

Preclinical efficacy of targeting FGF autocrine signaling in mesothelioma with the FGF ligand trap, FP-1039/GSK3052230



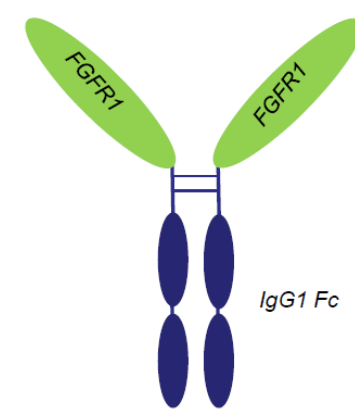
FivePrime

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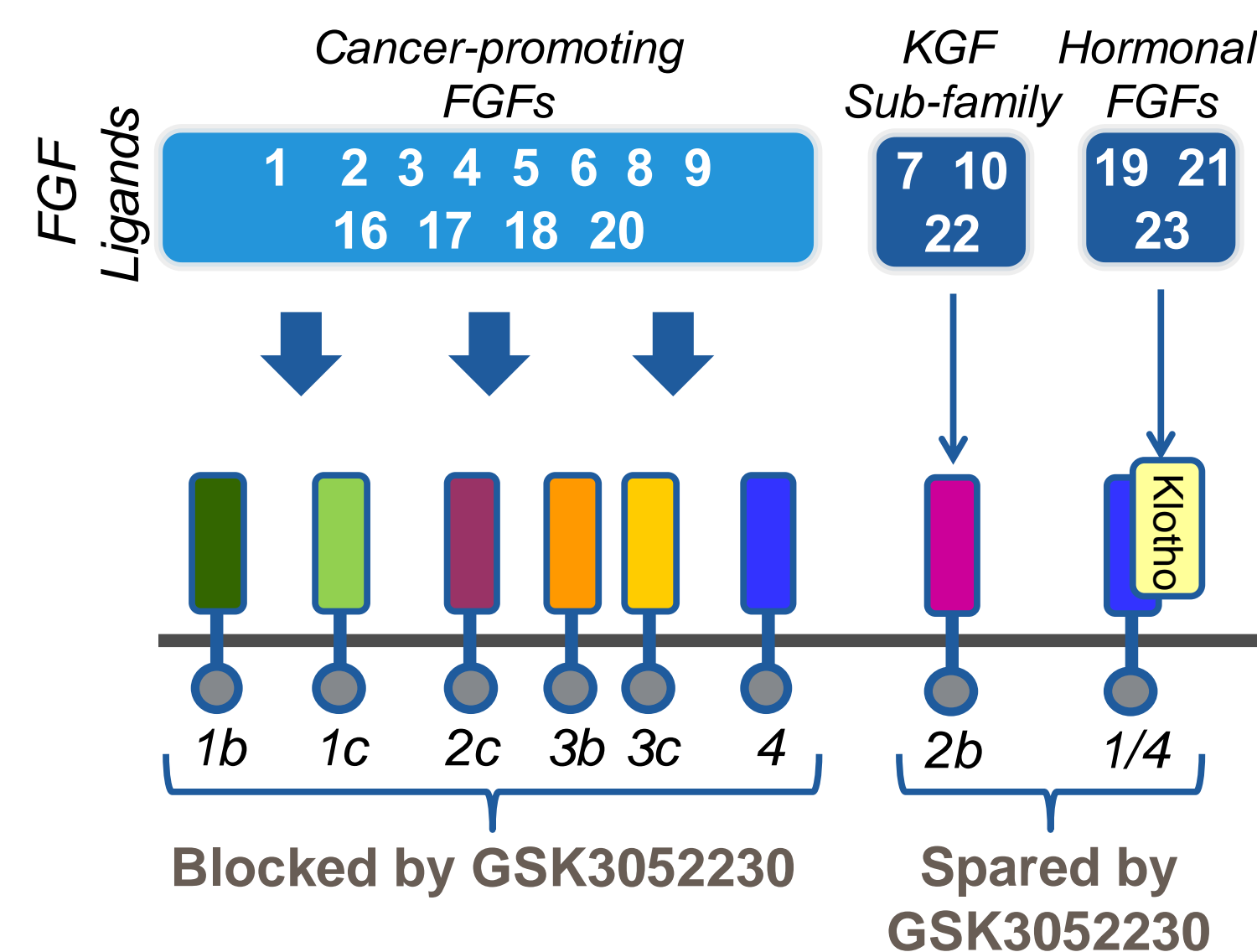
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FP-1039/GSK3052230 Background

- FGF Ligand Trap composed of the extracellular domain of Fibroblast Growth Factor Receptor 1 (FGFR1 isoform α-IIIc) linked to the hinge and Fc regions of human IgG1
- Harding TC et al. *Sci. Transl. Med.* 2013;5:1-9



GSK3052230 has a distinct selectivity profile in blocking multiple FGFRs



- GSK3052230 binds to multiple FGFs and blocks activation of several FGFRs
 - Affects FGF ligand-dependent pathways in cancer
- Does not block hormonal FGF signaling, avoiding the hyperphosphatemia, renal failure, retinal toxicities, and oral pain that have been observed clinically with small molecule pan-FGFR kinase inhibitors

