Cancer Pharmacology Lab
AIRC Start-up Unit

VUmc Cancer Center Amsterdam

Synergistic activity of the c-Met and tubulin inhibitor tivantinib (ARQ197) with pemetrexed in mesothelioma cells

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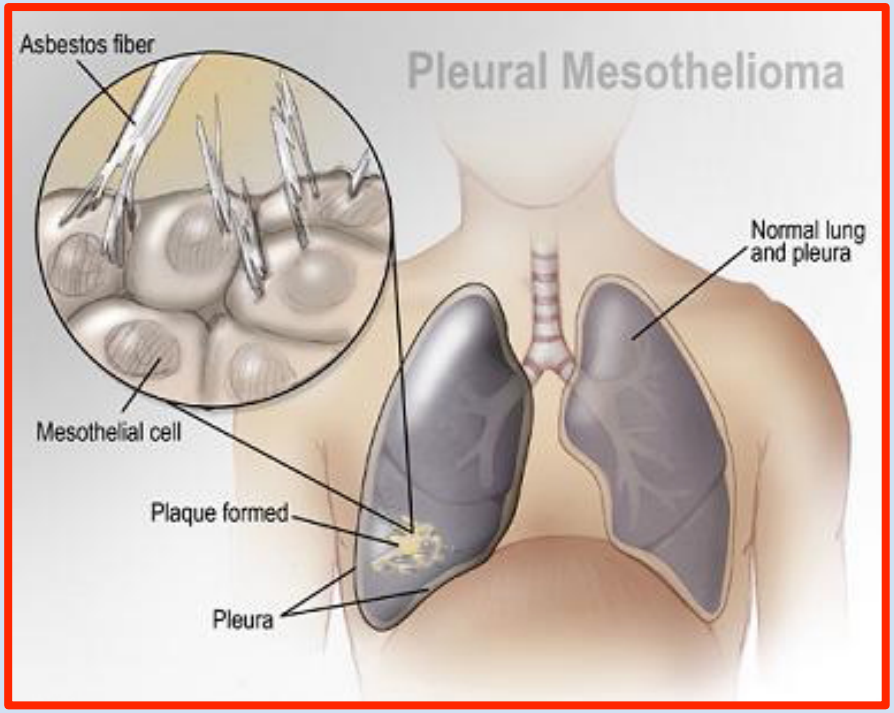
Malignant Pleural Mesothelioma MPM

Despite a clear understanding of MPM aetiology (i.e., asbestos exposure) the worldwide incidence continues to climb, and research directed towards better disease management are warranted

The majority of MPM patients are not eligible for surgery (85-90% in stage III/ IV) and are treated with cisplatin-pemetrexed chemotherapy

Most chemotherapeutic agents exhibit low intrinsic activity and most patients experience tumor progression or relapses within a year

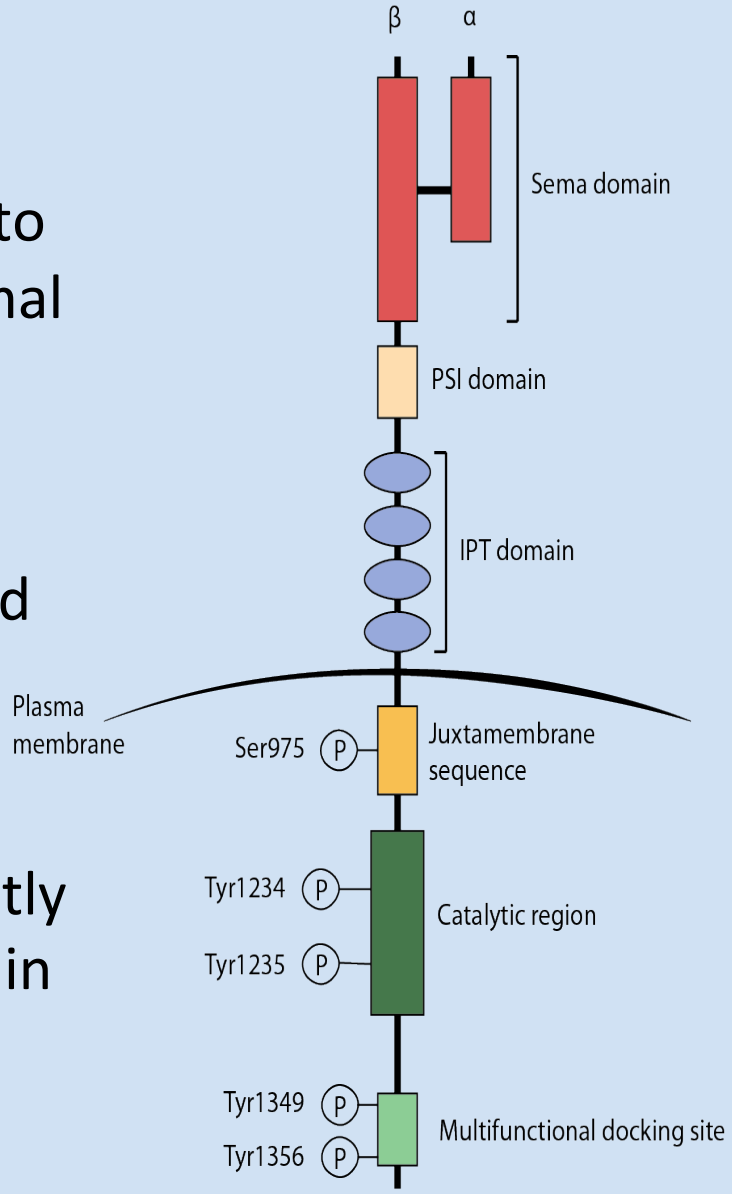


Why targeting c-MET?

