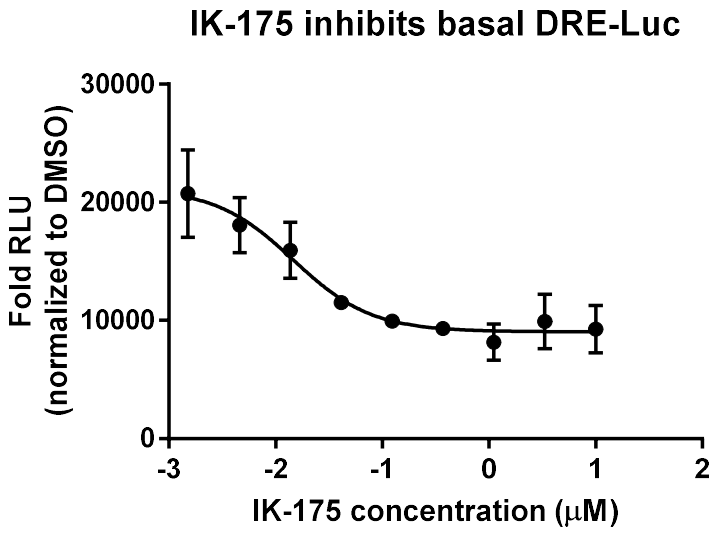
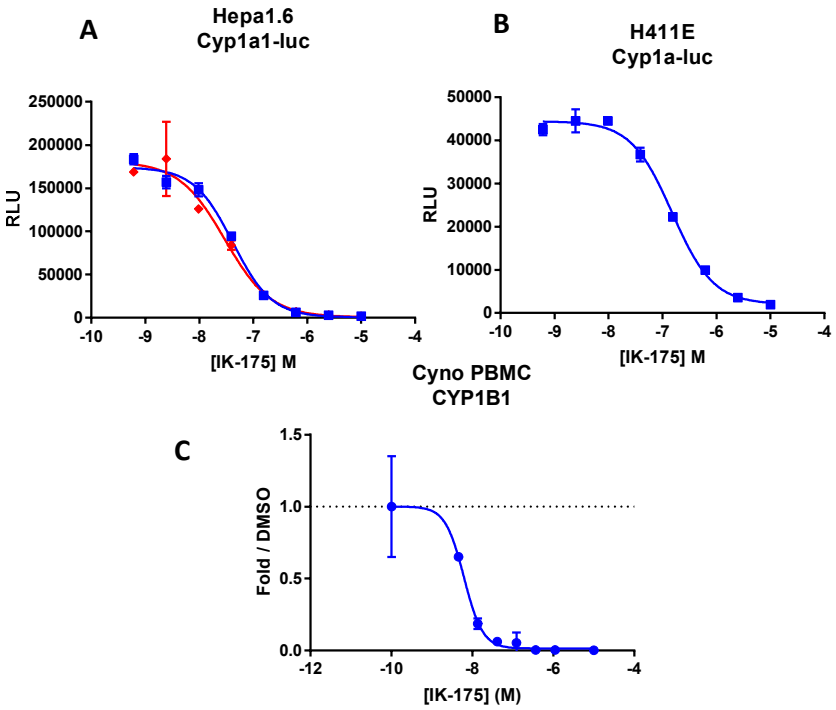
Supplementary Figure S1



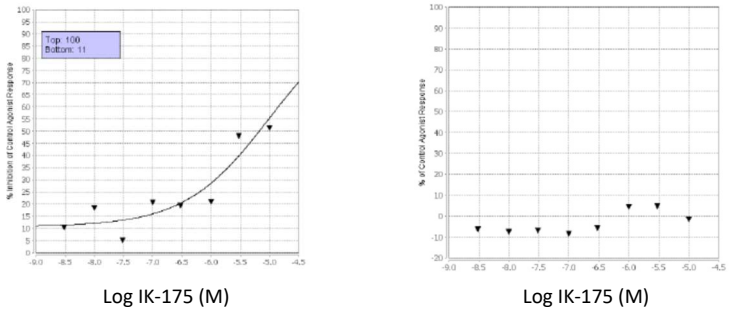
Supplementary Figure S1. IK-175 does not demonstrate AHR agonist activity and inhibits basal activity. IK-175 in HepG2 DRE-Luc assay with no added ligand (n = 1, performed in duplicate).