Identification of biomarkers that predict sensitivity to GSK3052230

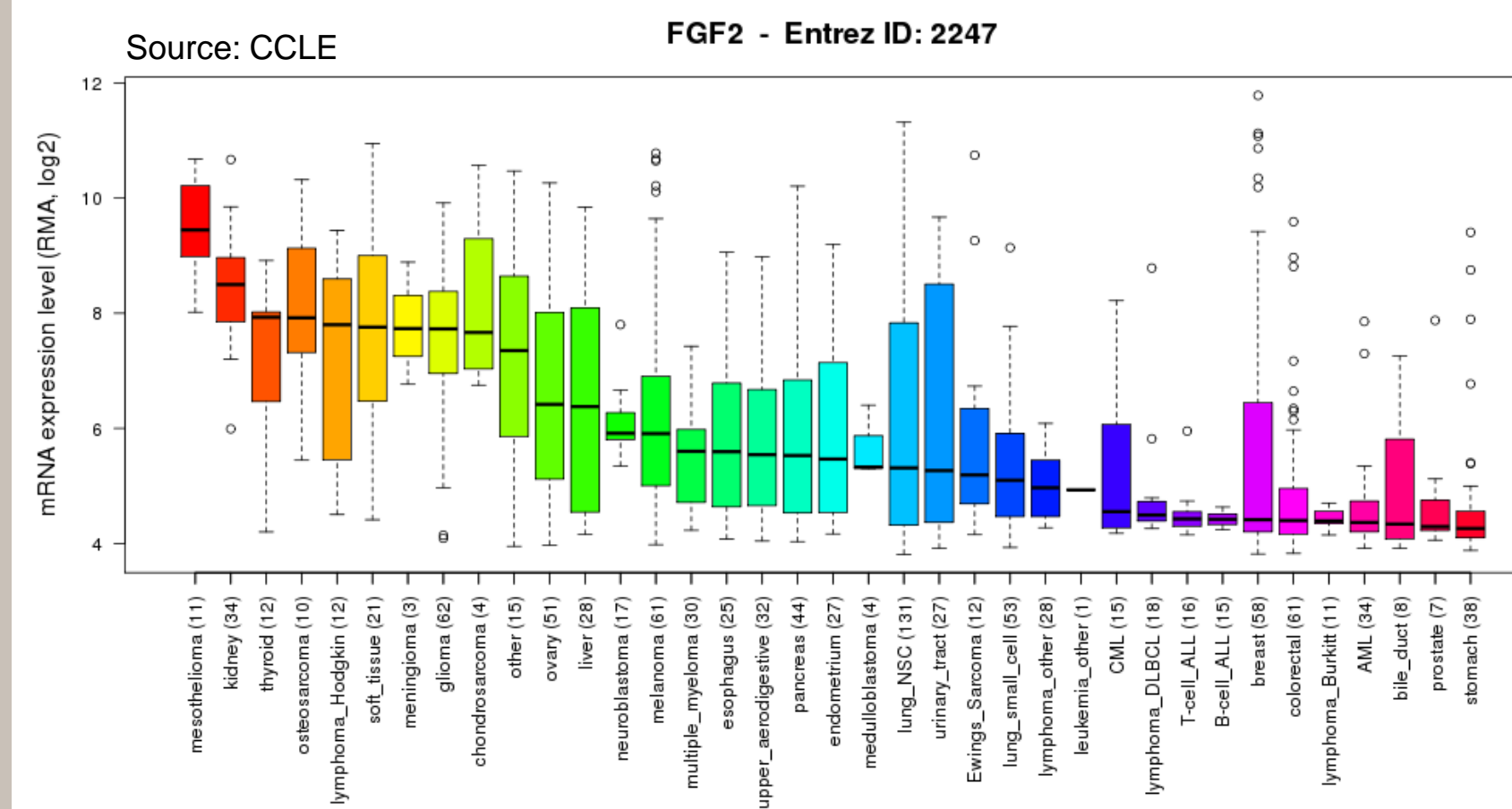
Table 2. RNA levels of FGF ligands and receptors correlated with FP-1039 efficacy in xenograft models.

Gene	Ratio*	p†
ETV4	2.897	0.01639
FGFR1	2.447	0.01669
FGFR3c	9.863	0.01944
FGF18	6.915	0.02227
FGF2	247.7	0.03569
FGFR1c	3.647	0.0431

*Gene expression ratio was determined by median gene expression in FP-1039 responders/median gene expression in nonresponders. †P value was determined by Mann-Whitney.