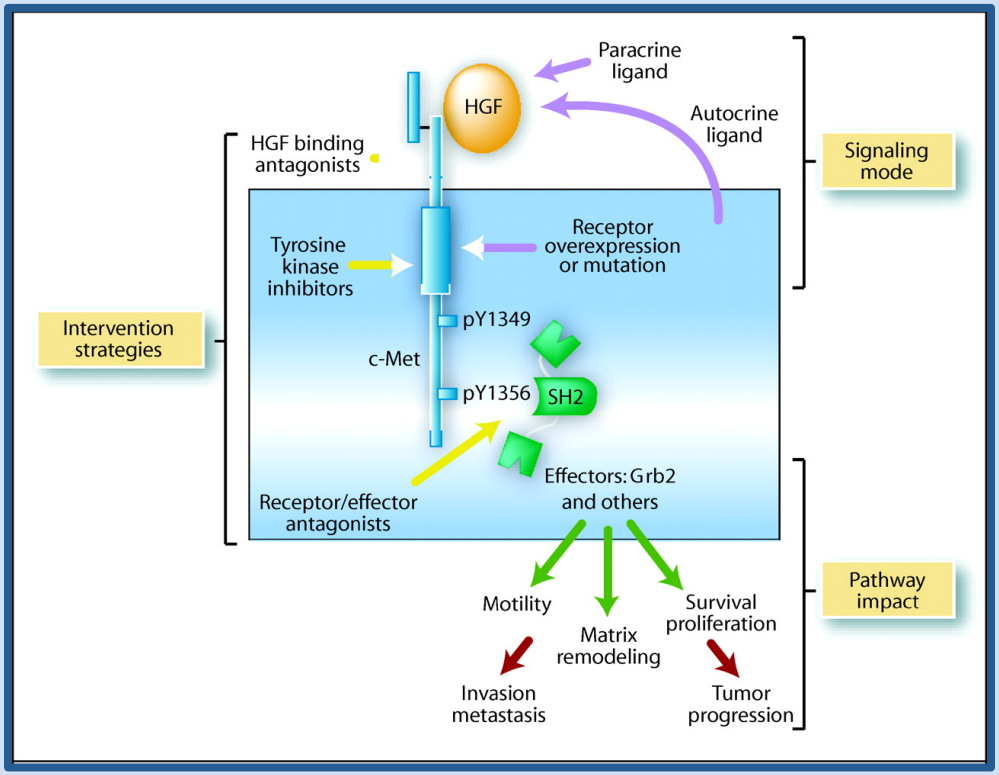
The expression of c-Met protein has been detected by immunohistochemistry in 70% to 100% of FFPE MPM samples but not in normal mesothelial cells

c-MET gene mutations have been reported in about 16% of MPM patients

c-Met plasma membrane localization recently emerged as a relevant prognosis biomarker in MPM

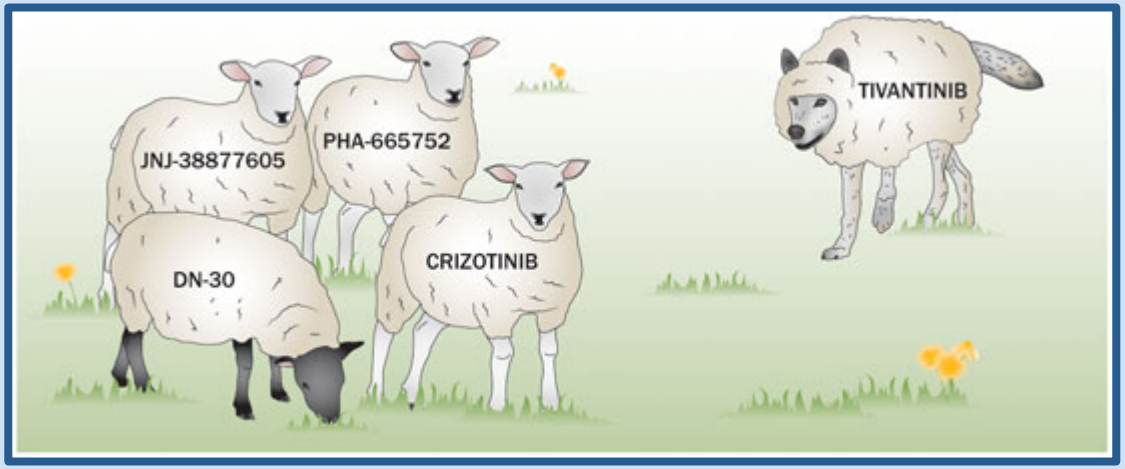


Drugs targeting c-Met



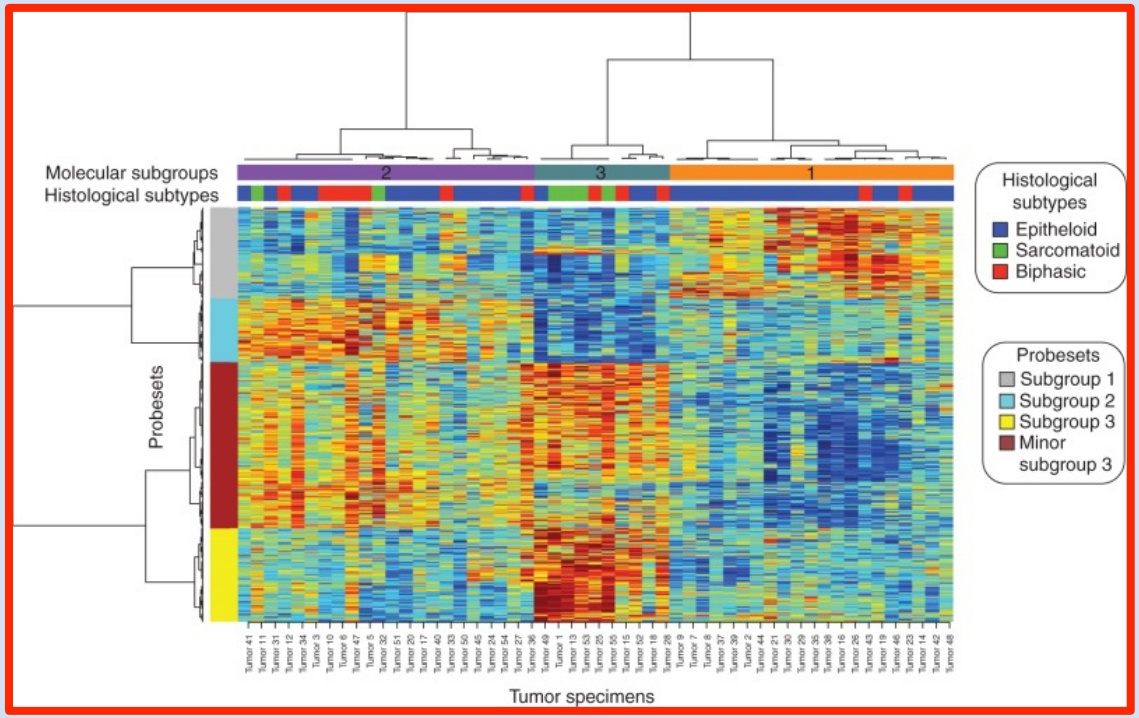
Considerable efforts have been made in the development of effective TKIs. Among these compounds, crizotinib cabozantinib and **tivantinib** are part of more advanced clinical development

