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

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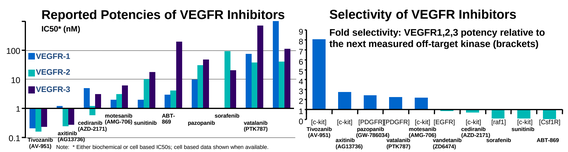
Abstract

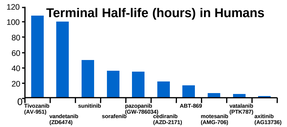
- All solid tumors are thought to require neovascularization. Therefore, pharmacologic inhibition of angiogenesis may represent an important component for treating many therapeutically challenging tumor types. One attractive anti-angiogenesis agent is the ATP competitive small molecule VEGFR inhibitor tivozanib (AV-951). Tivozanib exhibits picomolar inhibitory activity against all three VEGF receptors, a multi-day $T_{1/2}$ in humans, and demonstrates robust clinical activity in renal cell carcinoma, the signal tumor type for VEGF pathway inhibition. To test preclinical efficacy of tivozanib in other cancer types, we chose primary mouse tumor models due to their ability to capture the complex heterotypic interactions between tumor cells and the microenvironments. Our mouse tumor model strategy involves stepwise genetic manipulation of embryonic stem cells and chimera formation to enable direct tumor induction in tissues containing both normal and engineered cells. A HER2-driven breast cancer model, as well as an allelic series of lung cancer models containing EGFR, KRAS, or HER2 oncogenes, demonstrated that resultant adenocarcinomas arose within surrounding normal tissue and exhibited features of advanced malignancies (Zhou *et al* 2010, Kannan *et al* 2009).
- In this study, we tested the response of HER2-driven breast tumors, as well as KRAS- and EGFR-driven lung tumors, to the VEGFR inhibitor tivozanib in tumor-bearing chimeric mice. We observed that although tivozanib treatment conferred significant survival benefit to the tumor-bearing mice in all three models, it was not able to eradicate all tumor cells. Response to tivozanib in the breast cancer model was much more heterogeneous than in the lung cancer models, with some tumors exhibiting significant regression while others showing progression on treatment, either initially or after a period of response. In contrast, lung tumors showed more uniform response to tivozanib treatment initially, but tumors quickly grew back upon discontinuation of tivozanib treatment. 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 enduring efficacy.

Tivozanib (AV951)

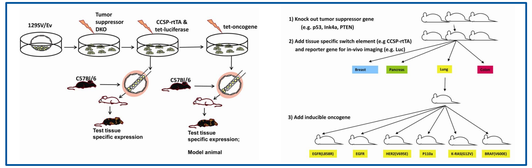
- Extremely potent (~200 pM) against all three VEGFRs (1,2,3)
- Highly selective
- 4.5 day $T_{1/2}$ in human studies
- Robust efficacy in 272 patient Phase 2 RCC trial
  - ORR: 25 - 40% (all RCC independent review--clear cell, nephrectomized investigator review)
  - PFS: 14.8 months in clear cell nephrectomized RCC patients (n=176)
- Safety profile consistent with on mechanism inhibition
  - Most common AEs are Hypertension and Hoarseness

Characteristics of selected VEGFR targeted TKIs



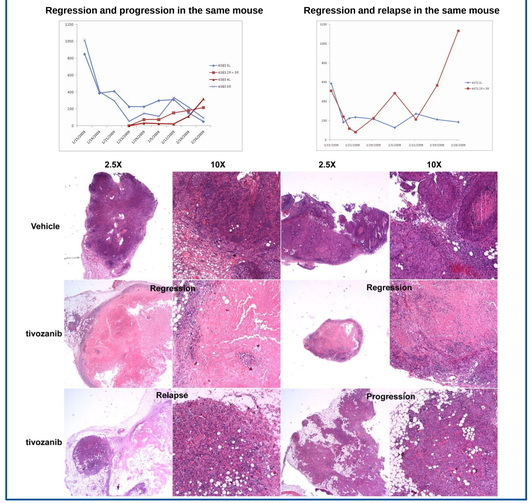


Modeling cancer in chimeric mice



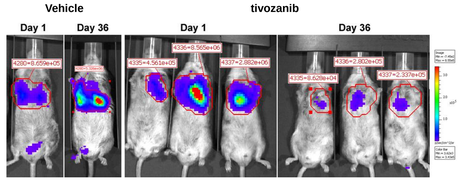
Regression of HER2^{V659E} driven breast tumors in response to tivozanib