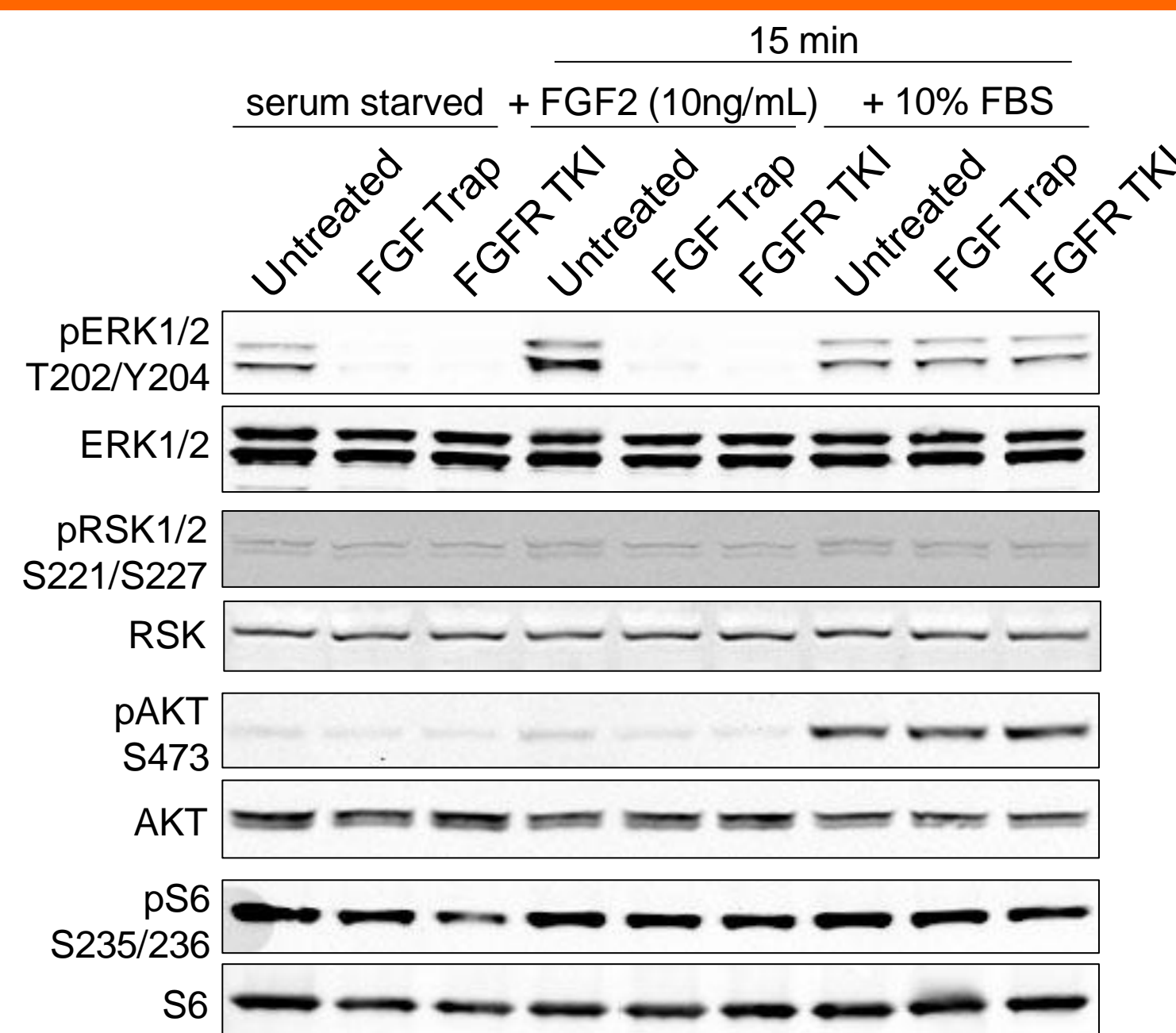
- FGF2 mRNA expression ratio was the highest of all statistically significant expression levels across all tumor xenografts
- Provides an opportunity for patient selection
- Provided the rationale to explore tumor types where FGF2 expression levels are high**