The «strange case» of tivantinib



Recent studies suggested that tivantinib inhibits microtubule polymerization in addition to inhibiting c-Met (*Michieli & Di Nicolantonio, Nat Rev Clin Oncol. 2013*)

Microarray data from MPM samples showed the cytoskeleton/spindle microtubules network was the second-most significantly affected networks (*Suraokar et al, Ann Oncol 2014*)

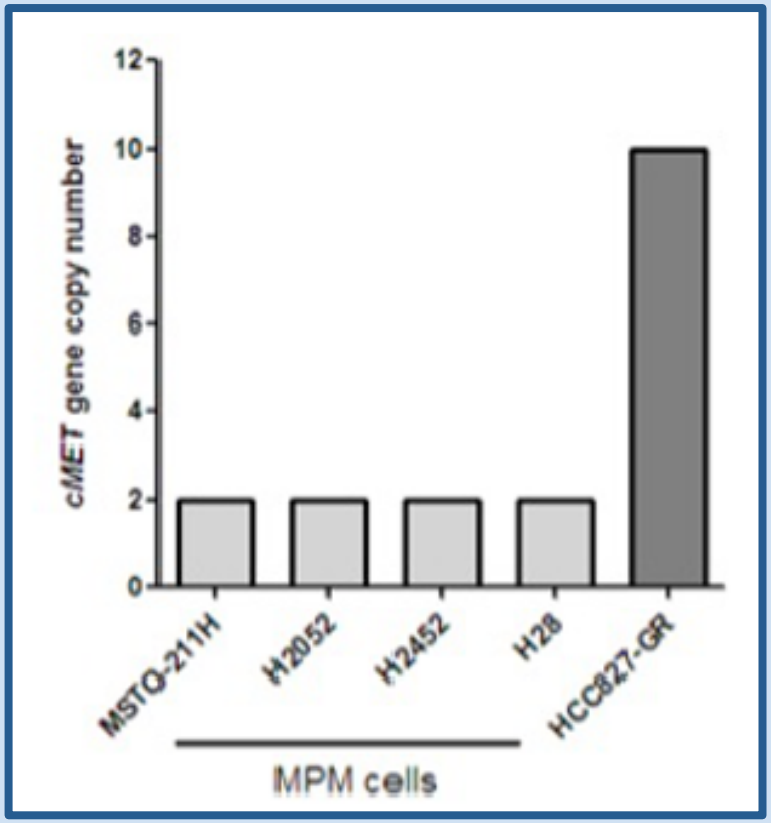


