Synergistic effect of c-Met inhibitor Salvotinib in combination with a VEGFR inhibitor Fruquintinib in clear cell renal cell carcinoma xenograft model

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Introduction

- Renal cell carcinoma (RCC) is the most common type of kidney tumor in human, of which approximatively 80%-90% is clear cell renal cell carcinoma (ccRCC).
- VEGFR-2-targeted therapies brought significant advancement in the treatment of RCC. However, resistance typically occurs in most cases following a transient period of clinical benefit.
- The hepatocyte growth factor (HGF) receptor c-Met activation appears to be one of the mechanisms of resistance to anti-VEGF therapies in ccRCC. Therefore, targeting both c-Met and VEGF pathways simultaneously may offer additional clinical benefit.
- In this report, a survival study of c-Met-expressing RCC xenograft model was described, in which combination of c-Met inhibitor Salvotinib (K1171112) and VEGFR inhibitor Fruquintinib (K11131594) was evaluated in multiple ccRCC xenograft models.

Materials and methods

- Human tumor samples: ccRCC archival tumor samples from 62 treatment-naive patients were obtained from a hospital in Shanghai for formalin fixed paraffin embedded.
- PDGFR-D: development and anti-tumor efficacy study: Fresh tumor specimens from treatment-naive patients were collected during surgery. The tumors were subsequently implanted into NOD/SCID mice (IL-2−/−), and subsequent mouse-to-mouse passages were made in additional NOD-SCID mice in route mice until the tumor size reached 300-500 mm3. After several passages in vivo, the PDGFR-D mice (2-3 generations) were used to evaluate the anti-tumor efficacy. For the orthotopic xenograft series, human ccRCC cells (A498, Caki-1, AG157, 786-O, and A463) were subcutaneously implanted into nude mice for anti-tumor efficacy evaluation.
- Immunohistochemistry (IHC) staining of c-Met in ccRCC xenograft models: The level of c-Met expression was fixed in 10% neutral buffered formalin, processed in paraffin and sectioned at 4 μm. Sections were manually treated with c-Met antibody (Cell Signaling Technology, #4512), followed by biotinylated secondary antibody and the DAB detection system.
- Met-ICH staining on ccRCC patient samples: The IHC staining on ccRCC patient samples was performed using the CNF1M anti-c-Met antibody (SP44) or Ventana antibody. The IHC staining was conducted at ZJAU Clinical Laboratory (Shanghai).
- Met-ICH scoring protocol: The whole staining section was carefully assessed. The staining intensity was categorically scored on a scale of 0, 1+, 2+, or 3+. The categorical score was defined as the intensity score with the largest percentage of tumor cells. Scores were assigned with 0% (0), 1% to 10% (1+), 11% to 50% (2+), and >50% (3+) percentage of tumor cells with positive staining were reviewed and 1 score was calculated. 1 score = 1231 (1% × 1 + 2% × 2 + 3% × 3% + 1% × 3%).

Results

- The expression of c-Met in ccRCC xenograft models. In Chinese patients with ccRCC, the expression of c-Met was detected by immunohistochemistry, and the results were evaluated as negative (0), weak (1+), moderate (2+), and strong (3+). The percentage of ccRCC cells with negative c-Met expression was 18%, 15%, 15%, 13%, and 15%, respectively, for A498, Caki-1, AG157, 786-O, and A463.

Summary

- c-Met expression was frequently detected in Chinese patients with ccRCC.
- Treatment with Salvotinib or Fruquintinib alone significantly induced tumor growth inhibition as single agents in ccRCC xenograft models, with high levels of c-Met expression. Significantly increased anti-tumor effect was observed in all models when the two agents were used in combination in K1171112, the anti-tumor effect was further increased with the increase of dosages to more than 10 mg/kg body weight.
- Consistent with more robust anti-tumor effect, the combination treatment produced stronger inhibition on tumor proliferation marker Ki67 and angiogenesis marker CD31, compared to other salvage c-Met and VEGFR agents. These results indicated that the observed synergistic effect might be attributed to the dual-hit on c-Met and tumor microenvironment.
- These results may highlight the potential clinical utility of Salvotinib in combination with Fruquintinib for the treatment of clear cell renal cell carcinoma with positive c-Met expression.

References