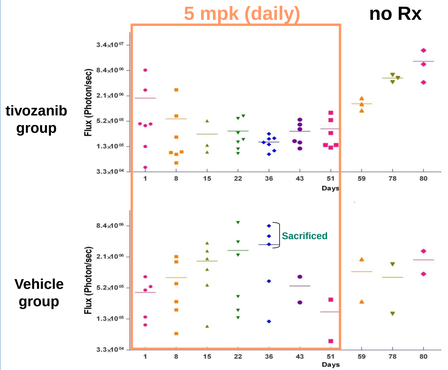
	Vehicle	tivozanib (5 mpk)
Total tumor count	28	45
Complete regression (CR)	0	6
Partial regression (PR)	1	25
Stable disease (SD)	4	12
Progressive disease (PD)	23	2
Relapse	NA	4
Response rate (CR + PR)	4%	69%
Disease control rate (CR + PR + SD)	18%	96%



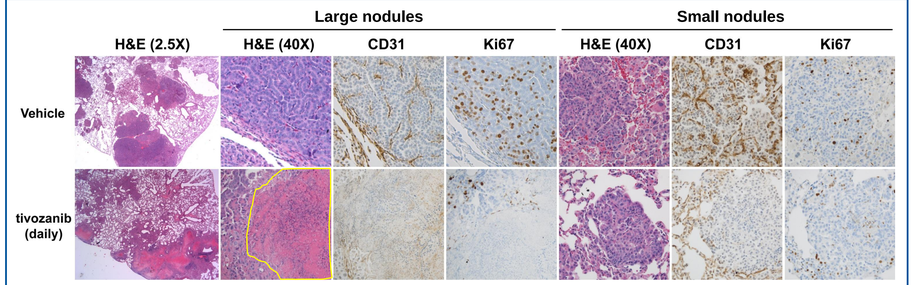
Regression of KRAS^{G12V} and EGFR^{L858R,T790M} driven lung tumors in response to tivozanib

Regression of KRAS^{G12V} lung tumors treated with tivozanib

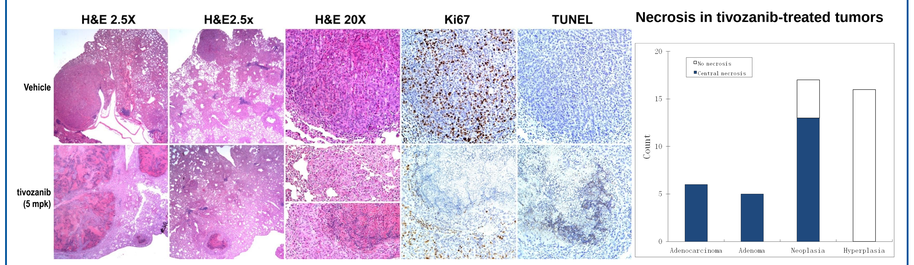




Characterization of KRAS^{G12V} tumors treated with tivozanib



Characterization of EGFR^{L858R,T790M} tumors treated with tivozanib



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 relapsed 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 adenomas treated with tivozanib, but not hyperplasia or small neoplastic 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-grew as evidenced by increase in bioluminescent signals

References

1.Zhou Y, et al. *Nat Biotechnol.* 2010;28(1):71-78.
2.Kannan, et al. *Proc Natl Acad Sci U S A.* 2009.
3.Bhargava, et. al. *Proc ASCO Genitourinary Symposium,* 2010.

Acknowledgments

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