Supplementary Figure S2



Supplementary Figure S2. IK-175 inhibits AHR in multiple species. **A, B** Cyp-Luc Assay. **A,** Murine Hepa1.6 cell line **B,** Rat H411E and **C,** CYP1B1 expression by QGP in cynomolgus monkey PBMCs.

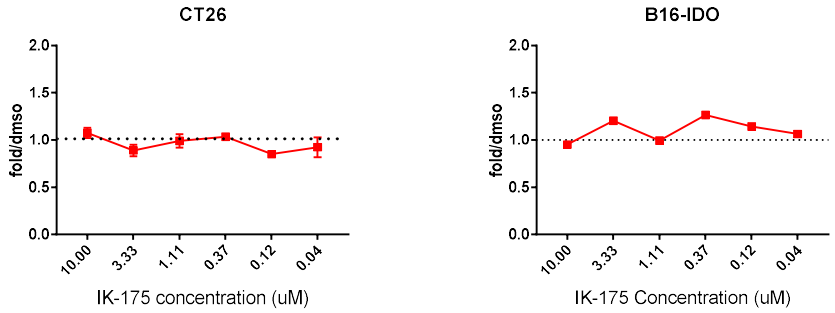
Supplementary Figure S3



Supplementary Figure S3. IK-175 demonstrates little to no activity in PXR assays **A,** PXR antagonist assay **B,** PXR agonist assay.

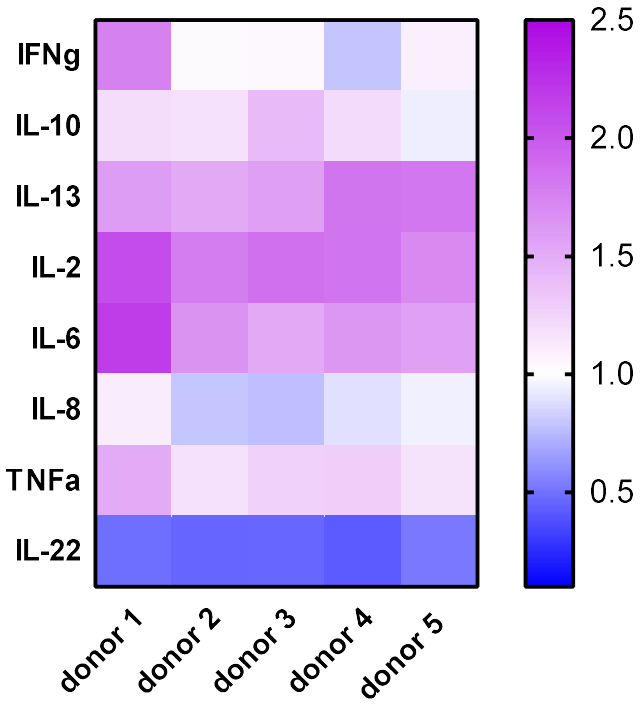
Supplementary Figure S4.

A.



Supplementary Figure S4. IK-175 has on the growth of murine tumor cells. Growth of CT26 (left) and B16-IDO (right) cells treated for 3 days with multiple IK-175 concentrations relative to DMSO. Cell viability was measured using cell titre glo (CTG) and is displayed relative to the DMSO control.

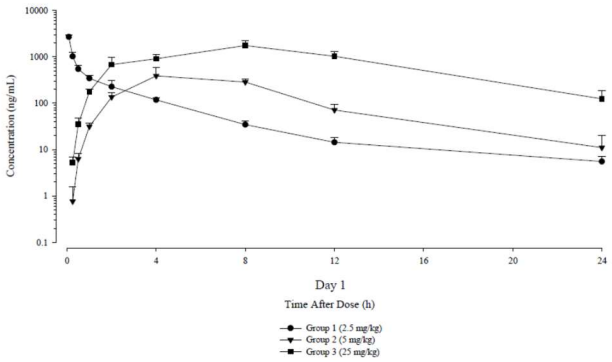
Supplementary Figure S5



Supplementary Figure 5. AHR inhibition effect on cytokines in activated T cells. Summary of fold-change over DMSO in cytokines from activated T cells from 5 individual donors treated with 1 µM KYN-101 (9); MSD analysis.

