Preclinical efficacy of the triple VEGFR inhibitor tivozanib (AV-951) in chimeric breast and lung tumor models

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Abstract

- All solid tumors are thought to require neovascularization. Therefore, pharmacological inhibition of angiogenesis may represent an important consideration for breast, lung, and other therapeutically challenging tumor types. One attractive anti-angiogenesis agent is the AV951 polyvalent small molecule VEGFR inhibitor tivozanib (AV951). In this study, we tested the response of HER2+ and EGFR-driven breast tumors in response to tivozanib (AV951) in chimeric breast and lung tumor models. These results indicate that both breast and lung cancer patients could potentially benefit from sustained anti-angiogenesis therapy, and combination of anti-angiogenesis with tumor targeting agents may be required for optimal clinical benefit.

Tivozanib (AV951)

- Extremely potent (~200 pM) against all three VEGFRs (1,2,3)
- Highly selective
- 4.5 day T1/2 in human studies
- Robust efficacy in 272 patient Phase 2 RCC trial
- OPRF: 25-40% (all VEGFR independent review—clear cell, nephrectomy investigator review)
- PFS: 14.8 months in clear cell nephrectomy (n=176)

Characteristics of selected VEGFR targeted TKIs

- Complete regression (CR+)
- PFS: 14.8 months in clear cell nephrectomy (n=176)
- Resistance rate (Rx+ PR): 62% (n=176)
- Disease control rate (CR+ PR+ SD): 88% (n=176)
- **Regression and relapse in the same mouse**

Regression of HER2V659E driven breast tumors in response to tivozanib

- **5 mpk (daily) no Rx**
- **Regression of HER2V659E driven breast tumors in response to tivozanib**

Regression of KRASG12V and EGFRL858R,T790M driven lung tumors in response to tivozanib

- **H&E (2.5X)**
- **H&E (40X)**
- **CD31**
- **K67**
- **H&E (40X)**
- **CD31**
- **K67**

Summary

- Primary tumors developed in chimeric breast (HER2) and lung (KRAS and EGFR) cancer models are largely sensitive to tivozanib single-agent treatment.
- We identified both tivozanib-sensitive and -resistant tumors in the breast HER2 model. These tumors can develop in the same mouse.
- 9% of the HER2 breast tumors released during tivozanib treatment. Relapse of one tumor does not affect the response of other tumors in the same mouse.
- Daily treatment with tivozanib of lung model chimeras resulted in substantial tumor load reduction, thereby conferring significant survival benefit to the tumor-bearing mice.
- Necrotic centers (rim phenotype) were observed in advanced adenocarcinomas and adenosens treated with tivozanib, but not hypoxia or small necrotic lesions, even though they completely lost intra-tumor vasculature.
- No evidence of metastasis or invasive resistance was observed over the course of treatment with tivozanib.
- Upon discontinuation of treatment with tivozanib, tumors re-grow as evidenced by increase in bioluminescent signals

References
- Sabel Chiu, Murray O. Robinson, Joerg Heyer. AVEO Pharmaceuticals, Inc., Cambridge, MA.