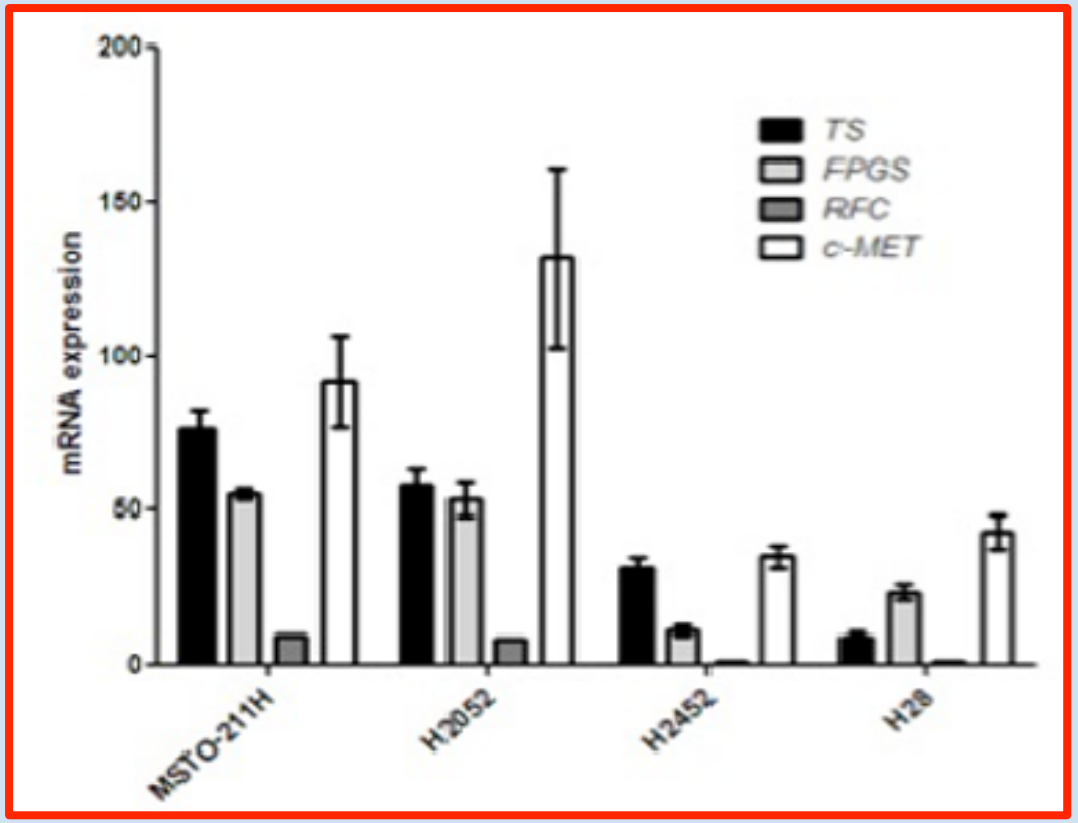
AIMs

1. To explore new chemical strategies to overcome the low intrinsic activity in MPM, evaluating tivantinib activity

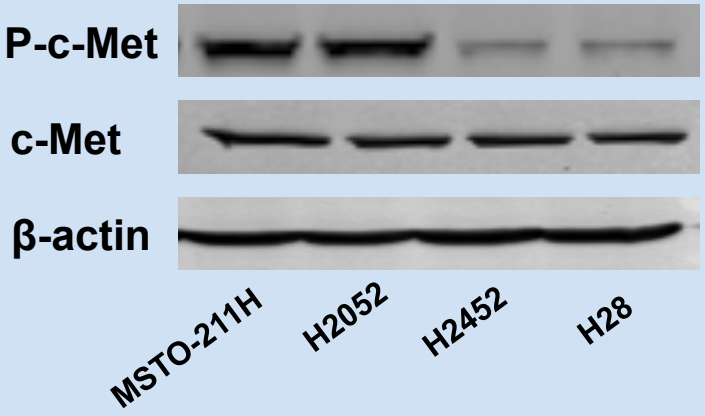
2. To evaluate the molecular and cellular characteristics underlying the interaction between pemetrexed and tivantinib

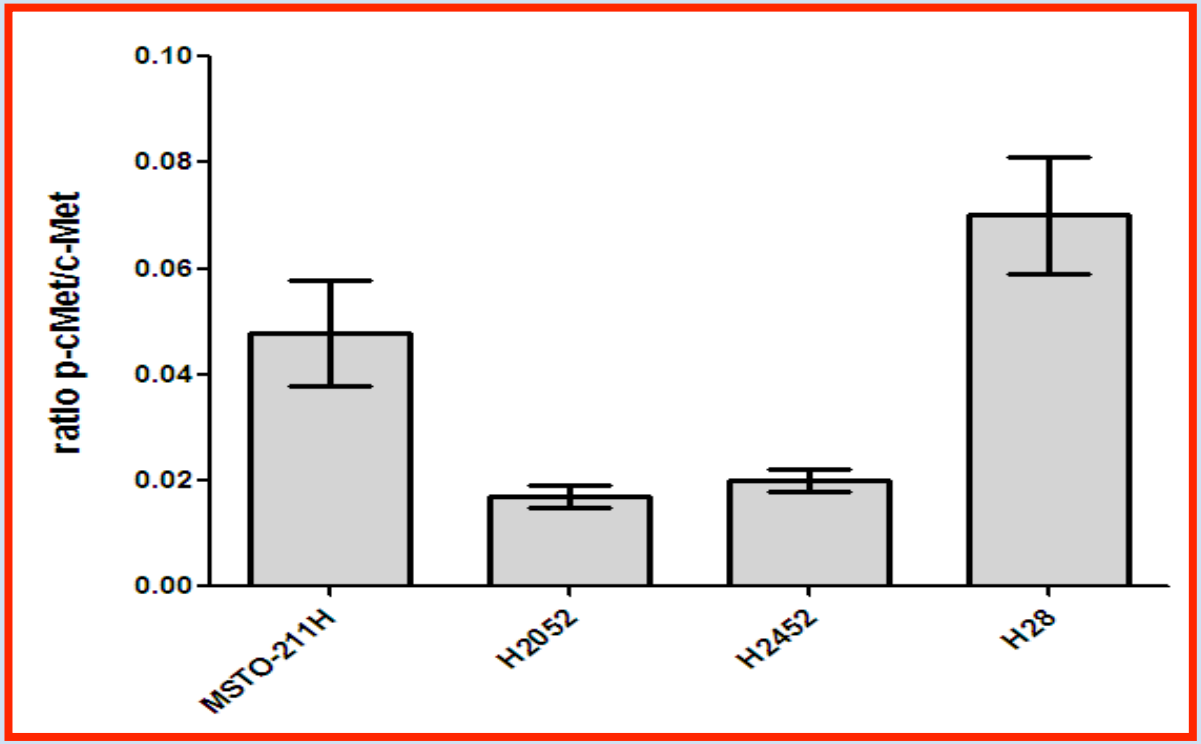
Genetic characteristics of the human MPM cell lines



