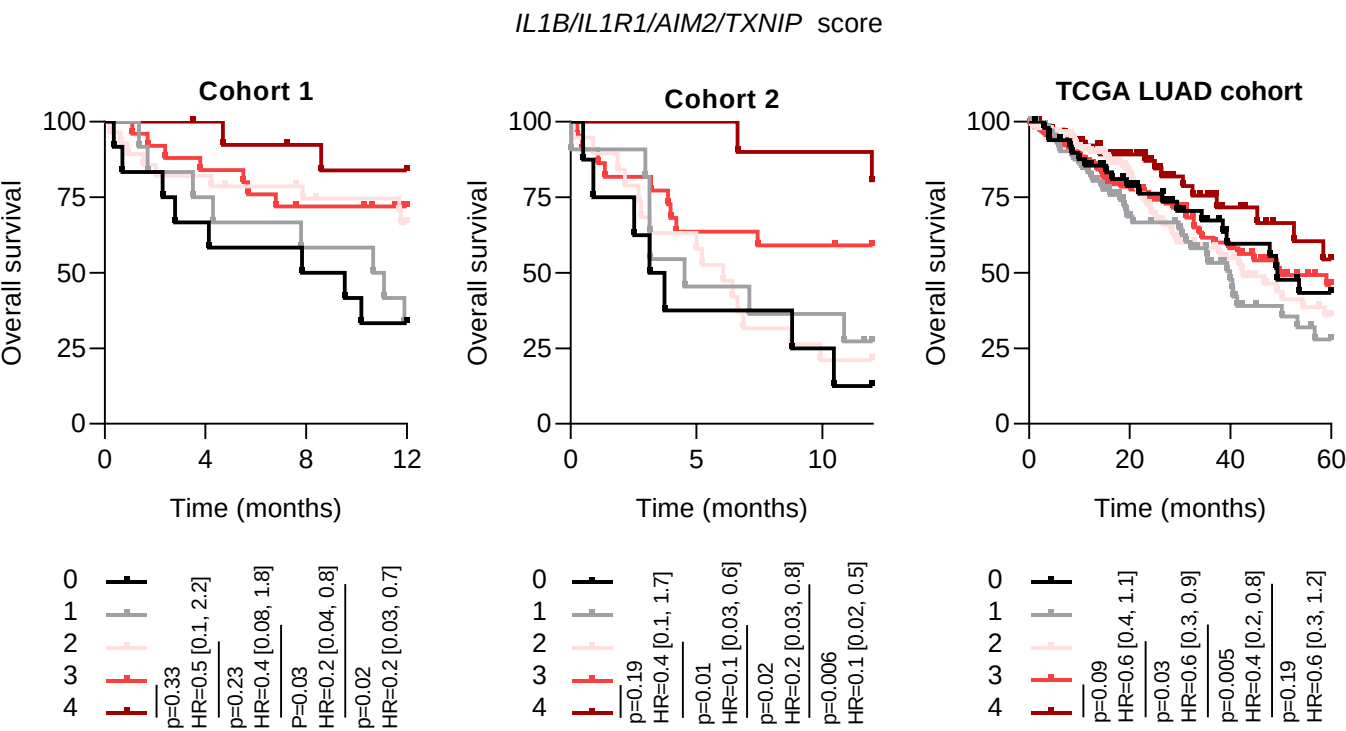
Supplementary Figure 14



Txnip overexpressing LLC1 tumor bearing mice were left untreated or treated with cisplatin (6mg/kg ip), pemetrexed (100mg/kg ip) at d9 (CDDP/Pem) or anti-PD-1 mAb (10mg/kg ip, 3 times a week from d9, for 3 weeks – αPD-1) or both. Tumor size was monitored (n=7).

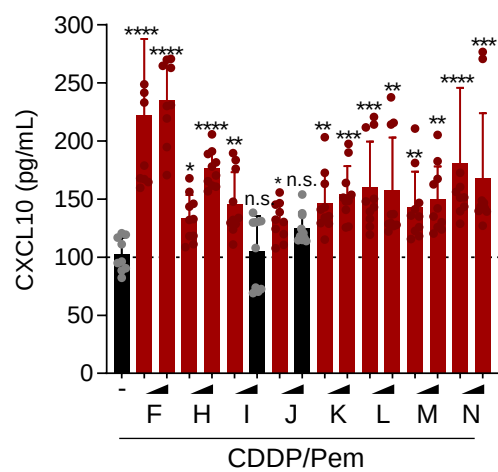
Data represent mean ± SEM. Two-way ANOVA. ***p<0.001.

Supplementary Figure 15



Kaplan–Meier estimation of overall survival in patients from cohort 1 (left panel), cohort 2 (middle panel) or the TCGA LUAD database (right panel). Patients were split into five groups with high (H) or low (L) expression of 0 to 4 genes (*IL1B*, *IL1R1*, *AIM2*, *TXNIP*). High expression was determined using the optimal cut-off estimated from maximally selected rank statistics. Log-rang t-test p-values.

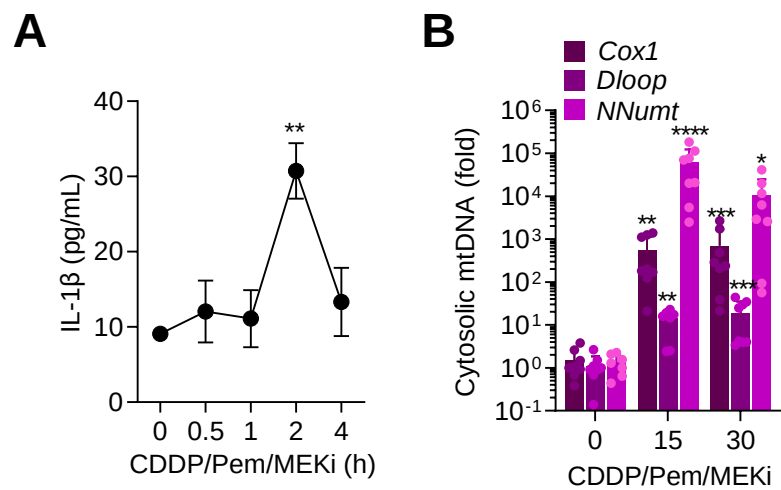
Supplementary Figure 16



LLC1 cells were pre-treated or not for 2 hours with indicated molecules and then with 3.7μM cisplatin (CDDP) and 33μM pemetrexed (Pem). After 24 hours of treatment, CXCL10 amounts were quantified by ELISA in cell supernatants (n=10). Molecules; F: Trametinib (0,1 and 1 μM), H: Panobinostat (5 and 25 nM), I: SNX-2112 (0,025 and 0,125 μM), J: Sunitinib (0,250 and 1,25 μM), K: YM-155 (0,01 and 0,05 μM), L: JNJ-26854165 (5 and 25 nM), M: Foretinib (2,5 and 12,5 nM), N: TW-37 (0,5 and 2,5 μM).

