Induction of resistances to the target therapies in patient derived xenograft models

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Summary

Oncogene activating mutations have been found to be oncogenic drivers in many different cancers, such as EGFR L858R mutation, EML4-ALK fusion (1, 2), CCDC6-RET or NCOA4-RET fusions (3), RSPO2,3 fusions, and c-met gene amplifications (4) in NSCLC (2, 5), CRC, gastric adenocarcinoma, etc. These oncogenes have also been demonstrated to be excellent drug targets for a number of approved target therapies. However, like any other cancer therapy so far, the treatments always led to the development of resistances to these therapies, rendering them ineffective in the end. Understanding the mechanisms causing these resistances can potentially facilitate overcoming the resistance.

We have recently established large collection of patient derived xenografts (PDXs), including NSCLC (4), CRC, and many other diseases. Among them is NSCLC-ADC LU6422 containing EGFR-L858R mutation, NSCLC-ADC LU1656 containing EML4-ALK fusion, NSCLC-LCC LU1901 containing c-met gene amplification, CRC CR1520 containing NCOA4-RET fusion and CRC CR2518 containing CCDC6-RET fusion. They all responded well to the corresponding targeting agents under treatments: LU6422 to Tarceva, LU1656 to crizotinib, LU1901 to crizotinib or other c-met inhibitors, CR1520 and CR2518 to Ponatinib as expected. However, these treatments eventually all led to resistances as seen in the clinic. We are interested in investigating the mechanisms of these induced resistances since it may reflect the resistances that might occur in patients in the clinic under the same treatments. We are currently profiling these resistant models and investigating the pharmacodynamics effects, and comparing them to those of their parental. Our preliminary findings indicated that "newly introduced or enriched preexisting mutation" could account for some of the observed induced resistance mechanisms

Results

Figure 1. CR2518, a CRC-PDX with CCDC6-RET fusion, was treated with ponatinib, a kinase inhibitor with strong ret kinase inhibition, and result in strong initial response by the treated tumors (below left, also J. Gozgit et al.,RET fusions identified in colorectal cancer PDX models are sensitive to the potent RET inhibitor ponatinib. AACR-Annual 2014. Poster**). However, prolonged treatment led to rapid development of complete resistance to ponatinib (below right, CR2545=CR2518R). RNAseq revealed that a new mutation at ret kinase domain in CR2545, V804M, a mutation known to cause significant changes in the binding mode of the inhibitor.**

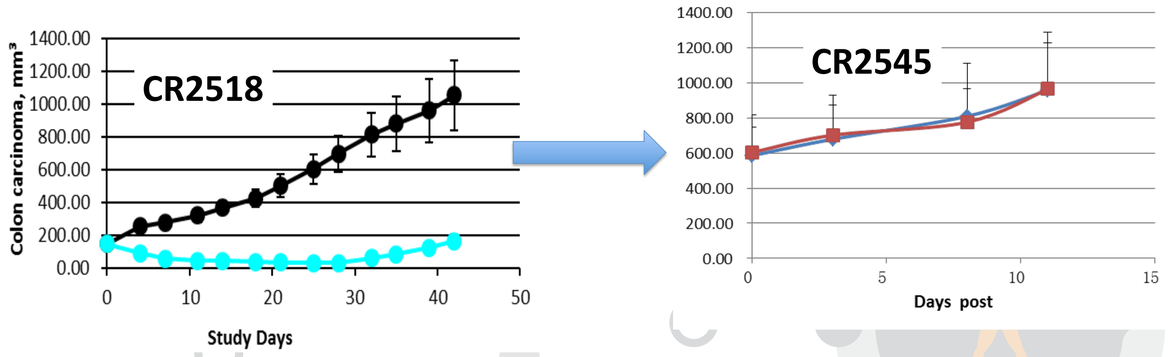
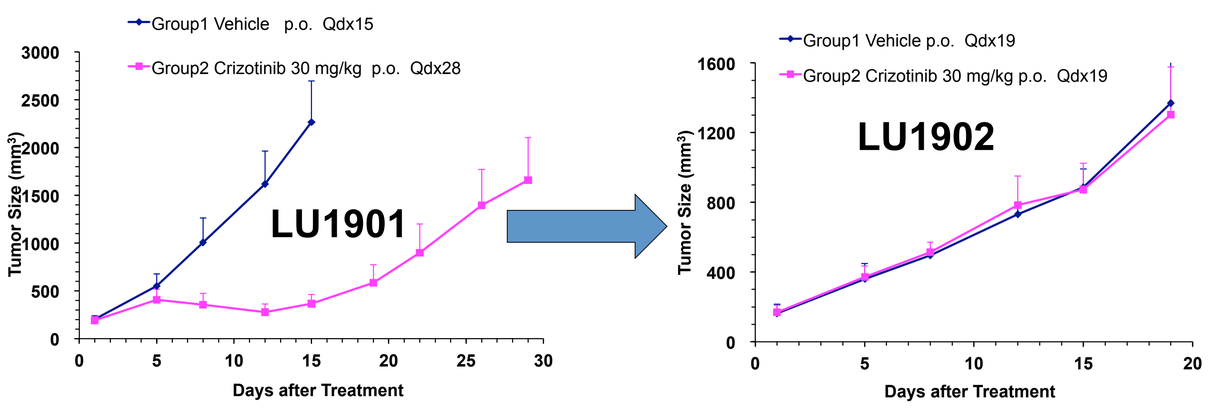


