Mutational Complexity Increases in Lung Adenocarcinoma (LADC) with the Development of Brain Metastasis (BM)

Matthew K Stein1, Mike G Martin1, Joanne Xiu2, Sandeep Mittal3, Surasak Phuphanich4, Aaron P Provenzano5, Sharon Michelbaugh1, Andrew J Brenner5, Deepa S Subramaniam2, Ashley L Sumrall8, Amy B Heimberger9, Santosh Kesari9, W Michael Korn2, Manjari K Pandey1

1West Cancer Center, Memphis, TN; 2Caris Life Sciences, Phoenix, AZ; 3Wayne State University/Karmanos Cancer Institute, Detroit, MI; 4Cedars-Sinai Medical Center, Los Angeles, CA; 5West Virginia University, Charleston, WV; 6The University of Texas Health Science Center, Houston, TX; 7Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; 8Levine Cancer Institute, Carolinas Medical Center, Charlotte, NC; 9The University of Texas MD Anderson Cancer Center, Department of Neurosurgery; Houston, TX; 10University of California, San Diego, La Jolla, CA

BACKGROUND

Up to 40% of LADC patients develop BM1-2 but little is known about the inciting molecular events.

METHODS

• We compared mutational profiles of LADC BM patients (pts) with primary (P) LADC submitted to Caris Life Sciences3 from 2015-2017.
• Testing included:
  • Tumor mutational burden (TMB)
  • Next-generation sequencing (NGS)
  • PD-L1
• Up to 40% of LADC patients develop BM1,2 but little is known about the inciting molecular events.
• NGS of 592 cancer-related genes was performed on formalin-fixed, paraffin-embedded (FFPE) tumor samples utilizing NextSeq platform (Illumina Inc., San Diego, CA). The 592 genes were enriched with a custom-designed SureSelect XT assay (Agilent Technologies, Santa Clara, CA, USA). Variants were detected with >99% confidence based upon allele frequency and amplicon coverage, with an average sequencing depth of coverage >500X and an analytic sensitivity of 5% variant frequency. NGS aberrations were test-defined as pathogenic (PATH), variants of undetermined significance or unclassified mutations (VUS).
• PD-L1 immunohistochemistry was completed on slides of FFPE tumor sections utilizing automated staining techniques with procedures in accordance with the requirements of the College of American Pathologists. Prior to January 2016, the antibody used against PD-L1 was SP142 (Spring Bioscience, Pleasanton, CA). Starting in January 2016 the primary antibody against PD-L1 was 22c3 (Dako, Santa Clara, CA) in non-small cell lung cancer (NSCLC) tumors, including LADC.
• Tumor mutational burden (TMB), reported in mutations per megabase (Mb), was determined by calculating the number of nonsynonymous somatic mutations identified by NGS after removing single nucleotide polymorphisms (SNP) identified in dbSNP (version 137) or in 1000 Genomes Project database (phase 3). 1.4 Mb were sequenced per tumor. TMB was test-defined as: high (H; ≥17 mutations/megabase), intermediate (I; 7-16) and low (L; 0-6).

RESULTS

Table 1. Characteristics of LADC BM vs. P samples.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Brain Metastasis (N=145)</th>
<th>Primary (N=1145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>64 (31-86)</td>
<td>70 (25-90)</td>
</tr>
<tr>
<td>Number Female (%)</td>
<td>83 (57)</td>
<td>669 (58)</td>
</tr>
<tr>
<td>PATHs (%)</td>
<td>KRAS</td>
<td>55 (38)</td>
</tr>
<tr>
<td></td>
<td>STK11</td>
<td>33 (23)</td>
</tr>
<tr>
<td></td>
<td>EGFR</td>
<td>17 (12)</td>
</tr>
<tr>
<td></td>
<td>BRAF</td>
<td>5 (3)</td>
</tr>
<tr>
<td></td>
<td>MET-amplified (%)</td>
<td>3 (2)</td>
</tr>
<tr>
<td></td>
<td>ALK-rearranged (%)</td>
<td>3 (2)</td>
</tr>
<tr>
<td></td>
<td>ROSI-arranged (%)</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>PD-L1 HIC (%)</td>
<td>≥1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥50%</td>
</tr>
</tbody>
</table>

• 145 BM and 1102 P pts had TMB data (Figure 1).
• BM cases were more-frequently TMB-H compared to P (39% (N=56) vs. 12% (366), P<0.0001) and less likely to be TMB-L (8% (12) vs. 33% (366), P=0.0002), 22
• BM cases were more-frequently TMB-H compared to P (39% (N=56) vs. 12% (366), P<0.0001) and less likely to be TMB-L (8% (12) vs. 33% (366), P=0.0002), 22
• Of 145 BM and 1106 P with PD-L1 testing, incidence of ≥1% (46% BM vs. 49% P) and ≥50% (24% vs. 23% BM cases were similar.

CONCLUSIONS

• Classic LADC biomarkers including PD-L1 (≥1% and ≥50%), EGFR, and KRAS were similar between BM and P cases.
• However, nearly 40% BM patients were TMB-H (≥25% more than P) and >90% either TMB-I or H, indicating an increased mutational complexity in BM development, suggesting immune checkpoint inhibitor use.4
• In addition to STK116 PATHs, RTK VUSs including: EPHA3, EPHA5, NTRK3, and EPB1 were more-frequently mutated and warrant further evaluation as biomarkers or targets in BM.

REFERENCES


Questions: Please contact
M.K. Stein, mkestein@westclinic.com
M.K. Pandey, mpandeyp@westclinic.com

Figure 1. TMB assessment of BM vs. P.

Figure 2. Comparison of RTK frequency between BM and P.

Table 1. Characteristics of LADC BM vs. P samples.