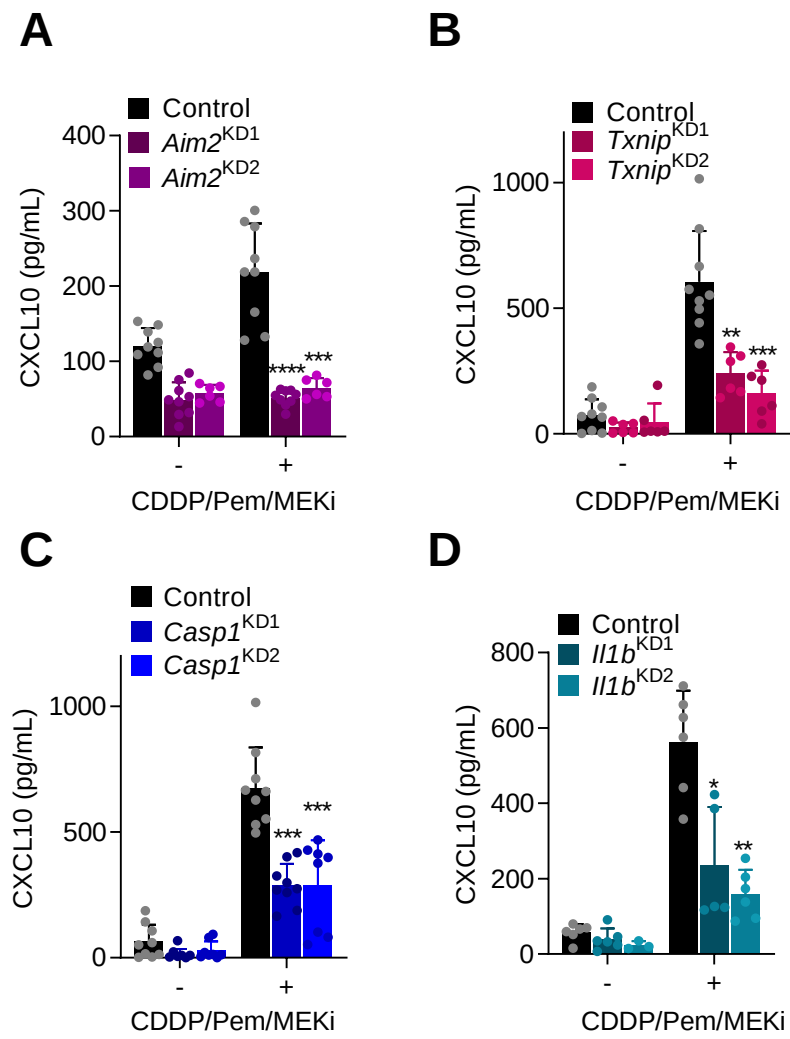
Data represent mean ± SD. Unpaired t-test comparing CDDP/Pem/- with other conditions. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, n.s., not significant.

Supplementary Figure 17



LLC1 cells were pre-treated or not for 2 hours with 100nM trametinib (MEKi) and then with 3.7μM cisplatin (CDDP) and 33μM pemetrexed (Pem). **A**, IL-1β amounts were quantified by ELISA in cell supernatants (n=5). **B**, RT-qPCR analysis of indicated mitochondrial genes was performed on cytosolic fractions, 0, 15 or 30 min after chemotherapy treatment (n=8). Data represent mean ± SD. Unpaired t-test comparing untreated with treated conditions. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

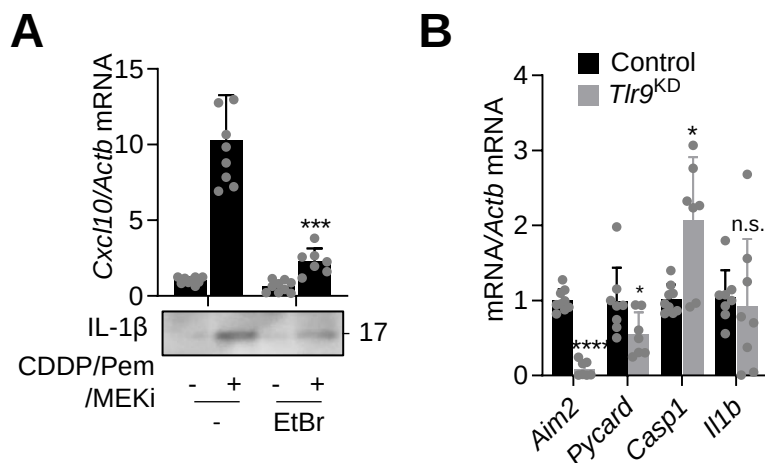
Supplementary Figure 18



Aim2 (A), *Txnip* (B), *Casp1* (C), *Il1b* (D) knock down or control LLC1 cells were pre-treated or not for 2 hours with 100 nM trametinib (MEKi) and then with 3.7μM cisplatin (CDDP) and 33μM pemetrexed (Pem). CXCL10 amounts were quantified by ELISA in cell supernatants after 24 hours of treatment (n=9).

Data represent mean ± SD (A to D). Unpaired t-test comparing treated KD cells with treated control cells. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Supplementary Figure 19



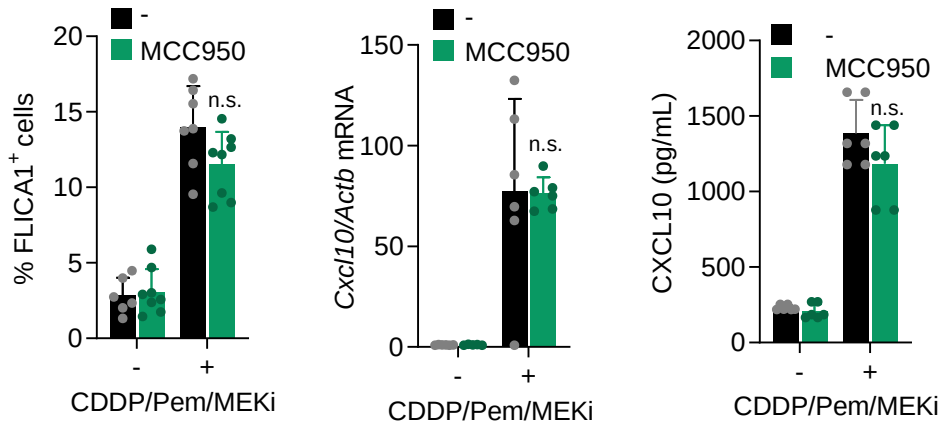
A, LLC1 cells were exposed or not to EtBr for three days. Cells were then pre-treated for 2 hours with 100nM trametinib (MEKi) and then with 3.7 μ M cisplatin (CDDP) and 33 μ M pemetrexed (Pem). After two hours of treatment, IL-1 β was quantified by Western Blot in cell supernatants. After 18 hours of treatment, *Cxcl10* mRNA expression was analyzed by RT-qPCR (n=9).