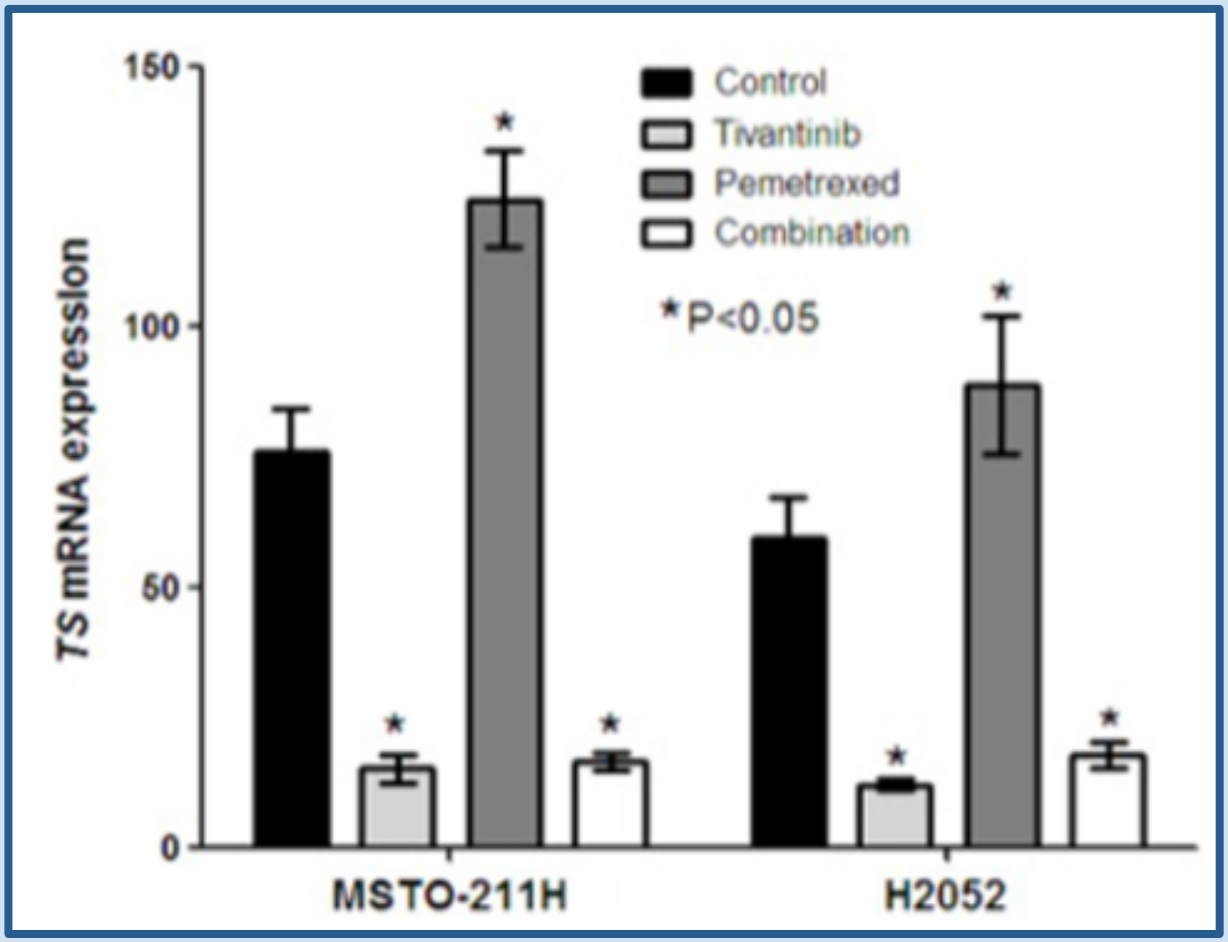


Expression and phosphorylation of c-Met



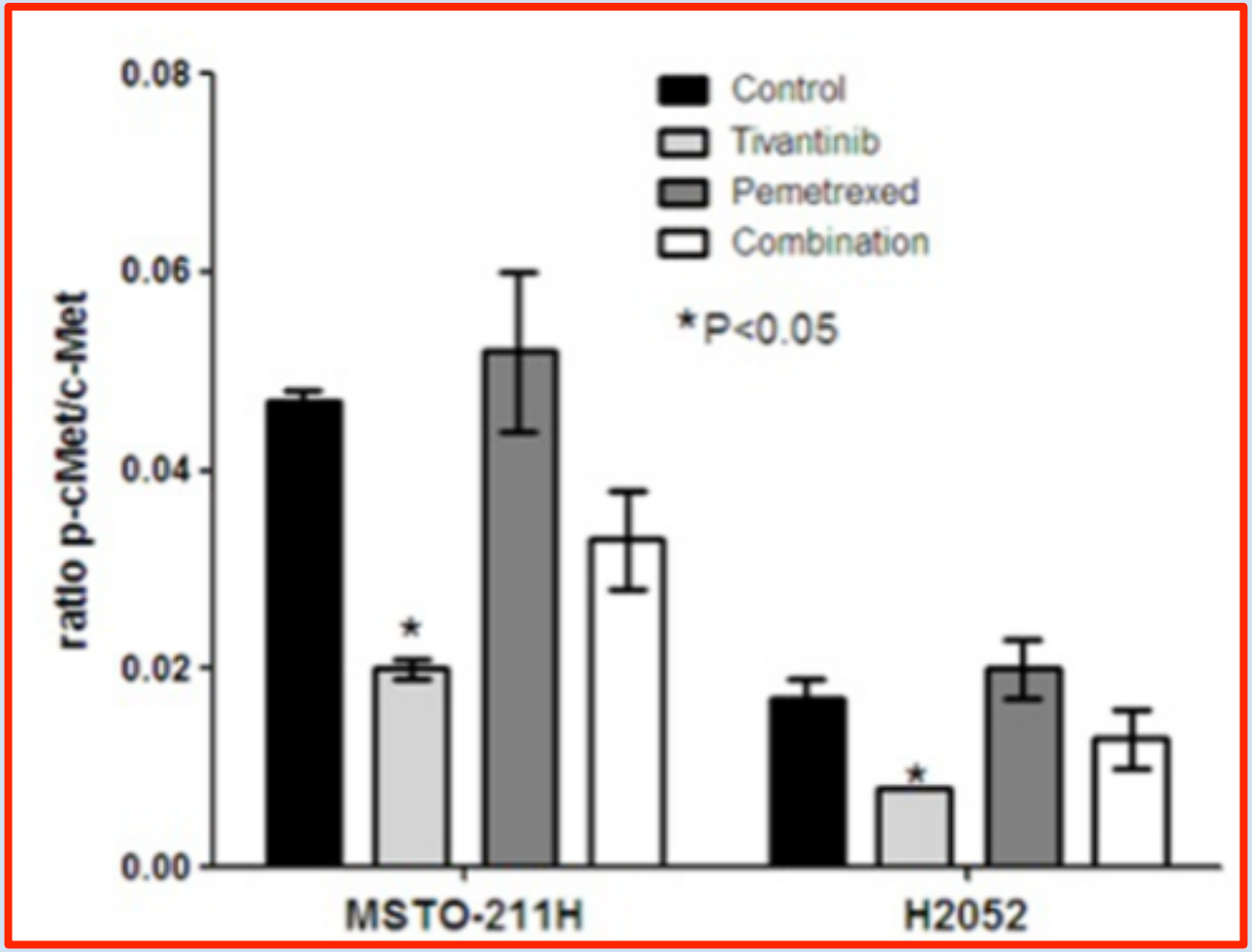


Modulation of TS & phospho-c-Met



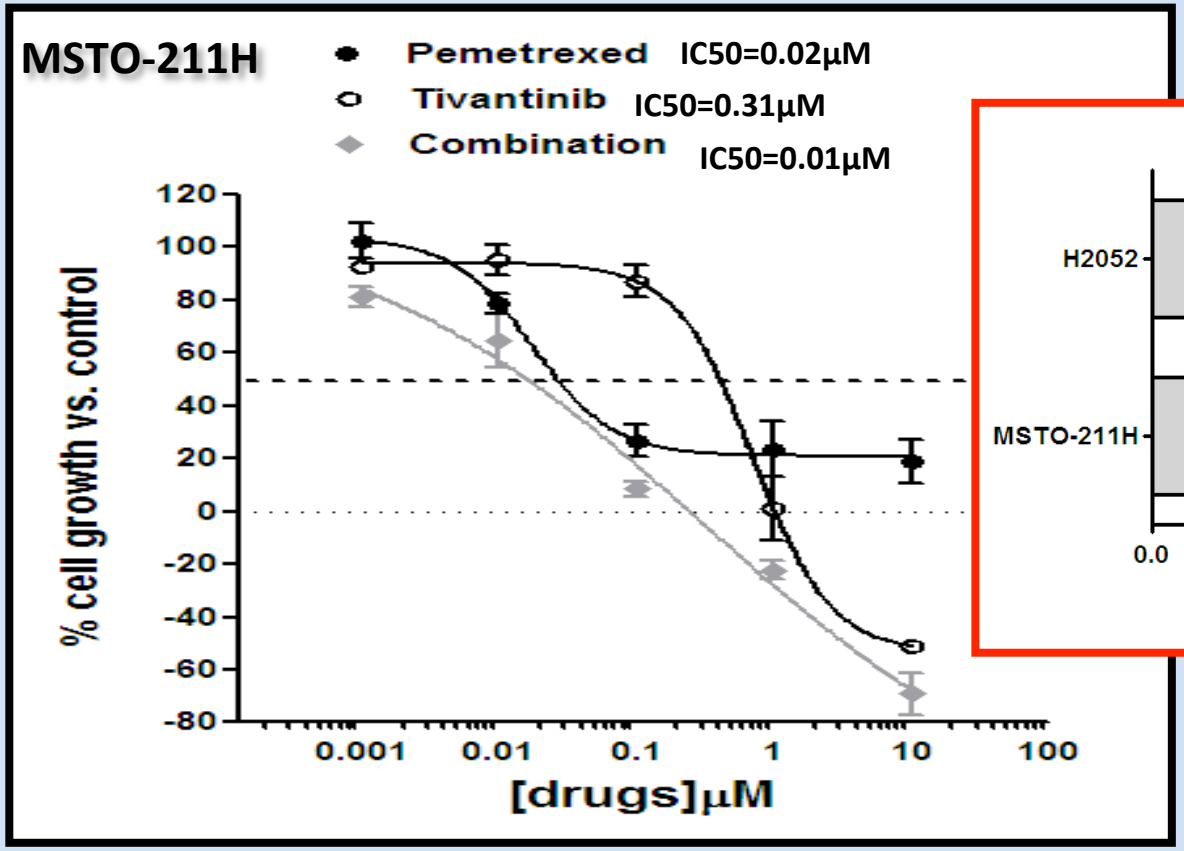
Modulation of TS expression

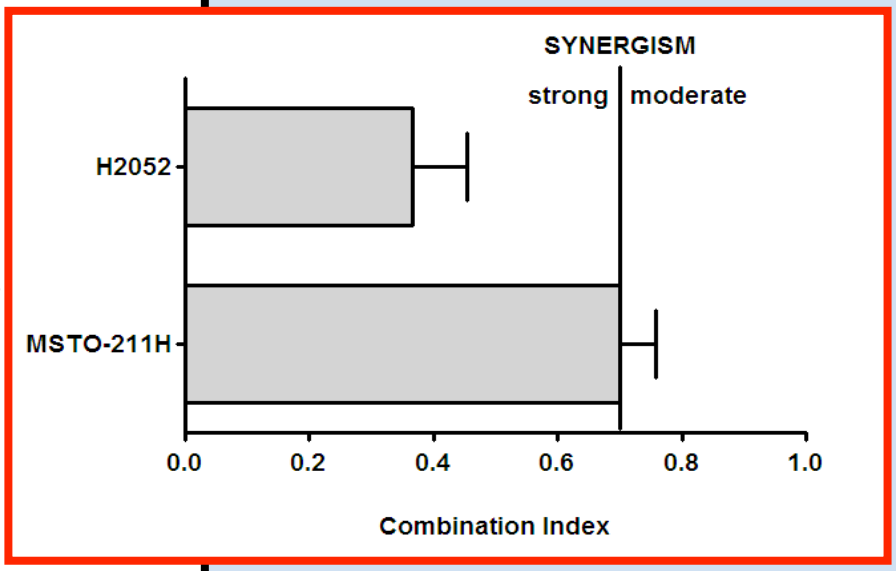
Modulation of TS & phospho-c-Met



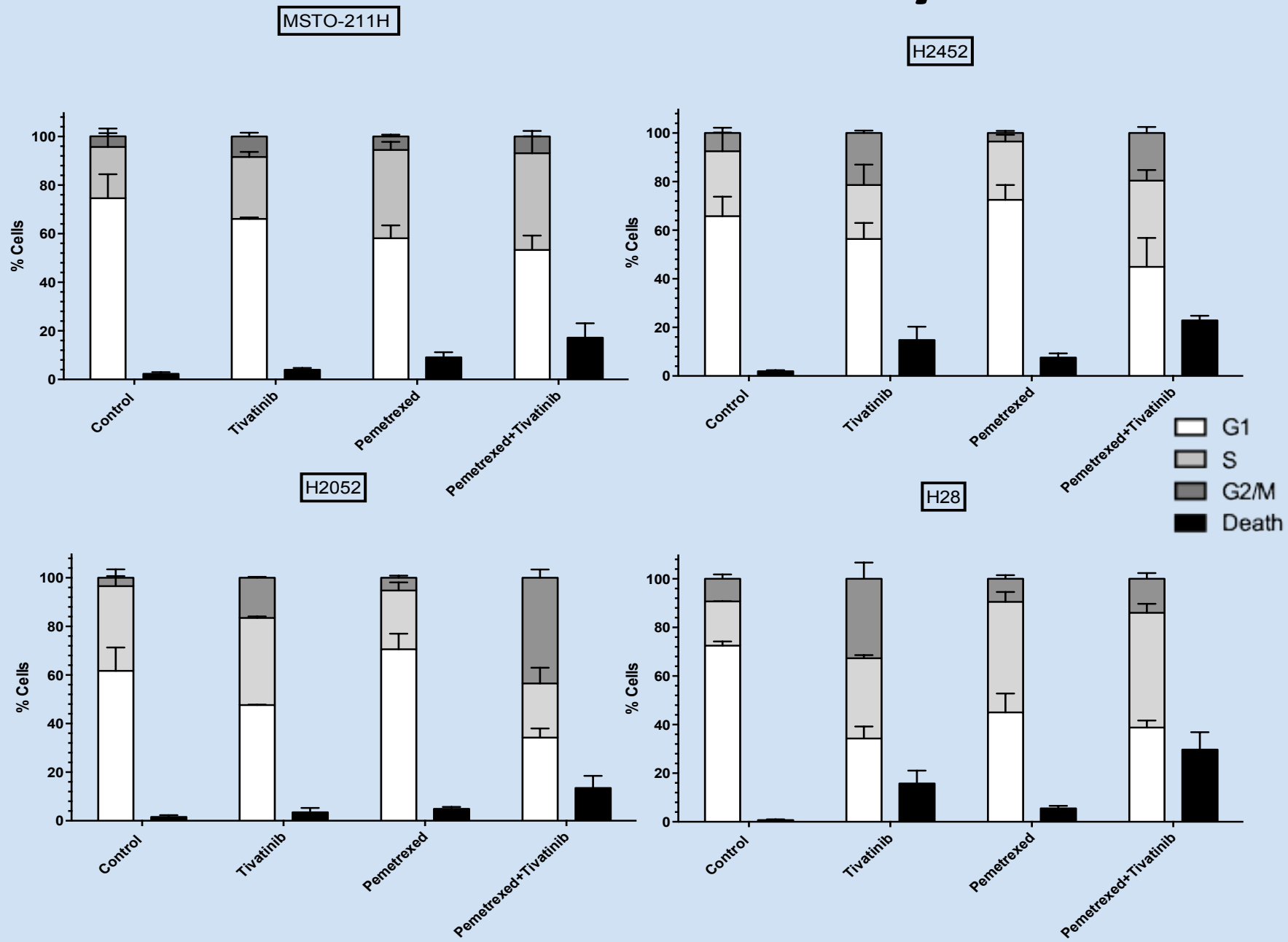