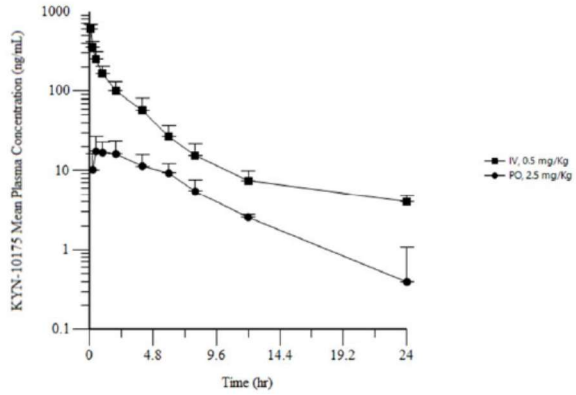
Supplementary Figure S6

A. Rat PK



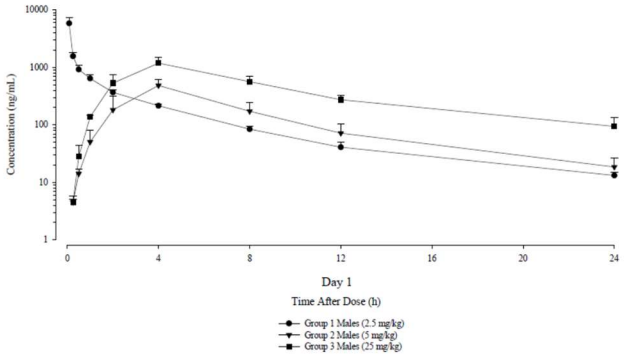
	IV (2.5 mg/kg)	PO (5 mg/kg)	PO (25 mg/kg)
C_{max} (ng/mL)	2680	438	1750
$T_{1/2}$ (h)	6.47	4.02	NA
AUC_{0-24} (h*ng/mL)	2170	3170	19900
Bioavailability (%)	-	73	91.5

B. Dog PK



	IV (0.5 mg/kg)	PO (2.5 mg/kg)
C_0 (ng/mL)	799	18.6
$T_{1/2}$ (h)	9.41	5.84
AUC_{last}(hr*ng/mL)	850	116
Bioavailability (%)	-	2.73

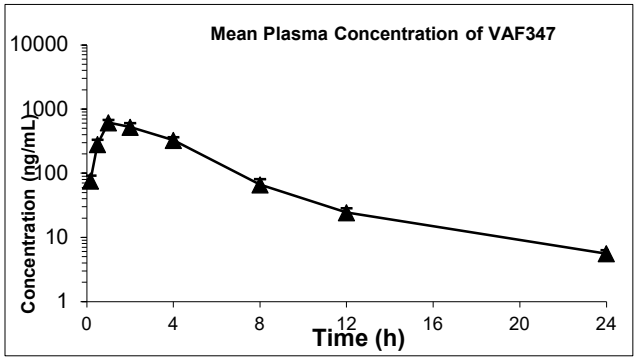
C. Monkey PK



	IV (2.5 mg/kg)	PO (5 mg/kg)	PO (25 mg/kg)
C_{max} (ng/mL)	5680	486	1190
$T_{1/2}$ (h)	5.85	5.3	6.75
AUC_{0-24} (h*ng/mL)	4300	3150	9500
Bioavailability (%)	-	36.7	22.1