B, The expression of indicated genes was analyzed by RT-qPCR in LLC1 control or *Tlr9* knock down (*Tlr9*^{KD}) cells (n=7).

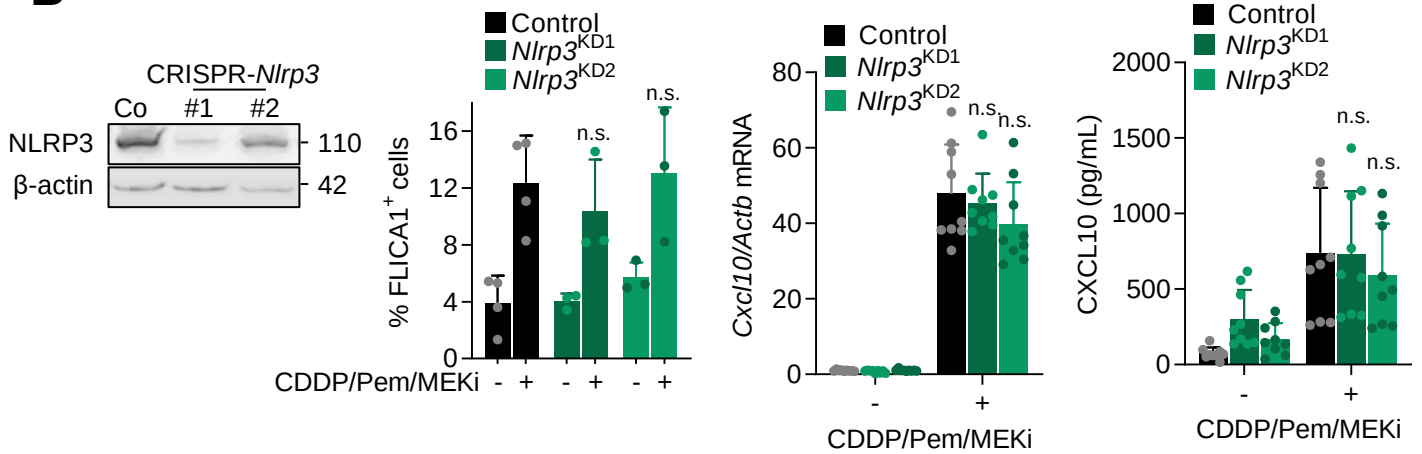
Data represent mean $\pm$ SD. Unpaired t-test comparing CDDP/Pem/MEKi with CDDP/Pem/MEKi/EtBr condition (**A**); or *Tlr9*^{KD} with control cells (**B**). *p<0.05, ***p<0.001, ****p<0.0001, n.s., not significant.

Supplementary Figure 20

A



B

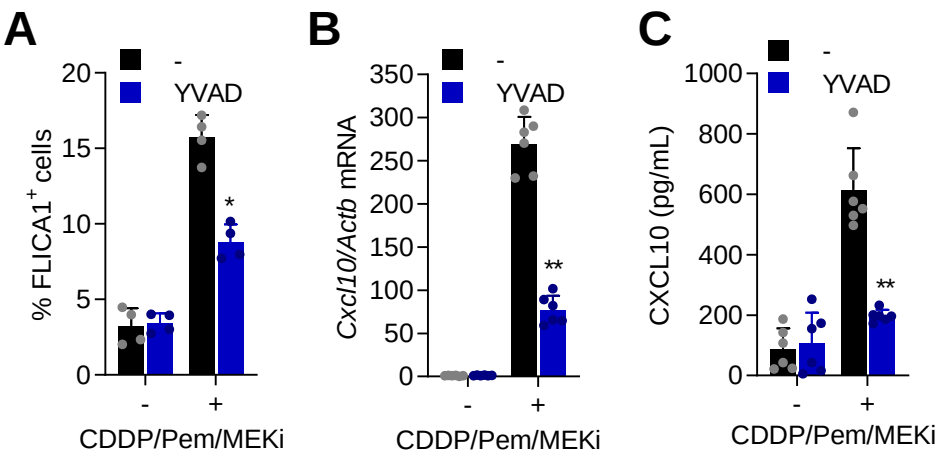


A, LLC1 cells were pre-treated or not for 2 hours with 100nM trametinib (MEKi) in the presence or absence of NLRP3 inhibitor (MCC950, 10 μM) and then treated or not with 3.7 μM cisplatin (CDDP) and 33 μM pemetrexed (Pem). Caspase-1 activity was assayed by flow cytometry (left panel), *Cxcl10* mRNA by RT-qPCR (middle panel) and CXCL10 in cell supernatant by ELISA (right panel) after 30 minutes, 18 or 24 hours respectively (n=6).

B, LLC1 control cells or invalidated for *Nlrp3* by CRISPR-Cas9 were treated with CDDP/Pem/MEKi or not as indicated above. NLRP3 expression was analyzed in untreated cells by Western Blot. β-Actin was used as a loading control. Numbers indicate molecular weights in kDa. Caspase-1 activity was assayed by flow cytometry (left panel), *Cxcl10* mRNA by RT-qPCR (middle panel) and CXCL10 in cell supernatant by ELISA (right panel) after 30 minutes, 18 or 24 hours respectively (n=3 or 9).

Data represent mean ± SD. Unpaired t-test comparing CDDP/Pem/MEKi with CDDP/Pem/MEKi/MCC950 condition (**A**); or *Nlrp3*^{KD} treated cells with control treated cells (**B**). n.s., not significant.