Figure 2. LU1901, a large cell NSCLC-PDX with c-met gene amplification was treated with crizotinib, a kinase inhibitor with strong c-met kinase inhibition, and result in strong initial response by the treated tumors (below left, M. Yang et al., Treatments of NSCLC-PDX with c-MET gene amplification by c-MET inhibitor lead to rapid development of drug resistance. AACR-Annual 2013. Poster**). However, prolonged treatment led to rapid development of complete resistance to ponatinib (below right, LU1902). RNAseq revealed that an EGFR mutation, G719A, at kinase domain was enriched in LU1903. G719A has been associated with increased sensitivity to EGFR-TKIs (7) or possibly drives the disease.**



LU1902

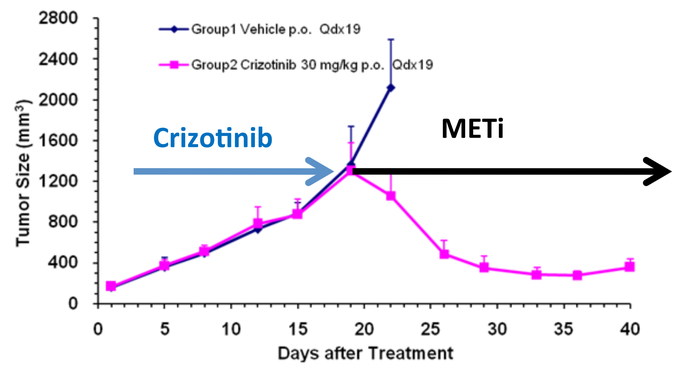


Figure 3. LU6422, a NSCLC-PDX with EGFR-L858 mutation, was treated with erlotinib, a reversible EGFR inhibitor, and result in strong initial response by the treated tumors (below). However, prolonged treatment led to development of resistance to erlotinib (below) LU6422R). We are currently investigating the mechanism of resistance.

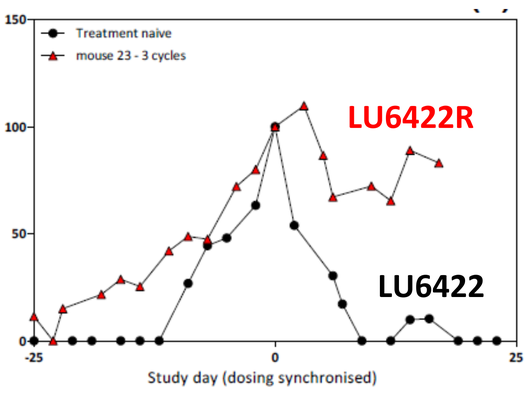
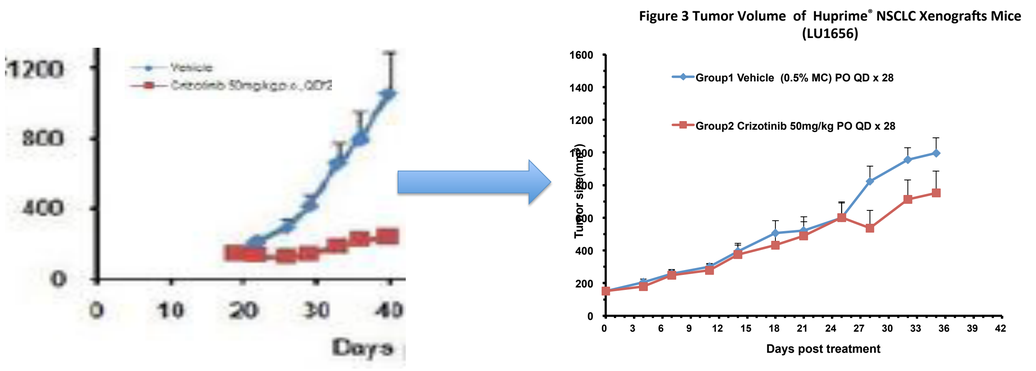


Figure 4. LU1656, a NSCLC-PDX with EML4-ALK fusion, was treated with crizotinib, a ALK kinase inhibitor, and result in strong initial response by the treated tumors (below left). However, prolonged treatment led to gradual development of partial resistance to crizotinib (below right, LU1656R). We are currently attempting to confirm this resistance and investigating the mechanism of resistance.



References

1. **Resistance to target therapy can readily be induced in PDX**
2. **PDX seems to be an effective experimental models to investigate drug resistance mechanism**
3. **PDX could also be an effective experimental model to find solutions overcoming the drug resistance.**

References

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