FGF2 mRNA expression in cancer cell lines

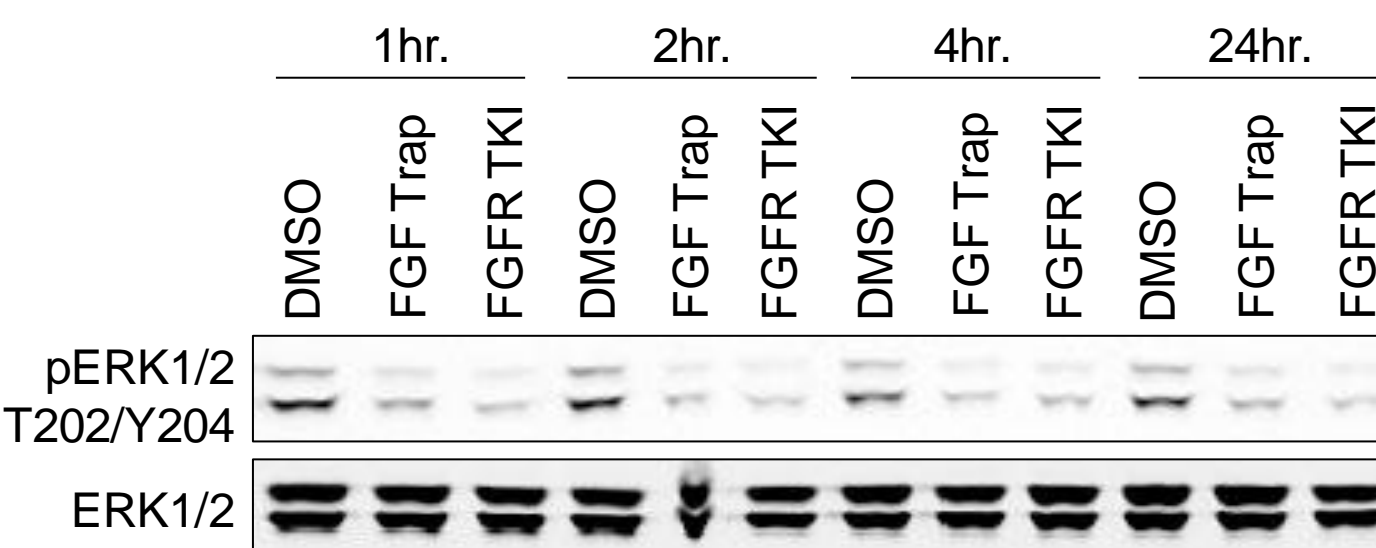


- FGF2 mRNA expression levels are highest in mesothelioma cell lines
 - NCI-H226: 9.9 RMA, log2 (see above)
 - MSTO-211H: 10.6
- Overexpression (>4-fold over median) also observed in ~50% of 1° mesothelioma specimens (not shown)