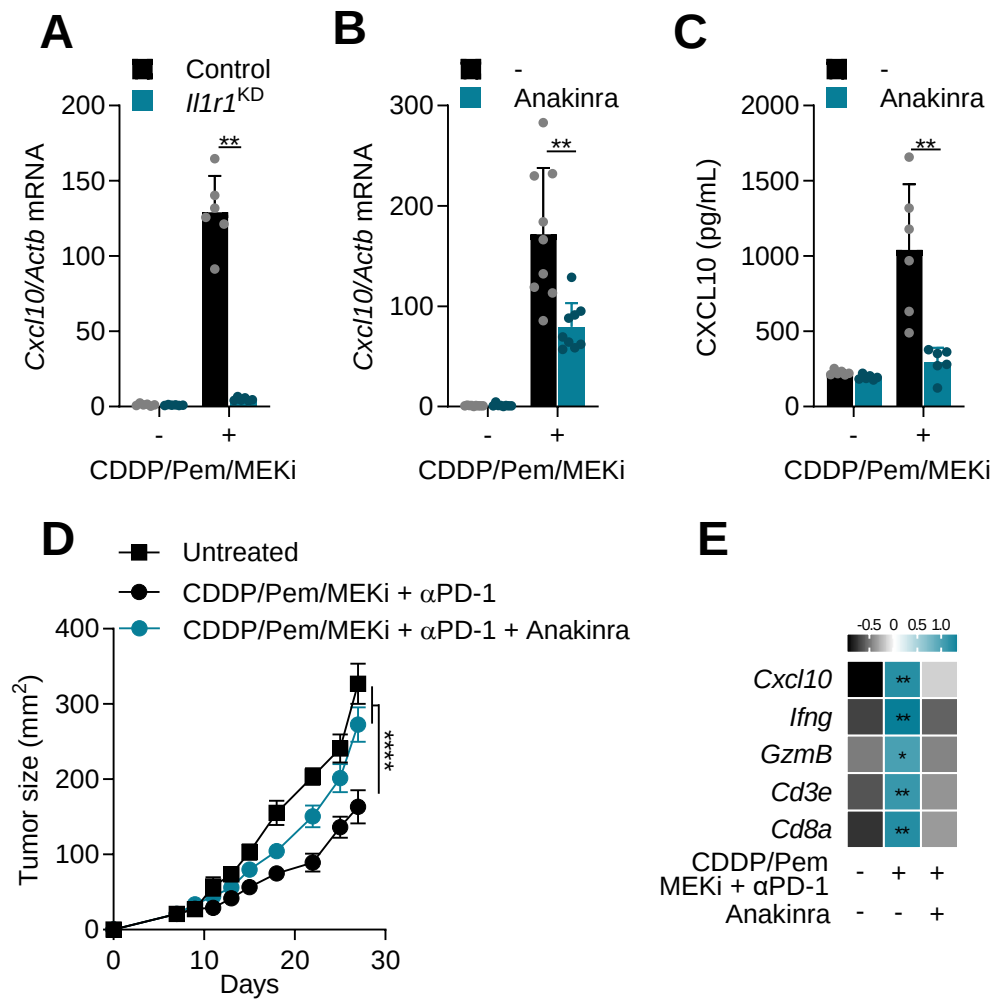
Supplementary Figure 21



LLC1 cells were pre-treated or not for 2 hours with 100nM trametinib (MEKi) in the presence or not of capase-1 inhibitor (YVAD, 50μM) and then treated or not with 3.7μM cisplatin (CDDP) and 33μM pemetrexed (Pem). Caspase-1 activity was assayed by flow cytometry (A), *Cxcl10* mRNA by RT-qPCR (B) and CXCL10 in cell supernatant by ELISA (C) after 30 minutes, 2, 18 or 24 hours respectively (n=4 or 6).

Data represent mean ± SD. Unpaired t-test comparing CDDP/Pem/MEKi with CDDP/Pem/MEKi/YVAD condition. *p<0.05, ***p<0.001.

Supplementary Figure 22



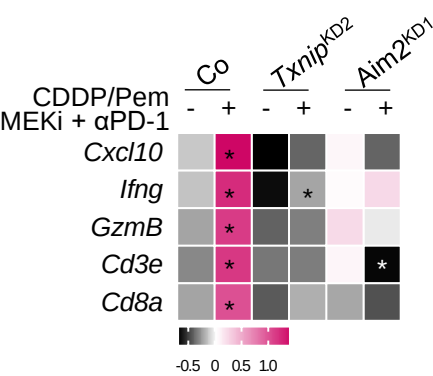
A, Control or *Il1r1*^{KD} LLC1 cells were pre-treated for 2 hours with 100nM trametinib (MEKi) and then with 3.7 μ M cisplatin (CDDP) and 33 μ M pemetrexed (Pem). After 18 hours of treatment, *Cxcl10* mRNA expression was analyzed by RT-qPCR (n=6).

B and C, LLC1 cells were treated as above in the presence or absence of anakinra (10 μ g/mL). After 18 hours of treatment, *Cxcl10* mRNA expression was analyzed by RT-qPCR (B, n=9). After 24 hours of treatment, CXCL10 amounts were quantified by ELISA in cell supernatants (C, n=6).

D and E, LLC1 tumor bearing C57BL/6 mice (s.c. injection at day 0) were treated or not daily p.o. with 1mg/kg trametinib (MEKi) for 9 days from day 7. Mice were then treated or not i.p. once with 6mg/kg cisplatin (CDDP) and 100mg/kg pemetrexed (Pem) at day 9 and three times a week with 10mg/kg anti-PD-1 Ab (from day 9). Anakinra (100mg/kg from day 7 for three weeks) was used when indicated. Tumor size was monitored (C, n=7) and tumor biopsies were recovered 8 days after chemotherapy to analyze indicated gene expression by RT-qPCR (D, n=5).

Data represent mean $\pm$ SEM (D) or $\pm$ SD (A to C) or z-score analysis (E). Unpaired t-test comparing indicated conditions (A to C); or untreated with treated conditions (E). Two-way ANOVA (D). *p<0.05, **p<0.01, ****p<0.0001, n.s., not significant. For panel E, no star means not significant.

Supplementary Figure 23

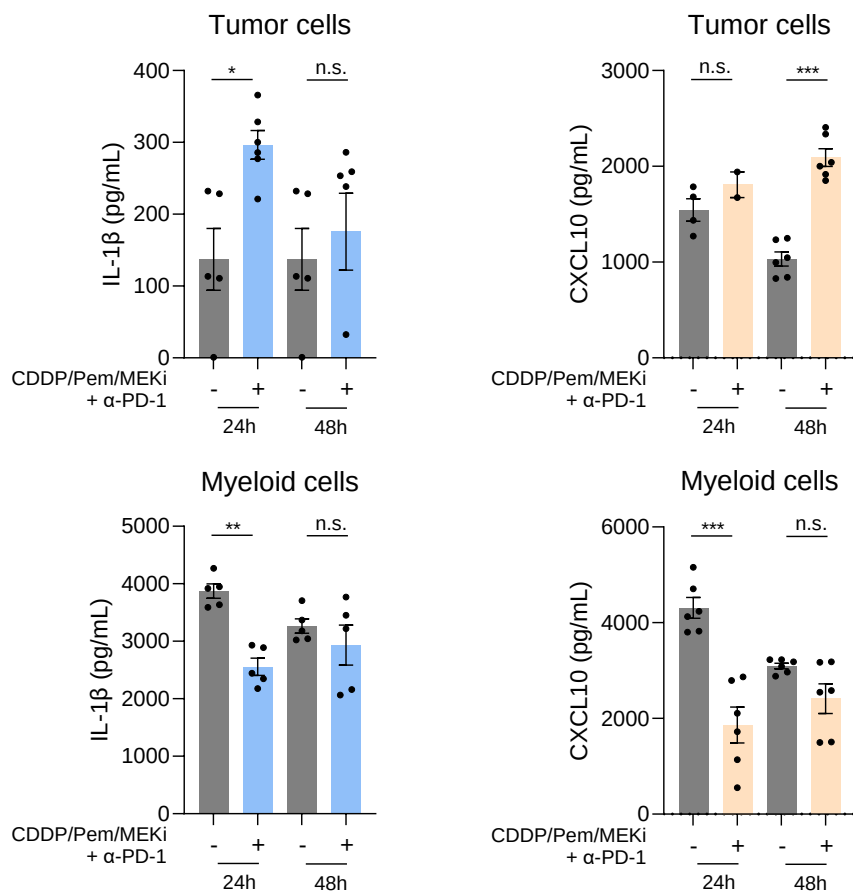


C57BL/6 mice were s.c. injected either with control, *Txnip*- or *Aim2*-deficient (KD) LLC1 cells and treated or not daily p.o. with 1mg/kg trametinib (MEKi) for 9 days from day 7. Mice were then treated or not i.p. once with 6mg/kg cisplatin (CDDP) and 100mg/kg pemetrexed (Pem) at day 9 and three times a week with 10mg/kg anti-PD-1 Ab (from day 9). Tumor biopsies (n=7) were recovered at day 8 after treatment to analyze indicated gene expression (z-score) by RT-qPCR.