Modulation of c-Met phosphorylation

Synergistic antiproliferative activity of tivantinib & pemetrexed

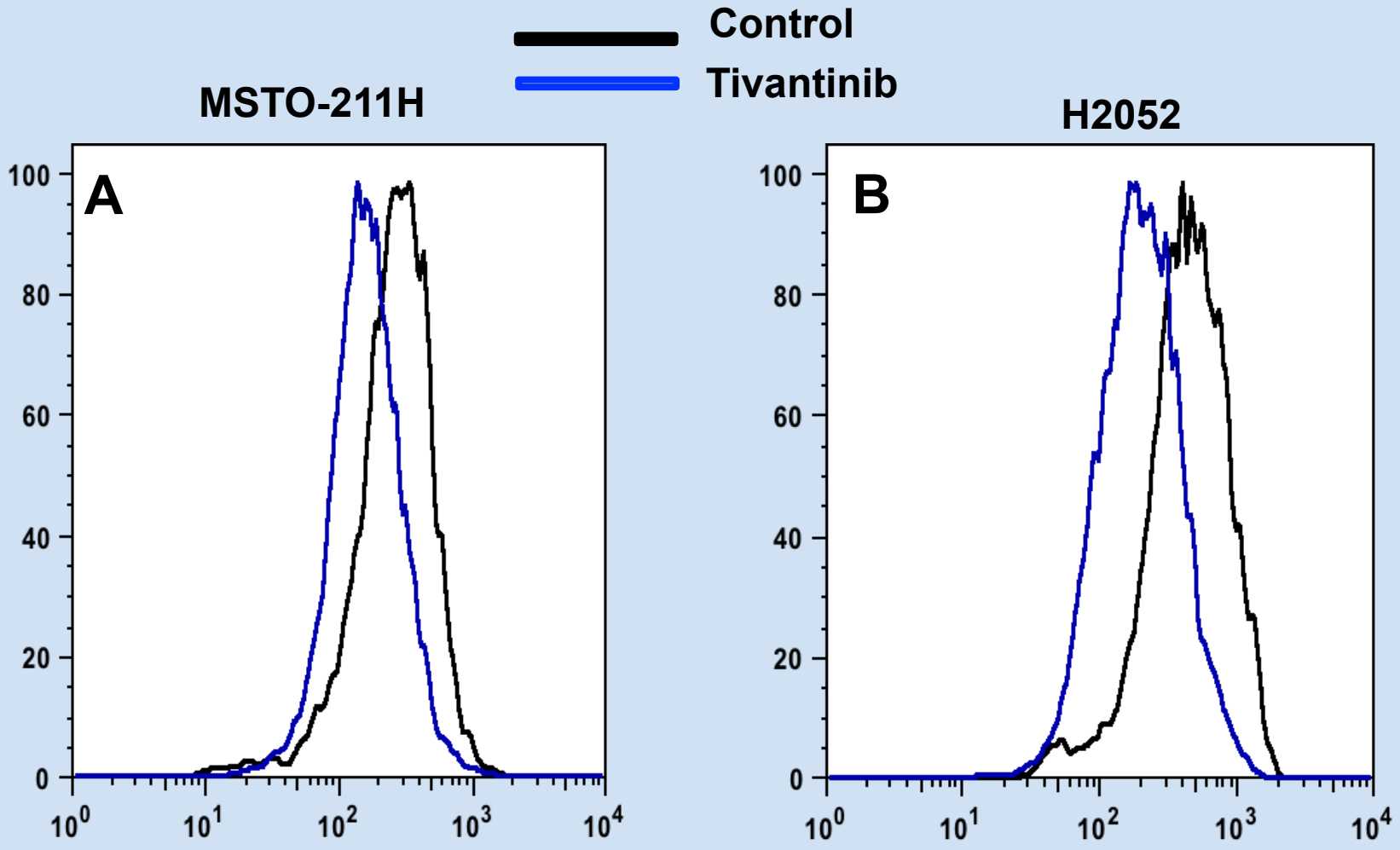




Effects on the cell cycle

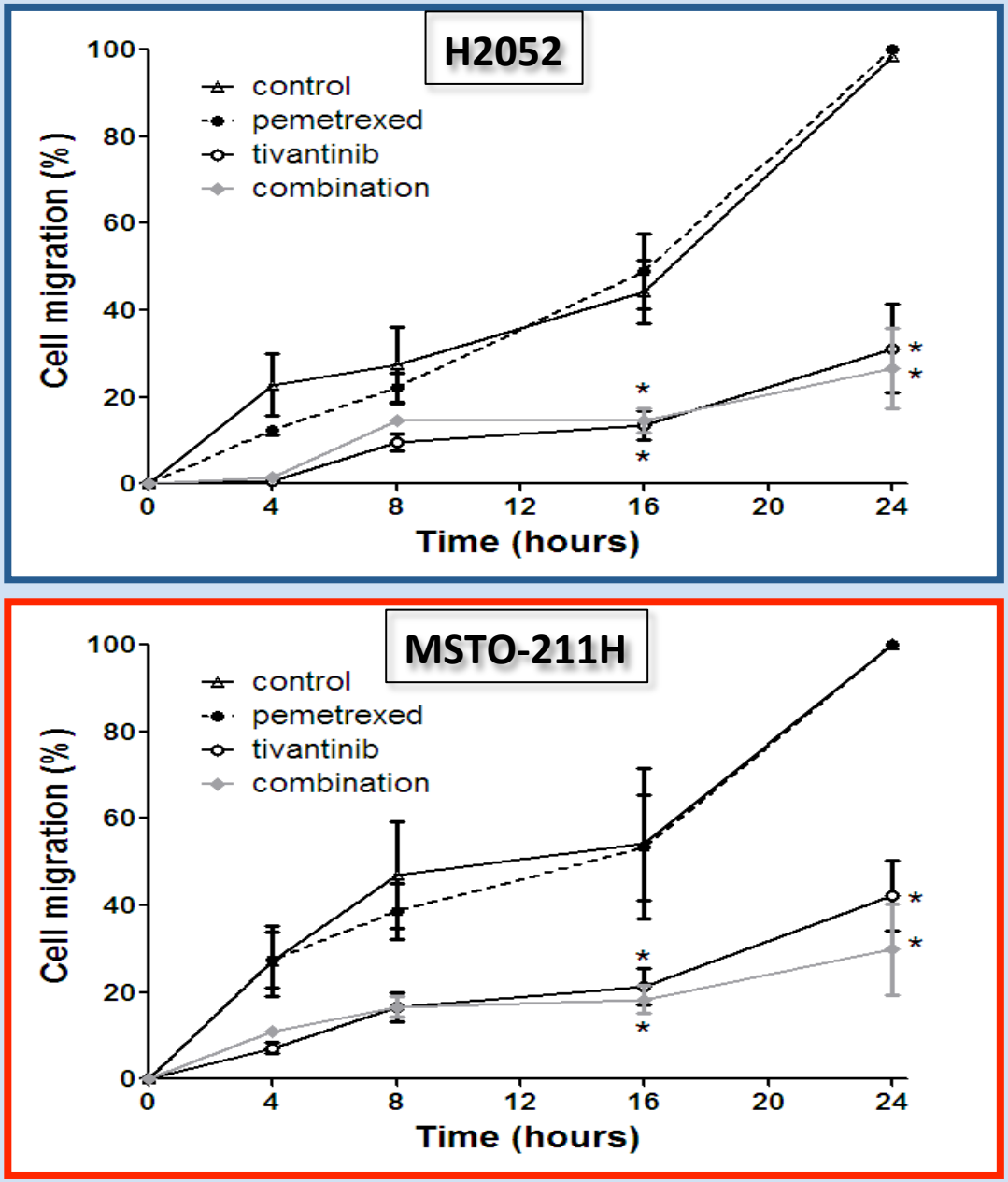


Tivantinib affects tubulin polymerization



Flow cytometry histograms, suggesting destabilization of the microtubules in both cell lines

Effects on cells migration



Summary

- ✓ We found a potent synergistic interaction between pemetrexed and tivantinib against MPM cell lines
- ✓ Mechanisms underlying this synergisms include: apoptosis induction, modulation of phosphorylation of c-Met and expression of TS, but also perturbation of microtubule dynamics
- ✓ In addition, we observed a significant reduction in cell migration
- ✓ These results support further *in vivo* studies on the combination of tivantinib &pemetrexed, as well as translational studies on the role of TS, c-Met and tubulin as predictive biomarkers

Thanks !

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