FS120, AN OX40/CD137 TETRAVALENT BISPECIFIC DUAL AGONIST ANTIBODY, SYNERGISTICALLY INCREASES THE ANTITUMOR ACTIVITY OF ANTI-PD-1 IN PRECLINICAL STUDIES

Matthew Lakins*, Wenjia Liao, Emma McConnell, Quincy Kaka, Jennifer Ofoedu, Cristian Gradinaru, Raffaella Giambalvo, Miguel Gaspar, Edmund Poon, Michelle Morrow, Neil Brewis. *F-star Therapeutics Inc, Cambridge, UK*

Background Immune checkpoint inhibitors have demonstrated durable clinical responses and an increase in overall survival for some patients with cancer. Next generation cancer immunotherapies, such as tumor necrosis factor receptor superfamily (TNFRSF) agonists, have potential to further improve on this success. FS120 is a tetravalent bispecific antibody targeting OX40 and CD137 (4-1BB), currently being evaluated in a Phase I clinical trial (NCT04648202). FS120 activates CD4⁺ and CD8⁺ T cells by concurrent binding to both targets via an FcγR-independent mechanism [1]. In preclinical tumor models, FS120 induced T cell proliferation and cytokine production associated with significant tumor regression, better than that observed with a monoclonal antibody combination. Here, we demonstrate the ability of FS120 to improve anti-PD-1 induced T cell activity, increasing tumor growth inhibition and survival, in syngeneic mouse tumor models, compared to monotherapy.

Methods FS120 < i >in vitro</i > activity in combination with anti-PD-1 was assessed by utilizing staphylococcal enterotoxin A (SEA) superantigen assays and mixed leukocyte reaction (MLR) assays. An anti-mouse OX40/CD137 bispecific antibody (FS120 surrogate) was tested in CT26 syngeneic mouse tumor models in combination with an anti-mouse PD-1 antibody to assess efficacy and pharmacodynamic endpoints, including T cell proliferation by < i>ex vivo</i> flow cytometry and serum cytokine levels.

Results FS120 in combination with anti-PD-1 enhanced primary human T cell activity, when compared to either monotherapy, in both SEA and MLR assays. FS120 surrogate significantly improved survival of CT26 tumor-bearing mice treated with anti-mPD-1 antibody. FS120 surrogate and anti-PD-1 combination significantly enhanced serum interferon-gamma levels and increased proliferating granzyme B⁺ CD8⁺ T cells in the blood of tumor-bearing mice, when compared to either monotherapy treatments.

Conclusions FS120 combination with anti-PD-1 enhances T cell activity in multiple human primary immune assays. In combination with anti-PD-1, FS120 surrogate increased the antitumor efficacy with pharmacodynamic changes related specifically to T cell activation, when compared to monotherapies. These data support the development of FS120 in combination with anti-PD-1 in patients with hard-to-treat cancers who may not benefit fully from either treatment as a monotherapy.

REFERENCES

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Ethics Approval Murine studies were conducted under a U.K. Home Office License in accordance with the U.K. Animal (Scientific Procedures) Act 1986 and EU Directive EU 2010/63.

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