Human population based engineered breast tumor model for in vivo biomarker discovery

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Abstract
Human breast cancer development is a complex pathological process driven by genetic changes in normal epithelial cells that lead to uncontrolled growth in a permissive microenvironment. Therefore, it is not surprising that tumors from different patients exhibit variable responses to standard care therapy with unfortunately only a small percentage of patients benefiting from therapy. It has therefore become increasingly clear that a multimodal approach is required to result in a favorable treatment outcome. In this report, we describe a population-based approach for response prediction featuring genetically engineered tumors derived from genetically defined human-in-mouse models of cancer.

We describe an innovative approach for genetically engineering a normal human breast tumor model utilizing HER2 and SV40 early region (KS) or KRAS and SV40 early region (KS) in vivo in a Human-In-Mouse (HIM) tissue transgenic model. The HIM and KS HIM tumor lines develop human breast adenocarcinomas that are histologically similar to those observed in patients. Also similar to that observed in human tumors, micrometastatic profiling demonstrated significant inter tumor variation among the established tumors. Moreover, the KS HIM tumors could cluster with breast tumor tissue from patients with a poor prognosis breast cancer outcome due to the established tumor lineage phenotype. The HIM tumor model is the only established tumor model that is a true population based approach enabling us to identify and validate biomarkers of therapeutic response in an in vivo human tumor model.

Understanding responsive patient populations can make the difference between approval and failure.

- Our population-based approach is not to evaluate drugs in rodent studies – tissue failing in an unselected population, but in vivo using engineered human tissue system.

HIM breast tumor model:
- Tissue transgenic human breast tumor model. The HIM breast tumor model is a naturally occurring variation in the human breast-tumor microenvironment. Therefore, it is not surprising that tumors from different patients exhibit variable responses to standard care therapy with unfortunately only a small percentage of patients benefiting from therapy. It has therefore become increasingly clear that a multimodal approach is required to result in a favorable treatment outcome.

- KS HIM tumors resemble different subtypes of breast carcinomas.

- 87.5***

- Propagated HER2-driven tumors are sensitive to trastuzumab.

- High degree of tumor variation both within and across genotypes.

Propagated and Archiving primary HIM tumors to establish population based breast tumor model

Primary tumor
Fast Propagation
Second Propagation
X 50 primary tumors

Frozen Activated Tumor Material

Drug efficacy studies

Hematopathology

Angiogenesis

Signature pathways

Array CGH

HIM tumors resemble different subtypes of human breast cancer

- Extremely potent (~200 vs. 40% (all RCC independent review)

- Safety profile consistent with on mechanism inhibition

- This population based approach enables us to identify and validate biomarkers of therapeutic response in an in vivo human tumor model.

Conclusion

- Human population based in vivo Biomarker Discovery Platform has been established using genetically engineered HIM models.

- HIM tumors exhibited variable response to treatment with thousands and will be used to validate tivozanib predictive signatures.

- This population-based approach enables us to identify and validate biomarkers of therapeutic response in an in vivo human tumor model.

Tivozanib: potent selective VEGFR TKI

- Extremely potent (~200(pM) against all three VEGFRs (1,2,3).

- Highly selective.

- 4.5 day T64 in human studies.

- Robust efficacy in 272 patient Phase 2/3 trial. (ORR: 35-40% in RCC independent response review).

- PFS: 14.8 mos in clear cell metastasis.

- Most common AEs are Hypertension and Hoarseness.

HIM line

HIM lines exhibited variable responses to treatment with tivozanib

- KS HIM lines exhibited variable responses to treatment with tivozanib

- therapy (HIM)

- therapy (HIM)

- therapy (HIM)

- therapy (HIM)

- therapy (HIM)

- therapy (HIM)