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

P-c-Met

c-Met

β-actin

MSTO-211H  H2052  H2452  H28

![Graph showing the ratio of p-Met/c-Met for different cell lines.](image)
Modulation of TS & phospho-c-Met
Modulation of TS & phospho-c-Met

Modulation of c-Met phosphorylation
Synergistic antiproliferative activity of tivantinib & pemetrexed

MSTO-211H

- Pemetrexed: IC50 = 0.02 μM
- Tivantinib: IC50 = 0.31 μM
- Combination: IC50 = 0.01 μM

SYNERGISM
- Strong
- Moderate

Combination Index

H2052

MSTO-211H
Effects on the cell cycle

Control
Tivatinib
Pemetrexed
Pemetrexed+Tivatinib

% Cells

G1
S
G2/M
Death

MSTO-211H
H2052
H2452
H28
Tivantinib affects tubulin polymerization

Flow cytometry histograms, suggesting destabilization of the microtubules in both cell lines
Effects on cells migration

**H2052**

- control
- pemetrexed
- tivantinib
- combination

**MSTO-211H**

- control
- pemetrexed
- tivantinib
- combination
We found a potent synergistic interaction between pemetrexed and tivantinib against MPM cell lines.

Mechanisms underlying this synergism 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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