Synergistic tumor-suppressive effect of apatinib (rivoceranib), a selective VEGFR-2 inhibitor, in combination with immunotherapy in a syngeneic murine lung cancer model

Bumjin Kim*, Arlo N. McGinn, Cheol Hee Park, Sung Chul Kim
LSK BioPartners, Inc. (BLK LSK BioPharma), Salt Lake City, UT

Background

- While angiogenesis inhibition is best known for its ability to limit the spread of new vessels, it is also known to normalize immature tumor microvessels at 55% (p<0.01) which is hypothesized to decrease the immunosuppressive tumor microenvironment and increase the number of tumor-infiltrating lymphocytes in the tumor environment. These mechanisms should enhance the antitumor immune response and suggest potential synergy between antiangiogenesis and immunotherapy agents.

- A number of preclinical studies have supported the benefit of combining antiangiogenesis therapy with immunotherapy: monoclonal antibodies targeting VEGF and VEGFR-2, as well as multi-kine, small-molecule inhibitors targeting VEGF have shown synergistic efficacy in various tumor models.

- Those studies determined that the combination may limit tumor growth due to increased anti-tumor T-cell populations (e.g. CD4^+ and CD8^+ cells), as well as CAF-mediated inflammation. These mechanisms should enhance the antitumor immune response and suggest potential synergy between antiangiogenesis and immunotherapy agents.

Methods

Dosing period

- After tumor size reached 60-80 mm^3
- 25-day dosing followed by 1-week observation

Dosing groups (n=10 for each group)

- Vehicle control (q.d. x21)
- Anti-muPD-1 (10 mg/kg, b.i.w. x6)
- Apatinib (300 mg/kg, q.d. x21)
- Apatinib + Anti-muPD-1 combo

Results

Tumor growth inhibition

- At day 20, tumor growth inhibition (%TGI) of anti-muPD-1 monotherapy was 22% (p=0.05), and TGI of apatinib monotherapy was 37% (p<0.01).
- The tumor volume on day 20 was lower in the apatinib + anti-muPD-1 combination group than in the vehicle control group (p<0.01). (Figure 1)

Sample analysis

- Tumor volume and body weight measurement
- Flow cytometry: tumor infiltrating immune cells
- Histology & IHC: tumor necrosis

(A) Changes in TGI from vehicle control group

(B) IHC of CD3^+ and CD68^+ cell populations

Conclusions

- Central tumor necrosis, which is a typical feature of hypoxia, was prominently observed in the apatinib monotherapy group and partially observed in the anti-muPD-1 monotherapy group.
- Tumor necrosis was prominent and widely-distributed in the combination treatment group compared to other treatments.

References

4. Corresponding author: @lskbiopharma.com

Copyright of this article belongs to LSK Biopharma and may not be reproduced without written permission from the authors.

#2756