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 tumor 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 multiplatform approach: sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH/FISH).

Results: EGFR mutation (MT) rate was 12.7% (135/1059), of which 57% overexpressed EGFR (IHC) and 61% had EGFR gene amplification (FISH). This describes dependence on the EGFR pathway and potential importance of dual inhibition with cetuximab and EGFR TKIs. 66% and 7% of EGFR MT patients were MET high (IHC) and amplified (CISH), 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 TKIs (Huang, et al. 2011) and possible cross-resistance to radiotherapy. ALK translocations were observed in 101 of 3611 (2.8%) patients, among which 19%, 3% and 2% carried concurrent EGFR, MET and HER2 amplification (ISH), respectively, suggesting the potential for combining crizotinib with agents such as cetuximab, onartuzumab or trastuzumab. BRAF mutation was observed in 3.3% (34/1061), among which EGFR and MET were high by IHC (both have been implicated in resistance to BRAFi in other tumor types) in 58% 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 to biomarker testing and potential role of combination treatment strategies.

Background

With increased understanding of molecular alterations in NSCLC, recent research has shown a number of signaling nodes are activated within signaling pathways. Targeting molecular alterations individually, however, often leads to suboptimal responses, and inevitable resistance mechanisms. Integration of targeted therapies with cytotoxic agents, as well as novel combinations of targeted therapies, is hoped to further increase therapeutic potential of single-agent inhibitor strategies. We explored a database of theranostic biomarker frequencies in NSCLC adenocarcinomas to explore the overlapping events that may result in potential novel combination strategies.

Methods

6,785 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

Overall mutation rates for major oncogenic drivers are shown to the right, in "Major Targetable alterations in NSCLC" and are represented by different colored headings. Analysis of each driver subgroup is represented in tables below - color of top row correlates with the driver alteration.

Proposed Combination Strategies

Combination of targeted agents

Combination of targeted agents + traditional chemotherapy

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
BRAF mutation	3.5 (61/1731)	dabrafenib	NRAS mutation	0.4 (5/1256)	MEK inhibitors

MEK Inhibitor combinations - KRAS mutation positive patients

Additional Target	% (n)	Proposed Combination
RRM1 low	**84** (879/1042)	+ gemcitabine
TS low	**72** (747/1037)	+ pemetrexed
PTEN loss, mutation	**47** (524/1115), **2** (5/288)	+ PAM pathway i
TOPO1 positive	**42** (409/982)	+ irinotecan
EGFR positive, amplified	**41** (176/434), **22** (146/673)	+ cetuximab
cMET positive, amplified	**34** (127/369), **3.4** (13/378)	+ cMET-targeted therapy
SPARC positive	**29** (298/1032)	+ nab-paclitaxel
TUBB3 low, TLE3 positive	**24** (63/286), **21** (92/440)	+ taxane
EGFR mutation	**2** (21/1172)	+ EGFR-targeted therapy

cMET inhibitor combinations – cMET positive or amplified patients

Additional Target	% (n)	Proposed Combination
RRM1 low	**82** (464/565)	+ gemcitabine
ERCC1 low	**69** (82/119)	+ platinum
TOPO1 positive	**58** (290/502)	+ irinotecan
EGFR positive	**51** (305/597)	+ cetuximab
SPARC positive	**39** (209/539)	+ nab-paclitaxel
TUBB3 low, TLE3 positive	**28** (141/503), **18** (103/578)	+ taxane
PTEN loss	**26** (155/605)	+ PAM pathway i

BRAF inhibitor combinations – BRAF mutation positive patients

Additional Target	% (n)	Proposed Combination
RRM1 low	**88** (36/41)	+ gemcitabine
ERCC1 low	**78** (14/18)	+ platinum
TS low	**74** (28/38)	+ pemetrexed
TOPO1 positive	**57** (17/30)	+ irinotecan
EGFR positive	**47** (23/49)	+ cetuximab
PTEN loss	**47** (24/51)	+ PAM pathway i
TUBB3 low, TLE3 positive	**41** (12/29), **9** (4/47)	+ taxane
cMET positive, amplified	**32** (15/47), **10** (4/40)	+ cMET i
SPARC positive	**28** (11/40)	+ nab-paclitaxel
KRAS mutation	**5** (3/60)	+ MEK i

Erlotinib (E) combinations - EGFR mutation positive patients

Additional Target	% (n)	Proposed Combination
RRM1 low	**83** (435/520)	+ gemcitabine
TS low	**74** (384/522)	E + pemetrexed
ERCC1 low	**69**(303/440)	E+ platinum
EGFR positive, amplified	**57** (114/199), **56** (176/312)	+ cetuximab
TP53 mutation	**54** (70/129)	+ chemo + cell cycle checkpoint i
PTEN loss, mutation	**51** (279/547), **0.8**(1/125)	+ PAM pathway i
TOPO2A positive	**51** (225/442)	+ etoposide
TOPO1 positive	**47** (226/485)	+ irinotecan
TUBB3 low, TLE3 positive	**46** (49/107), **14** (15/107)	+ taxane
MGMT low	**42**(205/489)	+ temozolomide
cMET positive, amplified	**38** (75/199), **11** (19/172)	+ onartuzumab
ER positive	**9** (43/479)	E+ tamoxifen
PIK3CA mutation	**4** (8/199)	E + PAM pathway i
ALK rearrangement	**0.5** (2/377)	E + crizotinib

PAM (PIK3CA/AKT/mTOR) pathway inhibitor combinations – PIK3CA mutation positive or PTEN lost

Additional Target	% (n)	Proposed Combination
RRM1 low	**77** (3575/4690)	+ gemcitabine
TS low	**70** (3238/4633)	+ pemetrexed
cMET positive	**68** (1186/1741)	+ cMET i
TOPO2A positive	**62** (1538/2489)	+ etoposide
MGMT low	**51** (1375/2705)	+ temozolomide
TP53 mutation	**49** (389/801)	+ chemo + cell cycle checkpoint i
TOPO1 positive	**46** (2045/4407)	+ irinotecan
TUBB3 low, TLE3 positive	**38** (435/1138), **25** (435/1740)	+ taxane
SPARC positive	**32** (1482/4660)	+ nab-paclitaxel
KRAS mutation	**30** (1128/3791)	+ MEK i

Crizotinib (C) combinations – ALK or ROS1 positive patients

Additional Target	% (n)	Proposed Combination
RRM1 low	**80** (63/79)	+ gemcitabine
TS low	**80** (63/79)	+ pemetrexed
EGFR positive, amplified	**63** (34/54), 18 (7/38)	+ cetuximab
ERCC1 low	**61** (34/56)	+ platinum
TOPO1 positive	**57** (41/72)	+ irinotecan
cMET positive, amplified	**44** (23/52), 4 (2/52)	+ cMET-targeted therapy
PTEN loss	**36** (31/87)	+ PAM pathway i
SPARC positive	**31** (25/80)	+ nab-paclitaxel
TUBB3 low, TLE3 positive	**25** (8/32), **23** (12/53)	+ taxane
TP53 mutation	**16** (6/38)	+ chemo + cell cycle checkpoint i

i = inhibitor

References

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Conclusions

- Combinations of targeted therapies with traditional cytotoxic chemotherapies, as well as novel combinations of targeted therapies is under active investigation
- Utilization of a multiplatform 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.