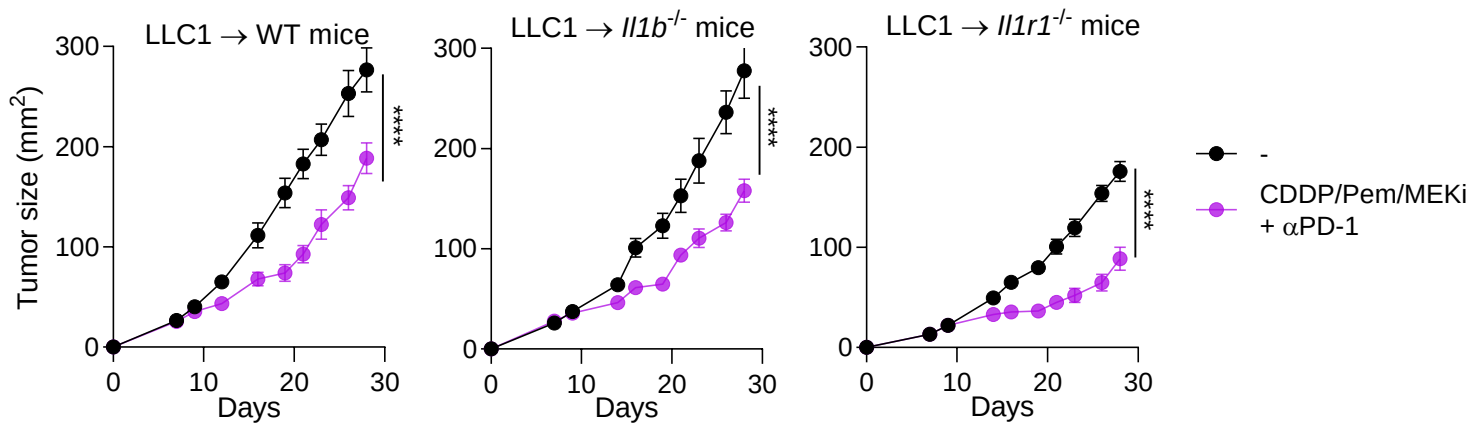
Data represent z-score analysis. Unpaired t-test comparing CDDP/Pem/MEKi conditions with corresponding untreated conditions for each cell type. *p<0.05, no star means not significant.

Supplementary Figure 24

A



B

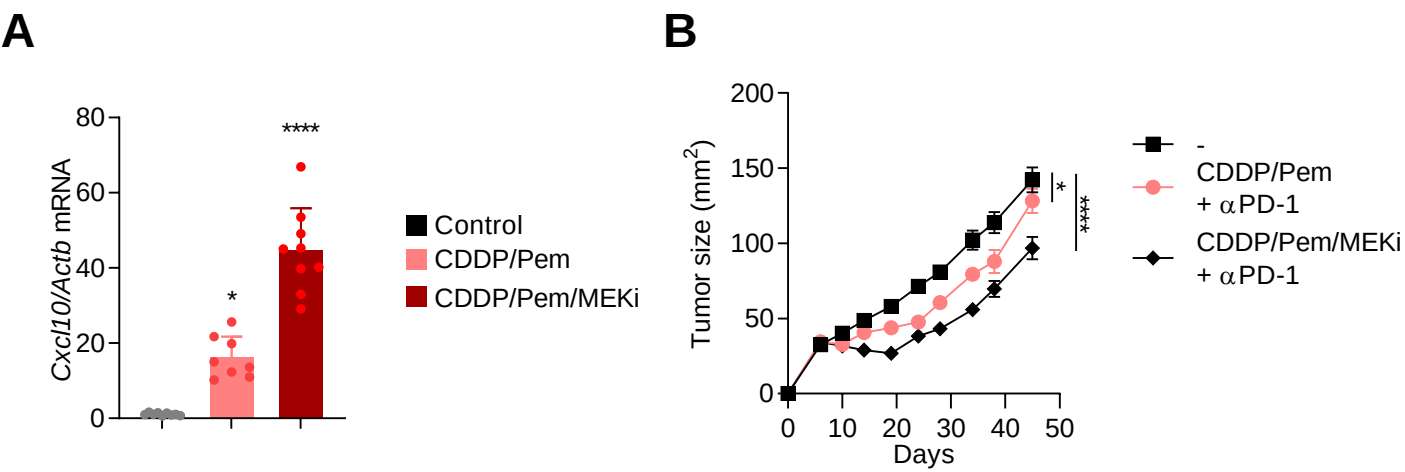


A, C57BL/6 mice were s.c. injected with LLC1 cells and treated or not daily p.o. with 1mg/kg trametinib (MEKi) for 9 days from day 7. Mice were then treated or not i.p. once with 6mg/kg cisplatin (CDDP), 100mg/kg pemetrexed (Pem) and 10mg/kg anti-PD-1 Ab at day 9. After 24 or 48 hours, tumors were recovered and tumor cells or myeloid cells were isolated and cultured ex vivo for 4 hours. Supernatants were collected and IL-1 β or CXCL10 amounts were quantified by ELISA (n=5).

B, WT, *Il1b*^{-/-} or *Il1r1*^{-/-} C57BL/6 mice were s.c. injected with LLC1 cells and treated or not daily p.o. with 1mg/kg trametinib (MEKi) for 9 days from day 7. Mice were then treated or not i.p. once with 6mg/kg cisplatin (CDDP) and 100mg/kg pemetrexed (Pem) at day 9 and three times a week with 10mg/kg anti-PD-1 Ab (from day 9). Tumor size was monitored (n=8).

Data represent mean $\pm$ SD (**A**) or $\pm$ SEM (**B**). Unpaired t-test comparing indicated conditions (**A**). Two-way ANOVA (**B**). *p<0.05, **p<0.01, ***p<0.0005, ****p<0.0001, n.s., not significant.