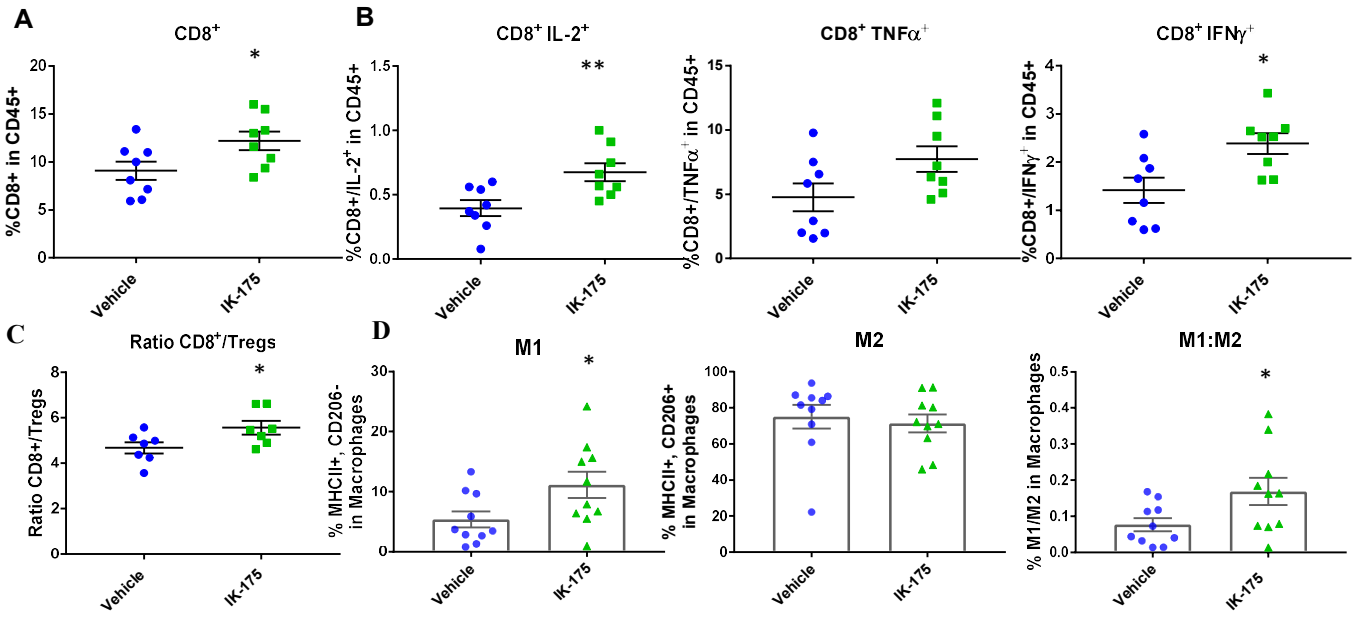
Supplementary Figure S6. Pharmacokinetics of IK-175 following single intravenous (IV) or oral (PO) administration in (A) Sprague Dawley rat, (B) beagle dog and (C) cynomolgus monkey. Time course of plasma exposure (mean (+SD) plasma concentration (ng/mL), (left) and PK parameters with dose administered in table (right).

Supplementary Figure S7



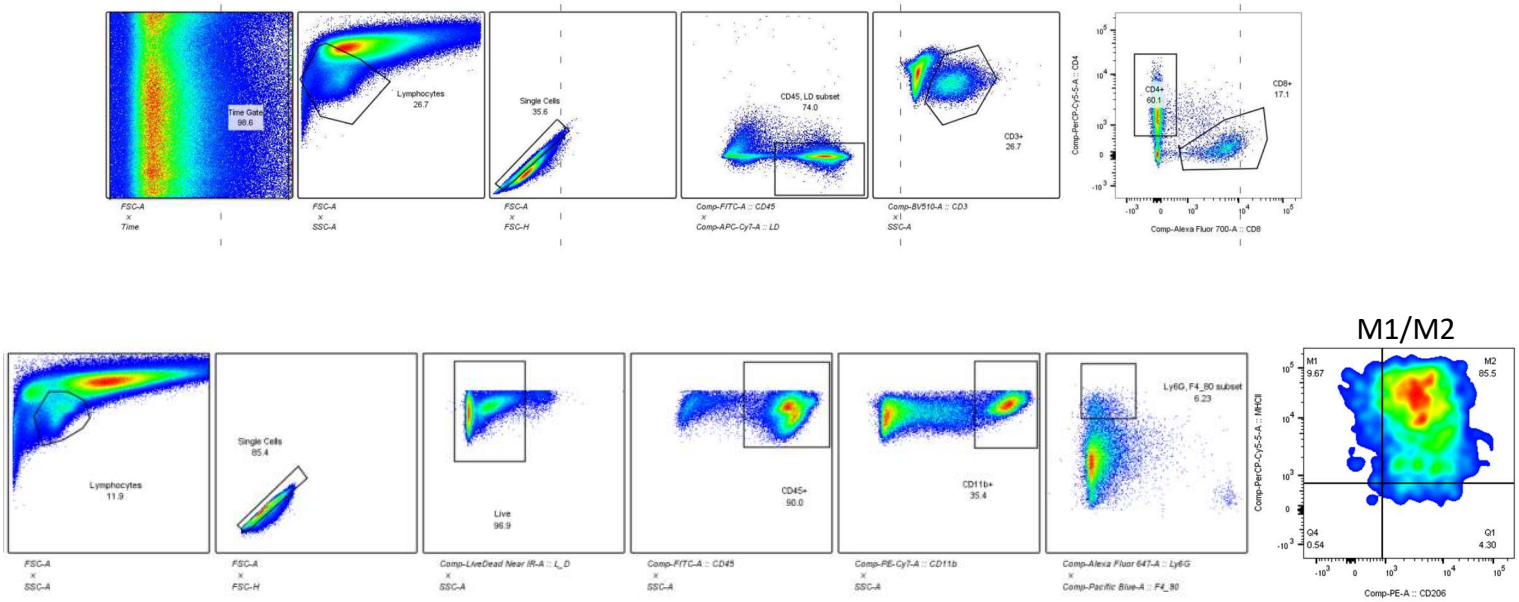
Supplementary Figure S7. Mean Plasma concentration of VAF347 with dosing of prodrug VAG539 (30 mg/kg orally).

