Tumor Biomarker Evaluation Of 6,785 Patients For Combination Treatment Strategies In NSCLC

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Abstract

Background: Non-small cell lung cancer (NSCLC) exhibits activation of multiple potential pathways. Presence of multiple aberrations may account for drug resistance as well as strategies for combination therapies. We examined concurrent aberrations of biomarkers in NSCLC to present an overview of potential patient cohorts who may benefit from such combinations.

Methods: 6785 NSCLC cases referred to Caris Life Sciences between 2009 thru 2013 were evaluated. Specific testing was performed and included a multiparameter approach: sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH/FISH).

Results: EGFR mutation (MT) rate was 12.7% (335/1059), of which 57% overexpressed EGFR (HER2) and 51% had EGFR gene amplification (FGF). This describes dependence on the EGFR pathway and potential importance of dual inhibition with cetuximab and EGFR TIs. 68% and 7% of EGFR MT patients were MET high (HIC) and amplified (CGH), respectively, suggesting potential benefit from dual targeting of EGFR and MET. Interestingly, TP53 mutations were observed in 54% of EGFR MT which has important implications for resistance to EGFR TIs (Huang, et al. 2011) and possible cross-resistance to radiotherapy. ALT translocations were observed in 101 of 3612 (2.8%) patients, among which 19%, 3% and 2% carried concurrent EGFR, MET and HER2 amplification (SHY), respectively, suggesting the potential for combining cetuximab with agents such as cetuximab, panitumumab or trastuzumab. BRAF mutation was observed in 3.3% (34/1061), among which EGFR and MET were high by IHC (both have been observed in resistance to BRAF in other tumor types) in 54% and 48%, respectively, indicating benefit from combination of newly approved dabrafenib with cetuximab or onartuzumab.

Conclusion: Our study shows that among treatment candidates of targeted therapies in NSCLC, a significant portion present activation of multiple pathways, therefore the majority of alterations are not mutually exclusive from other biomarkers. Also lending support for the importance of a multiplatform approach which consists of tests that have predictive utility for cytotoxic agents as well targeted therapies, provides guidance for combining agents.

Methods

6785 cases referred to Caris Life Sciences from 2009 through 2013 were evaluated; diagnoses were collected from referring physicians and classified at intake based on pathology and clinical history. Specific testing was performed per physician request and included a combination of sequencing (next generation sequencing [NGS], Sanger sequencing), protein expression (immunohistochemistry) and gene amplification (CISH or FISH).

Results

Major Targetable alterations in NSCLC

Target % (n) Targeted Agent Target % (n) Targeted Agent
KRAS mutation 30 (1292/4291) MEK inhibitors ALK rearrangement 3 (103/3612) crizotinib
EGFR mutation 15 (741/5030) erlotinib, afatinib ROS1 rearrangement 1 (18/1296) crizotinib
cMET amplification 6 (86/1517) crizotinib HER2 mutation 1 (8/1049) afatinib, trastuzumab
PIK3CA mutation 4 (61/1597) mTOR inhibitors AKT mutation 0.5 (5/1061) AKT inhibitors
ERBB2 amplification 3.5 (61/1731) dabrafenib NRAS mutation 0.4 (5/1256) MEK inhibitors

Conclusion

• Combinations of targeted therapies with traditional cytotoxic chemotherapies, as well as novel combinations of targeted therapies is under active investigation

• Utilization of a multiparameter approach which consists of tests that have predictive utility for cytotoxic agents as well targeted therapies, provides guidance for combining agents.

• These data support the continued investigation of optimizing combination therapy strategies for NSCLC.

• Our study shows that among treatment candidates of targeted therapies in NSCLC, a significant portion present activation of multiple pathways, therefore the majority of alterations are not mutually exclusive from other biomarkers.

References