Supplementary Figure 25

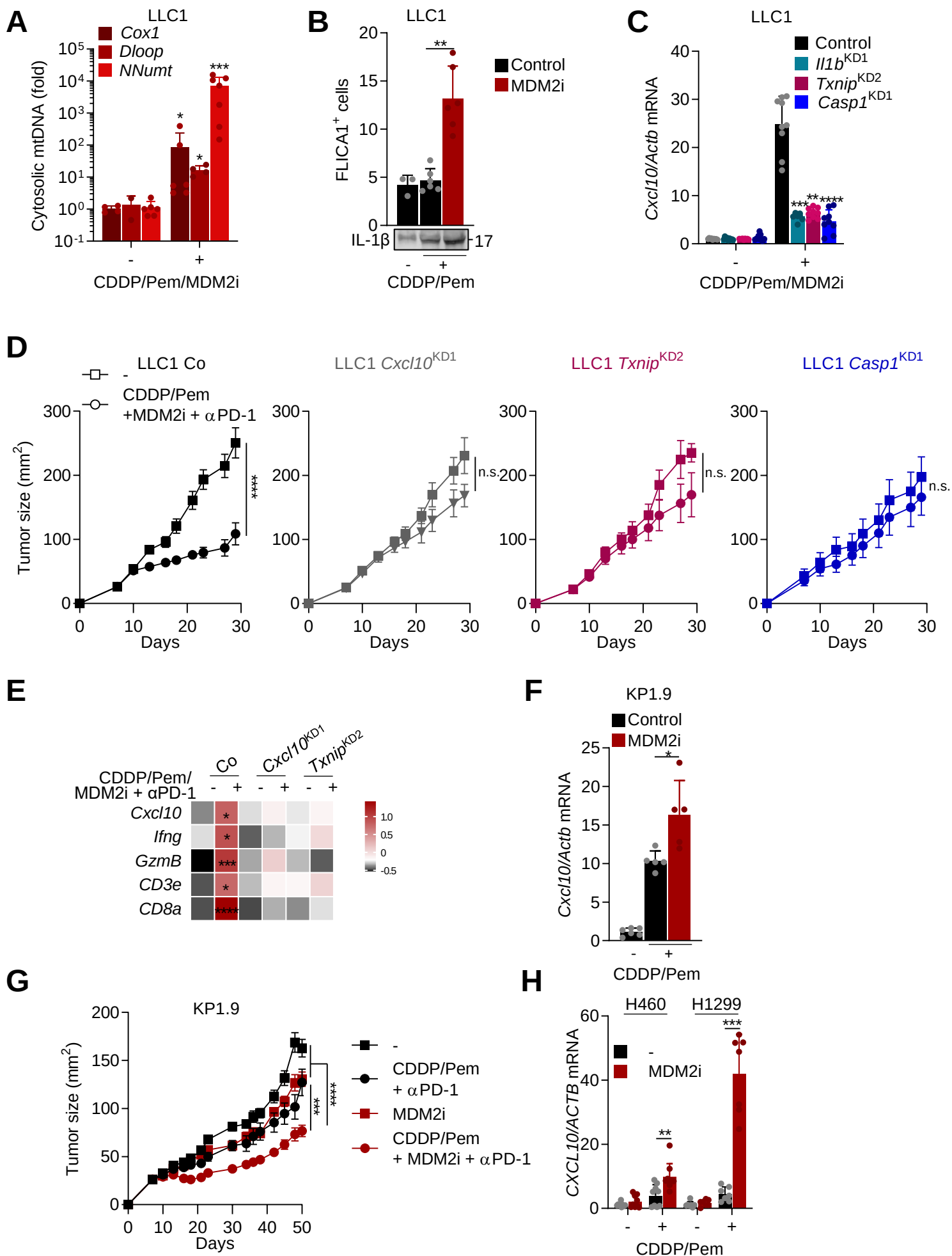


A, KP1.9 cells were pre-treated or not for 2 hours with 100nM trametinib (MEKi) and then treated or not with 3.7 μ M cisplatin (CDDP) and 33 μ M pemetrexed (Pem). *Cxcl10* mRNA expression was assayed by RT-qPCR after 18 hours of treatment (n=9).

B, KP1.9 tumor bearing C57BL/6 mice (s.c. injection at day 0) were treated or not daily with 1mg/kg trametinib (MEKi) for 9 days from day 7. Mice were then treated or not i.p. once with 6mg/kg cisplatin (CDDP) and 100mg/kg pemetrexed (Pem) at day 9 and three times a week with 10mg/kg anti-PD-1 Ab (from day 9). Tumor size (n=7 or 8) was monitored.

Data represent mean $\pm$ SEM (**B**) or $\pm$ SD (**A**). Unpaired t-test comparing untreated control condition with other conditions (**A**). Two-way ANOVA (**B**). *p<0.05, ****p<0.0001.

Supplementary Figure 26



A and B, LLC1 cells were pre-treated or not for 2 hours with 25 nM JNJ-26854165 (MDM2i) and then with 3.7 μ M cisplatin (CDDP) and 33 μ M pemetrexed (Pem). After 30 min of treatment, *Cox1*, *Dloop* and *Non-Numt* mitochondrial DNA expression was analyzed by RT-qPCR in cytosolic fractions (A, n=6). IL-1 β was quantified by Western Blot in cell supernatants 2 hours after treatment (lower panel) and caspase-1 activity was assayed after FLICA1 staining by flow cytometry, after 30 minutes of treatment (upper panel) (B, n=6).

C, Control LLC1 cells or deficient for *Txnip*, *Casp1* or *Il1b* were treated as in A. After 18 hours of treatment, *Cxcl10* mRNA expression was analyzed by RT-qPCR (n=9).

D and E, C57BL/6 mice were s.c. injected either with control or *Cxcl10*, *Casp1* or *Txnip*-deficient (KD) LLC1 cells and treated or not daily with MDM2i (10mg/kg) for 9 days from day 7. Mice were then treated or not i.p. once with 6mg/kg cisplatin (CDDP) and 100mg/kg pemetrexed (Pem) at day 9 and three times a week with 10mg/kg anti-PD-1 Ab (from day 9). Tumor size (n=7) was monitored (D) and tumor biopsies (n=6) for Control, *Cxcl10*, or *Txnip* KD tumors were recovered at day 8 after treatment to analyze indicated gene expression (z-score) by RT-qPCR (E).