Supplementary Figure S8



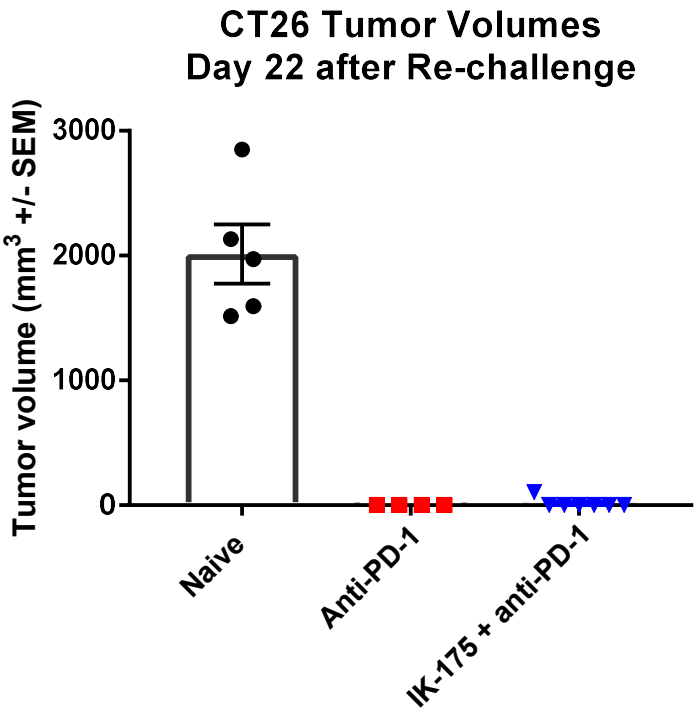
Supplementary Figure S8. IK-175 affects immune cells of TDLNs in CT26 tumor-bearing mice. Increase in total $CD8^+$ cells and IL-2, TNFα and IFNγ cytokines from ex vivo stimulation of immune cells in tumor draining lymph nodes from CT26 tumor-bearing mice treated with IK-175 (25 mg/kg orally for 7 days). **A,** Total $CD8^+$ cells. **B,** Cytokines measured after PMA and ionomycin stimulation: IL2, TNFα, IFNγ. **C,** $CD8^+$ and Treg ($CD4^+$/$FoxP3^+$/$CD25^+$) levels in unstimulated TDLN indicate an increase in CD8:Treg ratio. **D,** Increase in M1 myeloid cells (MHCII+, CD206-) after IK-175 treatment (50 mg/kg orally for 4 days); myeloid cell change also leads to increase in the ratio of M1:M2 cells (* $p < 0.05$, ** $p < 0.01$, unpaired t-test).

Supplementary Figure S9



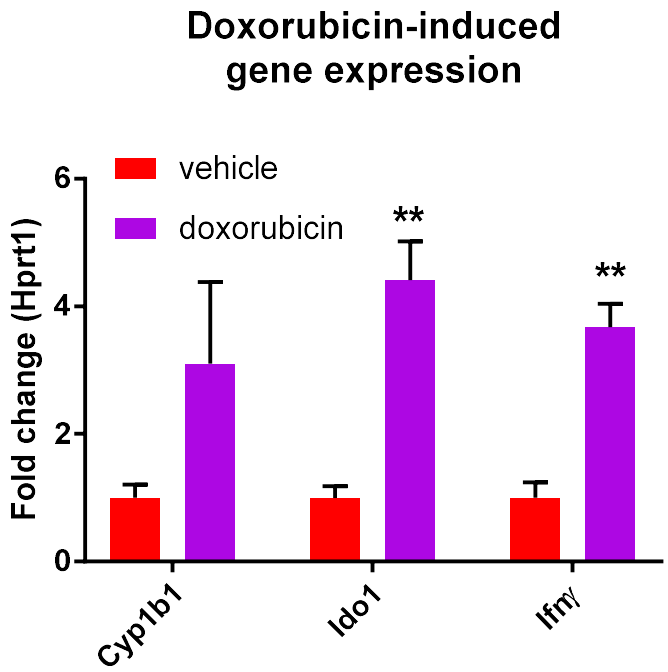
Supplementary Figure S9. Flow cytometry gating scheme for T cells (top) and myeloid cells (bottom)