FGF/FGFR pathway signaling in NCI-H226 mesothelioma cells

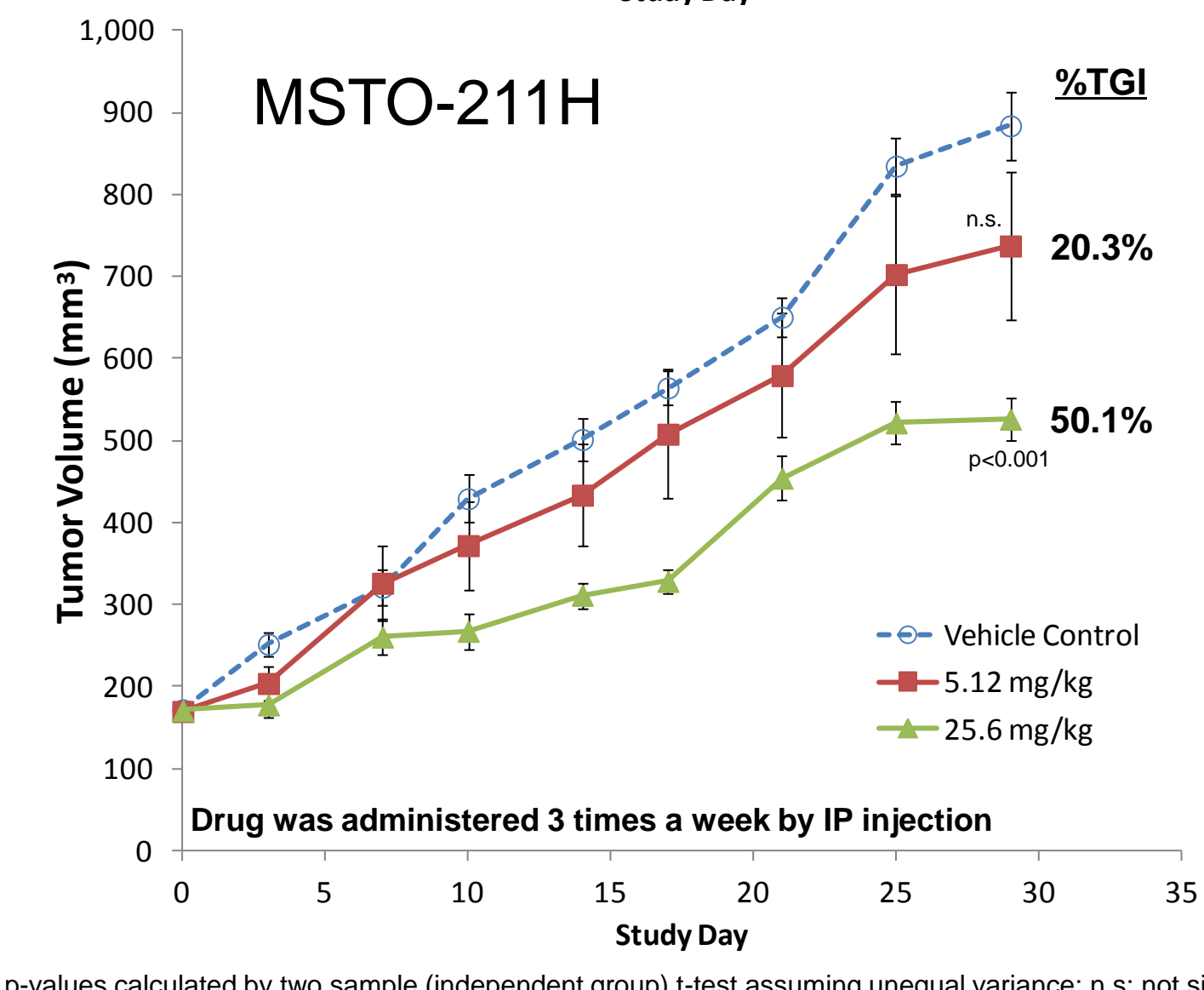
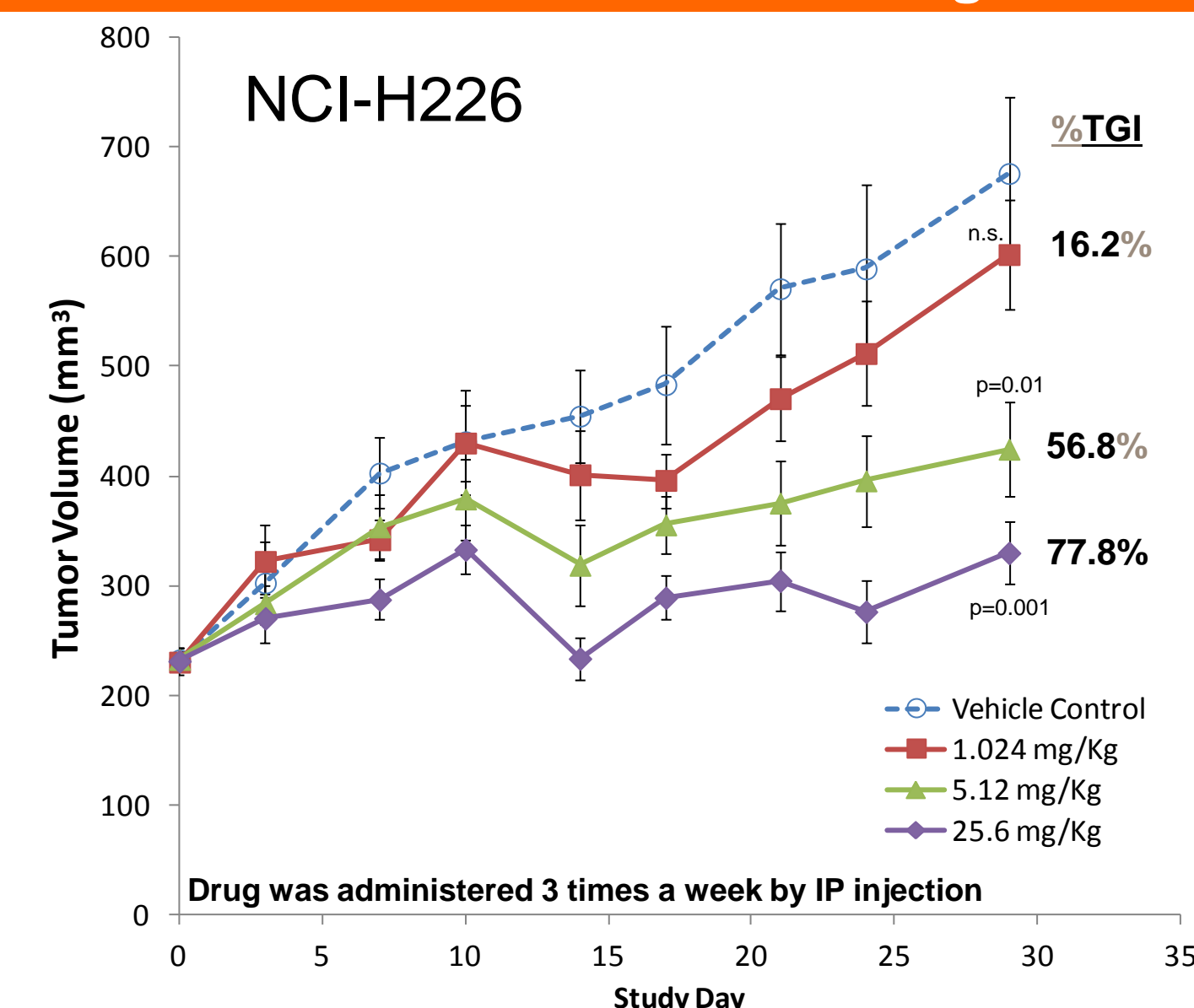


- FGF Trap (GSK3052230) and FGFR TKI (small molecule pan-FGFR kinase inhibitor) inhibit basal phospho-ERK levels and FGF2-induced phospho-ERK levels, yet both were ineffective at inhibiting signaling induced by acute serum (10% FBS) stimulation