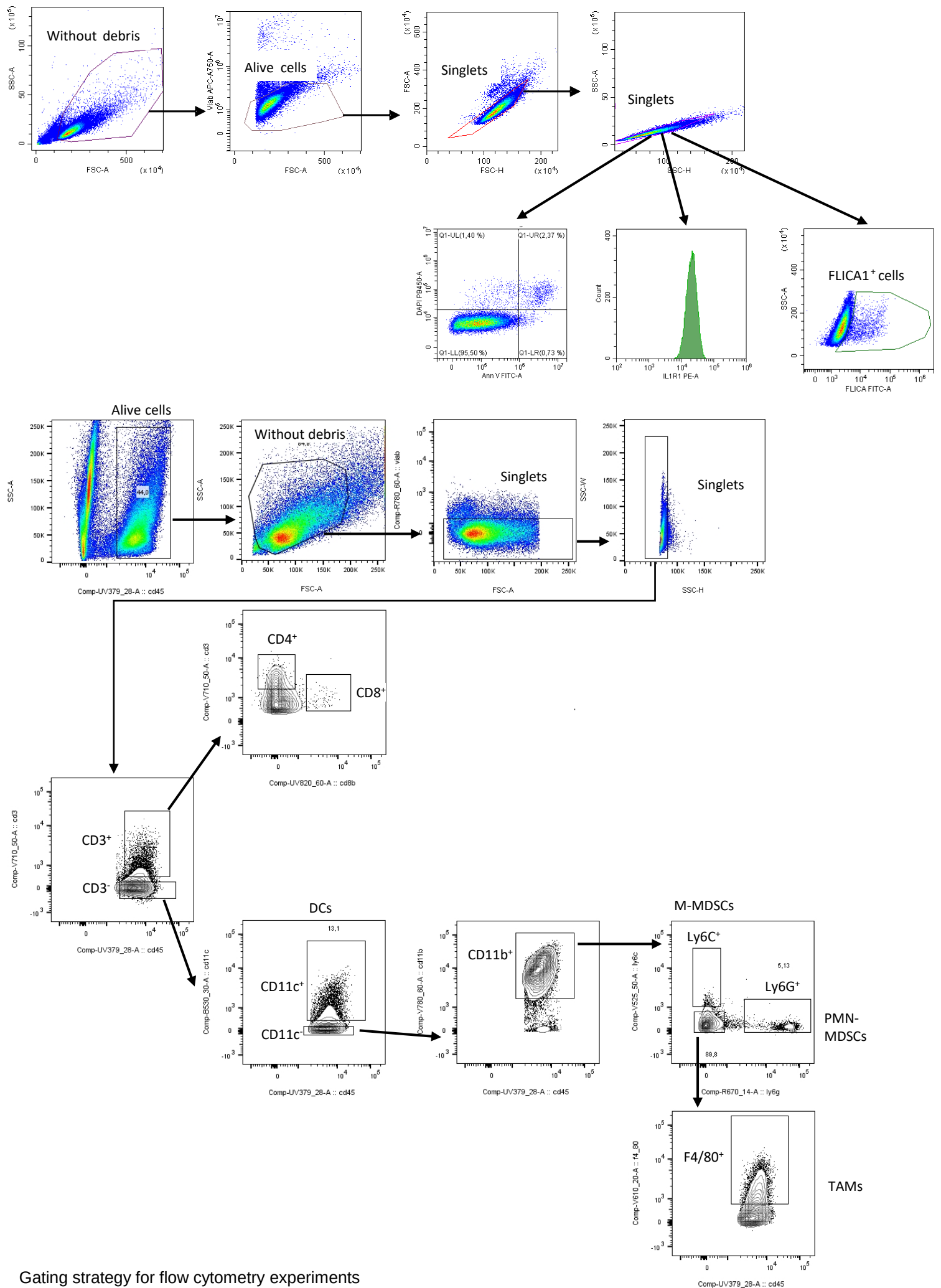
F, KP1.9 cells were pre-treated or not for 2 hours with 50nM MDM2i and then with 3.7 μ M cisplatin (CDDP) and 33 μ M pemetrexed (Pem). After 18 hours of treatment, *Cxcl10* mRNA expression was analyzed by RT-qPCR (n=6).

G, KP1.9 tumor bearing C57BL/6 mice (s.c. injection at day 0) were treated as in D. Tumor size (n=10) was monitored.

H, H460 and H1299 human lung cancer cells were treated as in A. After 18 hours of treatment, *CXCL10* mRNA expression was analyzed by RT-qPCR (H460: n=9; H1299: n=7).

Data represent mean $\pm$ SEM (**D and G**) or z-score analysis (**E**). Data represent mean $\pm$ SD of three independent experiments (**A to C, F and H**). Two-way ANOVA (**D and G**). Unpaired t-test comparing untreated with treated conditions (**A**); or indicated conditions (**B, F, and H**); or treated KD with treated control cells (**C**); CDDP/Pem/MDM2i conditions with corresponding untreated conditions for each cell type (**E**). *p<0.05, **p<0.01, ***p<0.0005, ****p<0.0001, ns, not significant. Panel E, no star means not significant.

Supplementary Figure 27



Gating strategy for flow cytometry experiments

Supplementary Table 1: Summary of clinical characteristics

Variable	Cohort 1 N=92	Cohort 2 N=70	p-value	Adjusted p-value
Sex			0.8	>0.9
Female	36 (39%)	29 (41%)		
Male	56 (61%)	41 (59%)		
Age at diagnosis	67 (59, 72)	65 (58, 71)	0.3	0.5
≤ 60	25 (27%)	27 (40%)	0.094	0.3
> 60	67 (73%)	41 (60%)		
NA	0	2		
Histological status			0.5	0.7
Adenocarcinoma	66 (72%)	54 (77%)		
Epidermoid	25 (27%)	14 (20%)		
Other	1 (1.1%)	2 (2.9%)		
Type of ICI			0.024	0.15
Anti PD-L1	4 (4.3%)	0 (0%)		
Anti PD-1	86 (93%)	64 (91%)		
Anti PD-1 + Anti CTLA-4	0 (0%)	3 (4.3%)		
Anti PD-L1 + Anti CTLA-4	1 (1.1%)	3 (4.3%)		
Other associations	1 (1.1%)	0 (0%)		
Smoking status			>0.9	>0.9
Never smoker	3 (7.0%)	5 (8.5%)		
Current or former smoker	40 (93%)	54 (92%)		
NA	49	11		

Continuous variables are described as median and interquartile range (IQR) and were compared between cohort 1 and cohort 2 with the two-sided Wilcoxon test. Categorical variables are described as number (%) and were compared between cohorts 1 and 2 using the two-sided Chi square or two-sided Fisher's exact test. P-values were adjusted using Benjamini-Hochberg FDR correction. ICI: Immune Checkpoint Inhibitors; NA: Not Available.

