Identification of resistance mechanisms to EGFR treatment in the real world using a clinicogenic database

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INTRODUCTION

• Use of targeted therapies often results in resistance mediated by genomic evolution. However, discovery of resistance mechanisms has historically been opportunistic.
• A more scalable approach may be to uncover resistance mechanisms from real world patient experience. Use of a clinico-genomic database (CGDB) that integrates electronic health record (EHR) and genomic data collected as part of routine clinical practice may overcome these hurdles.

METHODOLOGY

GENERATION OF THE CLINICOGENOMIC DATABASE

• We developed a real-world clinicogenic database (CGDB) of patients with non-small cell lung cancer (NSCLC), NGS testing and EHR data were linked through a HIPAA de-identification linking process (Singal et al, ASCO 2017).
• Patients (1) underwent profiling with Foundation Medicine’s FoundationOne next generation sequencing (NGS) assay as part of routine care, and (2) have electronic health record (EHR) data in the Flatiron Health database.
• A cohort of patients diagnosed with NSCLC having received a 1st or 2nd generation EGFR were subset for analysis.
• As demonstration of the ability to identify resistance mechanisms from real world data, we examined differences in alterations within EGFR-treated NSCLC patients pre- and post-EGFR treatment in a ‘hypothesis-agnostic’ manner, without interrogation of known resistance mechanisms a priori.

RESULTS

GENOMIC LANDSCAPE OF EGFR-TREATED PATIENTS

Figure 4. Long-tail plot of genes having short variants (SNVs and indels), copy number alterations, and/or complex arrangements (e.g. fusions). Comparison is done between patients sequenced pre- and post-treatment with an EGFR.

COPY NUMBER ALTERATIONS

Figure 6. Analysis of copy number variations demonstrated significant post-treatment enrichment of amplifications in AKT2 (0.84% vs 7.5%, p=0.001) and FGFR10 (1.3% vs 6.0%, p=0.02), RBB1 loss, a previously-observed resistance mechanism, was observed but did not reach significance.

EGFR SHORT VARIANTS

Figure 8. 51 distinct EGFR short variants were identified (top 25 shown). Only T790M was significantly enriched (3.4% pre-treatment vs 32.3% post-treatment, p<0.0001).

CONCLUSIONS

• Population-based analyses of a scalable, real-world clinicogenic database, derived from data generated as part of routine patient care, can recapitulate and generate hypotheses for novel mechanisms of resistance to EGFR inhibitors.
• ‘Hypothesis-agnostic’ examination of differences in alterations in an NSCLC cohort pre- and post-EGFR treatment led to re-identification of a subset of known EGFR resistance mechanisms. Re-identification of T790M as a resistance mechanism and determination of copy number variations (e.g. ERBB2 loss) in post-EGFR patients were demonstrated.
• Known mechanisms of acquired resistance (e.g. c-MET amplifications, HER2 aberrations) were not recapitulated in our analysis may be due to the size of the dataset at the time of the analysis and study design.
• These findings were made from the January 2017 version of the NSCLC-CGDB. A recent update of the CGDB (Jan 2018) exceeds 33,000+ patients overall and 4,000+ patients diagnosed with NSCLC.
• 600+ EGFR-treated patients are in the most recent dataset (January 2018) – nearly double the number of data points powering this analysis. Extension of the database and longitudinal follow-up over time may further elucidate novel mechanisms of resistance to a broad array of cancer therapies.

REFERENCES


EGFR COHORT SELECTION

Figure 3. Patients who received first and second generation EGFR inhibitors (EGFRi; afatinib, erlotinib, cetuximab, gefitinib, lapatinib, panitumumab) were segmented into those undergoing NGS profiling before treatment (‘pre-treatment cohort’) and those biopsied at least 3 months after treatment start (‘post-treatment cohort’).

EGFR SHORT VARIANTS

Figure 8. Long-tail plot of genes with short variants (SNVs and indels). Segmented by patients sequenced pre- and post-treatment with an EGFR. The frequency of RBB2 short variants was significantly lower in the post-treatment cohort (7.2% vs 0%, p<0.0005). Note: >85% of EGFR-treated patients were found to have an EGFR (V).