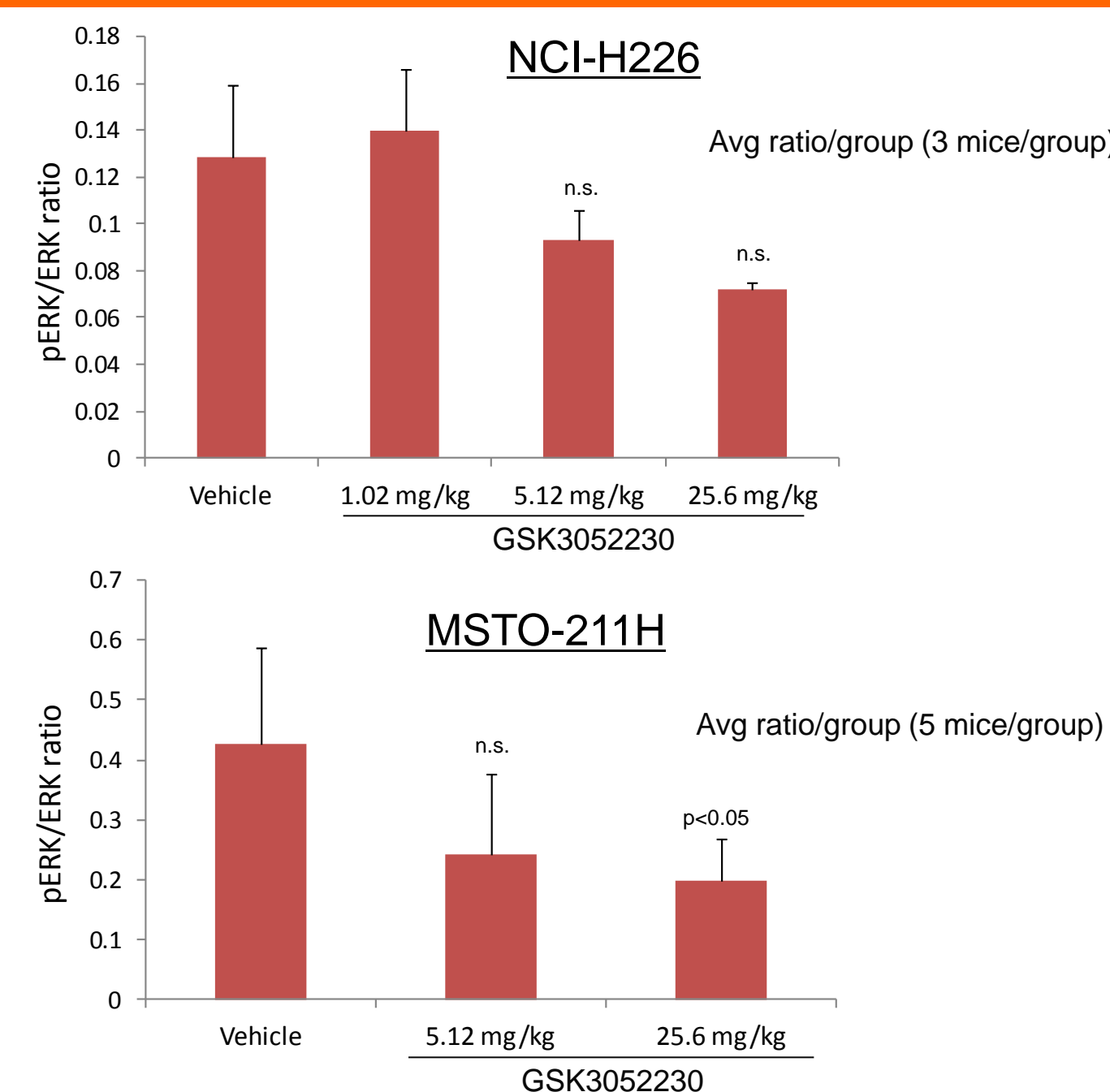


- Decreased phospho-ERK levels observed under full serum conditions (10% FBS) with both molecules.
- Similar results seen in MSTO-211H cells (not shown)