Supplementary Table2: Identified TXNIP inducer molecules

	Name	Targets	Dosage and administration route for in vivo experiments
A	Alisertib	Serine/threonine protein kinase Aurora A	
B	GDC-0941 / Pictilisib	PI3K	
C	GSK1210151A / I-BET151	Bromodomain and extra terminal (BET) family proteins BRD2, BRD3, and BRD4	
D	KW-2449	FLT3, ABL, ABLT315I and Aurora kinase	
E	Methylstat	Jumonji C domain-containing histone demethylase (JMJD)	
F	GSK212 / Trametinib	MEK	1mg/kg – p.o.
G	NVP-231	Ceramide kinase (CerK)	
H	Panobinostat / Farydak	HDAC	5mg/kg – i.p.
I	SNX-2112	Hsp90	10mg/kg – p.o.
J	Sunitinib / Sutent	Tyrosine Kinase Receptor	10mg/kg – p.o.
K	Sepantronium bromide / YM-155	Survivin	
L	JNJ-26854165 / Serdemetan	dissociate MDM2-p53 (p53 activator)	10mg/kg – p.o.
M	Foretinib / GSK1363089	cMet, VEGFR2	5mg/kg – p.o.
N	TW-37	Bcl2 family	5mg/kg – i.p.
O	GSK461364	Plk1	
P	GSK436 / dabrafenib	BRAF	

Supplementary Table 3: Oligonucleotides

Gene name	Forward	Reverse
QPCR		
mActB	ATGGAGGGGAATACAGCCC	TCTTTGCAGCTCCTTCGTT
mCd3e	AAGTAATGAGCTGGCTGCGT	ATGTTCTCGGCATCGTCCTG
mCd8a	TTCTGTCGTGCCAGTCCTTC	GCTTTCGGCTCCTGTGGTAG
mCox1	GCCCCAGATATAGCATTCCC	GTTTCATCCTGTTCTGCTCC
mCxcl9	TGCCATGAAGTCCGCTGTTT	CTAGGGTTCCTCGAACTCCAC
mCxcl10	CCAAGTGCTGCCGTCATTTT	TTCATCGTGGCAATGATCTCAAC
mDloop	AATCTACCATCTCCGTGAAACC	TCAGTTTAGCTACCCCCAAGTTTAA
mGzmB	CATGCTGCTAAAGCTGAAGAGT	GCACGTTTGGTCTTTGGGTC
mlfna1	ATTTCCCCTGACCCAGGAAGATG	CCCAGCACATTGGCAGAGG
mlfna2	AGGACAGGCAGGACTTTGGA	GCCTTCTGGATCTGCTGGTTA
mlfna4	AAGGACAGGAAGGATTTGGATT	GAGCCTTCTGGATCTGTTGGTT
mlfnb1	CGTGGGAGATGTCCTCAACT	CTGAAGATCTCTGCTCGGACC
mlfng	TGAGCTCATTGAATGCTTGG	ACAGCAAGGCGAAAAAGGAT
mNon-numt	CTAGAAACCCCGAAACCAA	CCAGCTATCACCAAGCTCGT
mTxnip	CCCTGACCTAATGGCACCAG	CACAATAGCCGCTTTGGGGA
hACTB	GTTGTGCGACGACGAGCG	GCACAGAGCCTCGCCTT
hCXCL10	GAGCCTACAGCAGAGGAACC	GCTGATGCAGGTACAGCGT
CRISPRCas9		
sgAim2_1	CACCGTGCCAGGAGCACACTCGACG	AAACCGTCGAGTGTGCTCCTGGCAC
sgAim2_2	CACCGTGCCACGTCGAGTGTGCTCC	AAACGGAGCACACTCGACGTGGCAC
sgCasp1_1	CACCGTCGTTTAATGTCCCGGGAAG	AAACCTTCCCGGGACATTAAACGAC
sgCasp1_2	CACCGGAGGGCAAGACGTGTACGAG	AAACCTCGTACACGTCTTGCCCTCC
sgIl1b_1	CACCGCATATGGGTCCGACAGCACG	AAACCGTGCTGTGCGACCCATATGC
sgIl1b_2	CACCGTGTGCCGTCTTTCATTACAC	AAACGTGTAAATGAAAGACGGCACAC
sgNlrp3_1	CACCGGAGGATGAACGTGTTCCAGA	AAACTCTGGAACACGTTTCATCCTCC
sgNlrp3_2	CACCGCATCGGCCGGAATAAATGC	AAACGCATTTTAGTCCGGCCGATGC
sgTxnip_1	CACCGATCACCATGATTGAGCCGAG	AAACCTCGGCTCAATCATGGTGATC
sgTxnip_2	CACCGGAACACGTGTTCCCGAATCG	AAACCGATTGCGGAACACGTGTTCC
sgIl1r1_1	CACCGGTATGTCCTATACGTTCCGG	AAACCCGGAACGTATAGGACATACC
sgCxcl10	CACCGAGCGGACCGTCCTTGCGAGA	AAACTCTCGCAAGGACGGTCCGCTC
sgTlr9	CACCGCACATCAAGTACTCGAAGGG	AAACCCCTTCGAGTACTTGATGTGC
siRNA		
siAIM2_1	GCAACGUGCUGACCAAAAtt	UUUUGGUGCAGCACGUUGCtt
siAIM2_2	GGAGAUAAAGGUUCGACUUAAtt	UAAGUCGAACCUUAUCUCtt

Supplementary Table 4: Antibodies

Target	Supplier	Reference	Lot number	Clone	Label	Dilution	Application
CD8	Sysy Ab	HS-361 003	1-12	polyclonal		1/100	IHC
AIM2	Abcam	Ab93015	1013062-14	polyclonal		1/1000	Western Blot
NLRP1	Novus Biological	NB100- 56148ss		polyclonal		1/1000	Western Blot
NLRP3	Novus Biological	NBP1- 77080	A40451906	polyclonal		1/1000	Western Blot
TXNIP	Invitrogen	40-3700	VK316985	polyclonal		1/1000	Western Blot
Cleaved IL- 1β (Asp117)		631245	3	E7V2A		1/1000	Western Blot
IL-1β	R&D Systems	MAB- 4011	166926	polyclonal		1/1000	Western Blot
ASK1	Cell Signaling Technology	3762S	2	polyclonal		1/1000	Western Blot
pASK1	Cell Signaling Technology	3764S	2	polyclonal		1/1000	Western Blot
αTubulin	Cell Signaling Technology	2144S		polyclonal		1/1000	Western Blot
ASC	Adipogen	AG-25B- 0006- C100	A40211902	polyclonal		1/1000	Western Blot
Caspase-1	Adipogen	AG-20B- 0044	A27141508	Casper2		1/1000	Western Blot
COX IV	Cell Signaling Technology	11967S	1	4D11-B3- E8		1/1000	Western Blot
β-actin	Sigma-Aldrich	A1978		AC15		1/1000	Western Blot
CD8	BD Biosciences	612898	3317931		BUV805	1/100	Flow Cytometry
CD45	BD Biosciences	564279	4276899		BUV395	1/100	Flow Cytometry
CD11c	Miltenyi Biotec	130-110- 700	5241110099		FITC	1/100	Flow Cytometry
Ly6G	Miltenyi Biotec	130-120- 734	5241110115		APC	1/100	Flow Cytometry
Ly6C	Miltenyi Biotec	130-102- 207	5250104643		Viogreen	1/20	Flow Cytometry
F4/80	BioLegend	123133	B426303		BV605	1/100	Flow Cytometry
CD3	BioLegend	100241	B363317		BV711	1/100	Flow Cytometry
CD11b	BioLegend	101243	B426555		BV785	1/100	Flow Cytometry