Supplementary Figure S10



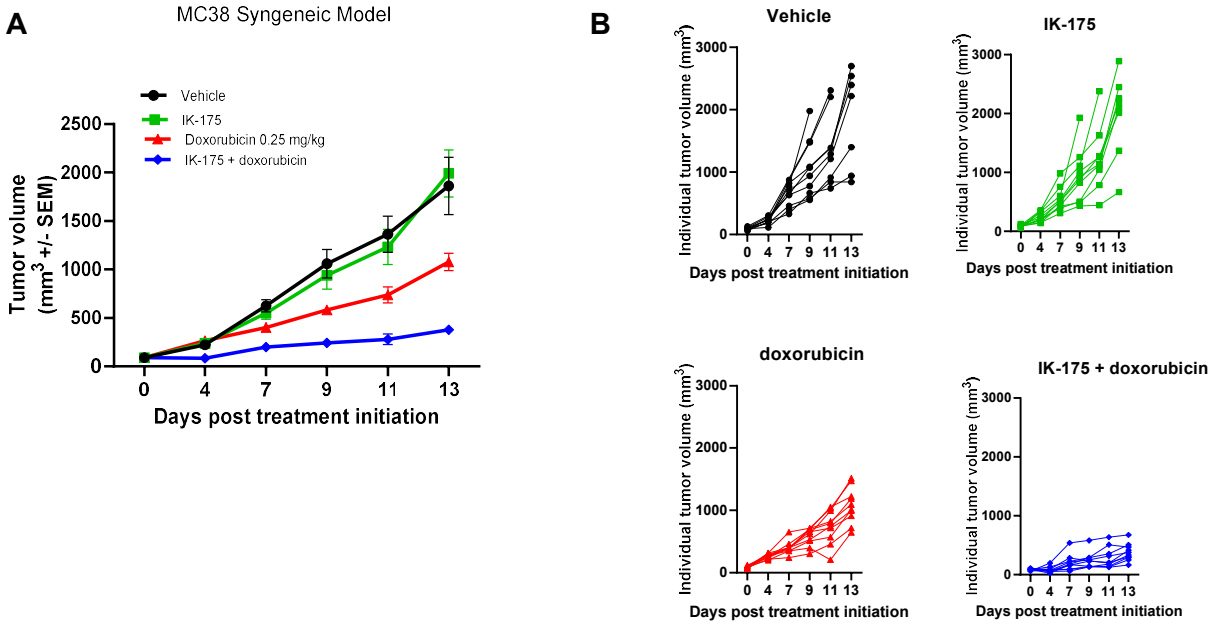
Supplementary Figure S10. Mice with CRs from tumor study in Figure 6C rechallenged with CT26 do not form tumors indicating immune memory.

Supplementary Figure S11



Supplementary Figure S11. AHR and IFN genes induced by liposomal doxorubicin in CT26 tumors. CT26 tumors treated with 2 doses liposomal doxorubicin (5 mg/kg) and gene expression compared with vehicle (** $p < 0.01$, unpaired t-test).

Supplementary Figure S12



Supplementary Figure S12. Tumor growth inhibition of MC38 tumor with IK-175 in combination with liposomal doxorubicin. **A,** Tumor growth with treated groups over time in CT26. IK-175 (25 mg/kg, orally, daily); liposomal doxorubicin (0.25 mg/kg, intravenously, every 7 days, 4 doses). Treatment started six days after cell inoculation. Tumor growth inhibition is 84% with IK-175 and liposomal doxorubicin. (liposomal doxorubicin vs vehicle, p = 0.05, IK-175 plus liposomal doxorubicin vs vehicle, p = 0.04, IK-175 plus liposomal doxorubicin vs liposomal doxorubicin, p = 0.02, IK-175 plus liposomal doxorubicin vs. IK-175, p = 0.05, IK-175 vs vehicle, not significant, unpaired t test) **B,** Individual tumors by group.