GSK3052230 inhibits tumor growth in mesothelioma tumor xenografts

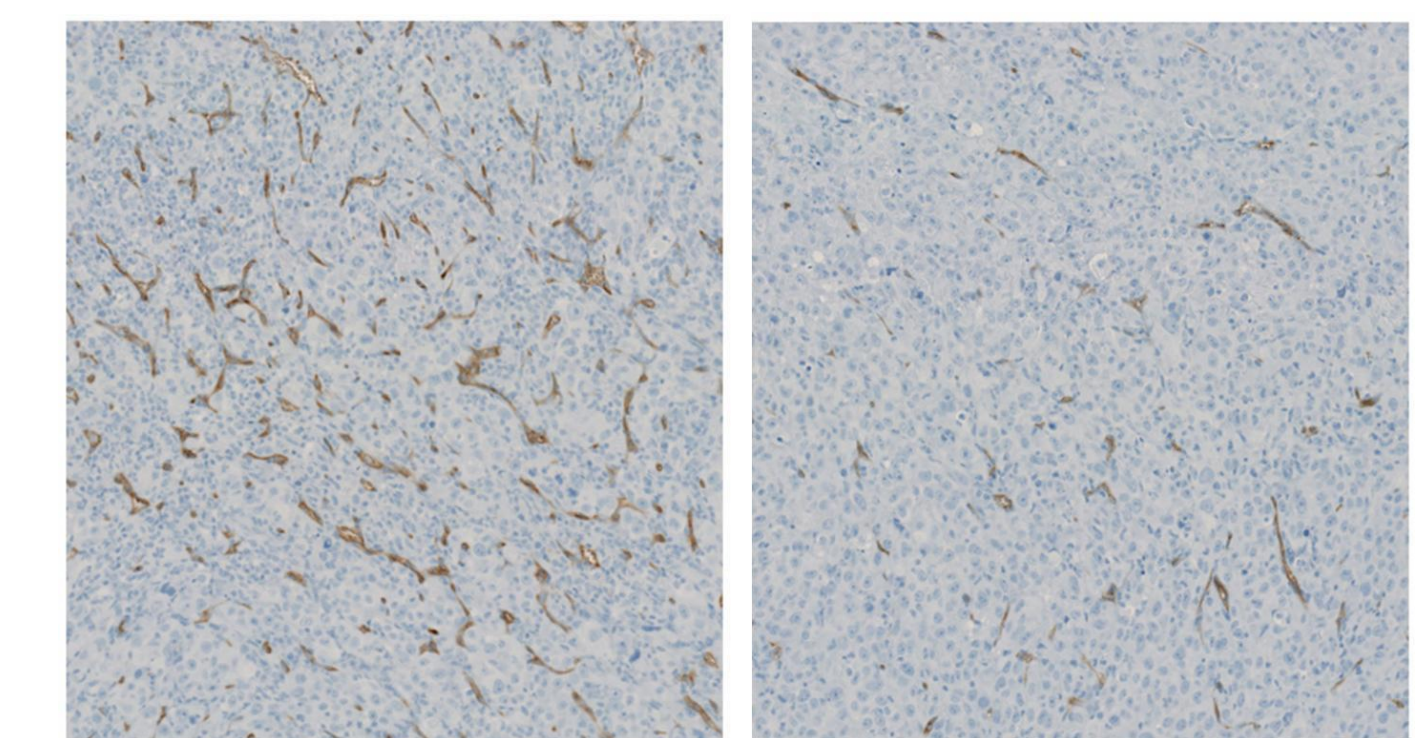


GSK3052230 reduces pERK levels in both NCI-H226 and MSTO-211H tumors



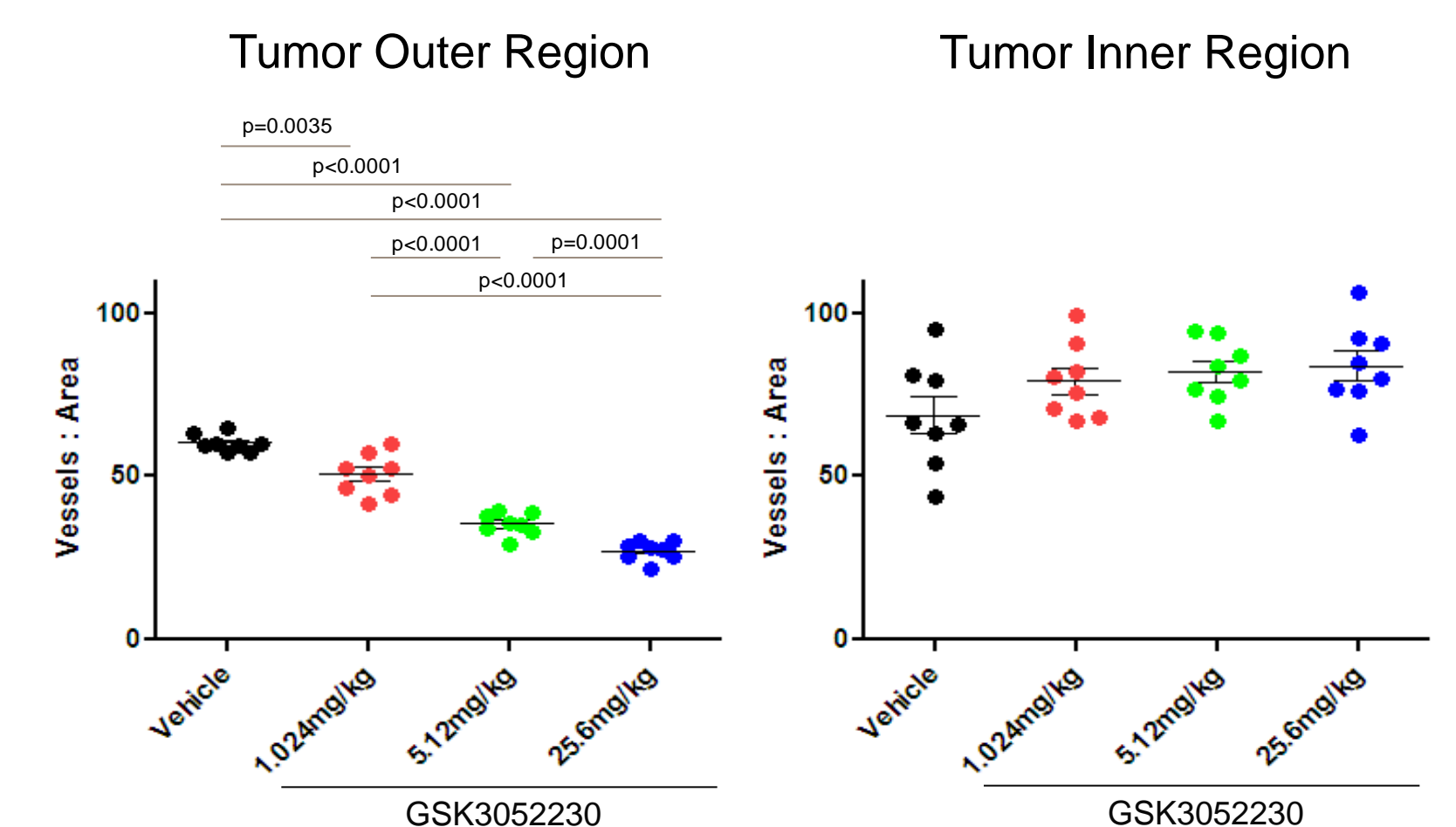
- pERK/ERK protein level ratios were determined by densitometry of western blot data
- p-values calculated by two sample (independent group) t-test assuming unequal variance; n.s.: not significant

GSK3052230 reduces tumor vessel density in NCI-H226 xenografts

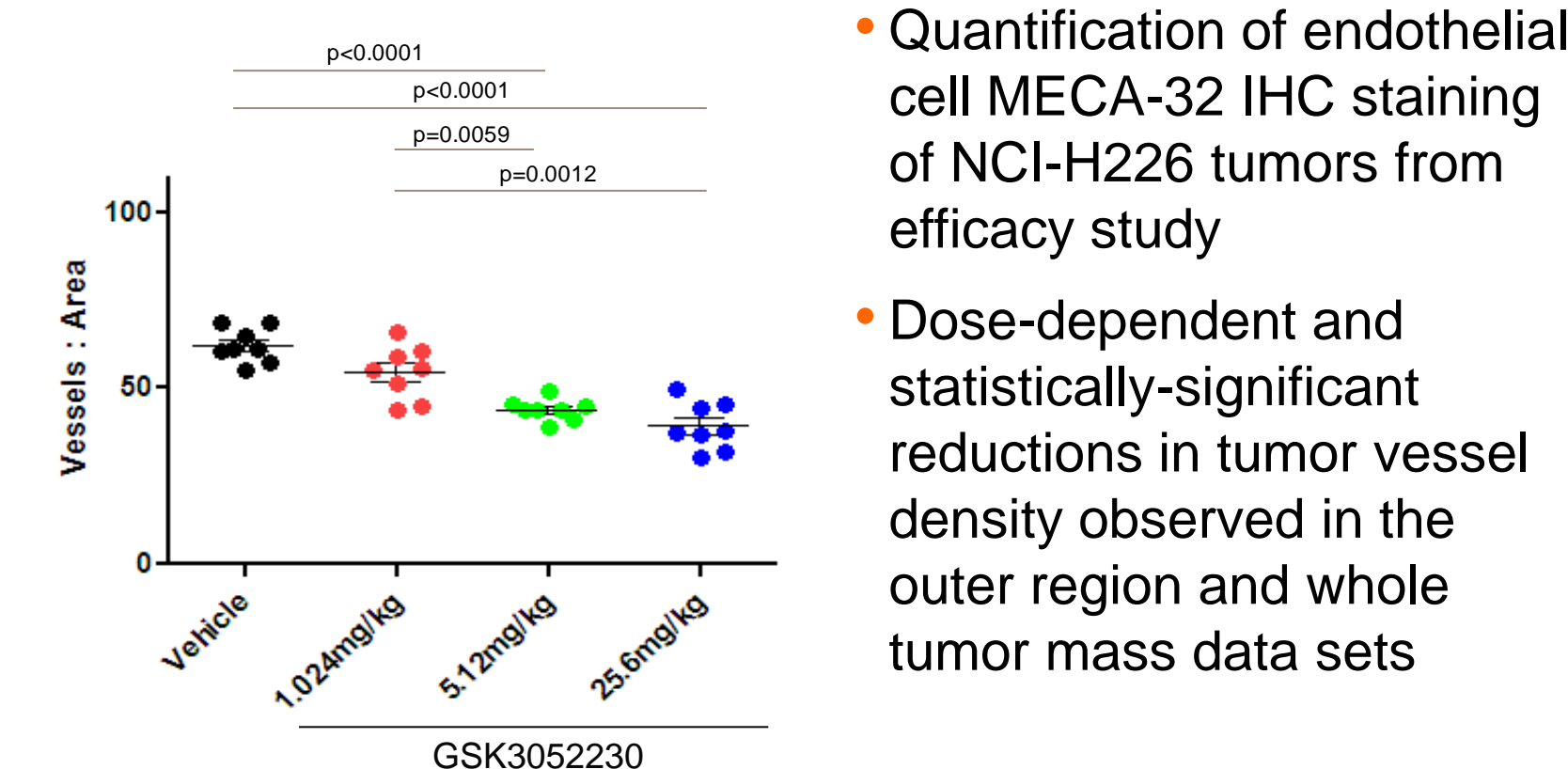


Vehicle 25.6 mg/kg

- Representative photomicrographs of vehicle-treated or GSK3052230-treated NCI-H226 xenograft tumors (outer region) stained for MECA-32 by IHC



Whole Tumor Mass



p-values calculated by one-way ANOVA assuming unequal variance. Bonferroni's multiple comparison test was used to adjust for the multiple comparisons.

Conclusions

- GSK3052230 inhibits tumor growth in mesothelioma xenografts that overexpress FGF2 by reducing FGF autocrine signaling and by inhibiting angiogenesis
- These data support the clinical evaluation of this drug in mesothelioma patients in a Phase Ib trial (NCT01868022)