Commentary

Genomics of lung cancer

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Comment on: Choi M, Kadara H, Zhang J, *et al*. Mutation profiles in early-stage lung squamous cell carcinoma with clinical follow-up and correlation with markers of immune function. Ann Oncol 2017;28:83-9.

Kadara H, Choi M, Zhang J, *et al*. Whole-exome sequencing and immune profiling of early-stage lung adenocarcinoma with fully annotated clinical follow-up. Ann Oncol 2016. [Epub ahead of print].

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Multi-platform investigation of non-small cell lung cancer has the capability of discovering clinically important biological pathways involved in cancer development, progression, prognosis and response to treatment in patients with lung cancer. These two complementary publications from this productive research group describe genomic analyses of the two commonest subtypes of lung cancer: lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). The investigators analyse primary whole exome sequencing (WES) data from resected early stage lung cancers, supplemented by combinatorial comparative analyses of available landmark data: The Cancer Genome Atlas (TCGA) (1,2).

In addition to describing the types and frequency of mutations, they provide a subset analysis of clinical relevance to survival and response to adjuvant therapy, as well as correlation with a panel of selected immune response biomarkers. The latter analyses are of topical interest given emerging evidence of clinical benefit from immunotherapies designed to address the immune checkpoints that tumours hijack to suppress host anti-cancer immunity.

The results are summarised in *Table 1*, which also provides a narrative comparison of the two lung cancer subtypes.

Briefly, in LUAD they found an average of 243 coding mutations, with 28 genes associated with an increased mutation burden based on a genome-wide threshold of $P<2.4\times10^{-6}$. Copy number variations (CNVs) were also identified, with gains in putative oncogenes and losses in tumour suppressor genes, as expected. Correlation between the primary data set and the publicly available TCGA data is reassuring as to face-validity. The observations between genomic changes and immune profiles by immunohistochemistry (IHC) and some clinical parameters (prognosis and response to adjuvant treatment) are interesting, and add to the accumulating knowledge of potential actionable biomarkers in this cancer phenotype.

In early stage LUSC, there were a mean of 209 exonic mutations, with 14 reaching statistically significance. Recurrent CNVs were also reported including gain of chromosome 3q, reaching a frequency of 70.4% in this sample-set. Mutations (apart from CDKN2 and MLL2) and CNVs appeared consistent between this cohort and TCGA dataset. Again there were correlations between genomic changes and immunoprofiling by IHC and certain clinical characteristics as summarised in *Table 1*. In contrast to LUAD where a high mutational burden corresponded with elevated immune markers including PD-L1, only CD57 expression was correlated in LUSC.

Strengths of these studies include technology platforms, depth of sequencing, and demonstration of general concordance with TCGA datasets. Many known genes were replicated and some new candidates have emerged. Functional correlation is of value in helping to decipher the meaning of genomic landscape aberrations in these cancers.

The relationship to prognosis and response to adjuvant therapy is interesting, but due to the relatively small sample size and absence of control data, it is mainly hypothesis generating, rather than a definitive demonstration of

Table 1 Summary of major findings in LUAD (Kadara *et al*. 2016) and LUSC (Choi *et al*. 2016)

Clinico-biological correlates	LUAD	LUSC
Methods		
WES	108 early stage (I–III) cases	108 early stage (I–III) cases
Sequencing depth average	221X	189X
Tumour content	≥30%	≥30%
Ever smokers	86%	100% (50% current)
Median follow-up time, months (range)		
To survival	50.6 [1–172]	42.8
To recurrence	35 [1–162]	28.9
PD-L1, PD-1, CD3, CD4, CD8, CD45RO, CD57, granzyme B, FOXP2, CD68 by immunohistochemistry	92 cases	91 cases
TCGA supplementary data set	387 cases	178 cases
Mutations		
Average coding mutations	243	209
Substitutions	Higher rates in smokers More C > A, C > T and C > A common	Most C > A
Significantly mutated genes	28	14
Most common	*TP53*	*TP53*
Known mutated genes	*TP53, KEAP1, STK11, NF1, ATM, KRAS, EGFR, PIK3CA, BRAF, SMARCA4, SETD2, RBM10, U2AF1*	*TP53, MLL2, PIK3CA, NFE2L2, KEAP1, PTEN, GRM8, FBXW7, RB1, CDKN2A*
Other mutated genes	*VCAN, ROBO2, BAZ2B, FOLH1, COLI2AI, HEPACAM2, TFHDE, UBA6, INHBA, SPATA18, ZNF479, EPRS, NFATC2, LRRIQ3, ALS2CRI1*	*CDH8, ADCY8, PTPRT, CALCR*
Mutually exclusive		*NFE2L2* and *KEAP1*
LOH		
Median events per tumour	4	21.5
Overall rate across the genome	10.6%	42.6%
CNV		
CN gain	*MCL1, TERT, EGFR, CDK6, MYC, MUC5AC, AKT1, ERBB2, BCL2L1*	*3q (SOX2, PIK3CA, TP63), MYC, BCL2L1, MCL1, CDK6, JAK3, AKT1, FGFR1, WHSC1L1*
CN loss	*SETD2, APC, PRDM1, TSC1, CDKN2A, TP53, STK11, SMARCA4*	*3P (SETD2, VHL), CDKN2A, PTCH1, APC*
Prognostic significance		
Poor RFS	*SETD2* mutations	*MLL2* (regardless of *TP53* status) in those without adjuvant treatment
Poor RFS in KRAS mutated tumours	Concurrent *STK11, ATM* mutations	
Poor response to adjuvant treatment		
Mutations	*EGFR, KEAP1, PIK3CA*	*FBXW7, KEAP1* (especially TP53 mutated tumors)
CNVs	Focal gains chr14 (*AKT1*)	

Table 1 (*continued*)

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Clinico-biological correlates	LUAD	LUSC
Immunological correlations		
Immune markers	Increased in smokers and those with relatively high mutation burdens, C > A transversions, *KRAS* and *TP53* mutations	Overall upregulated immune response seen in *CDKN2A* mutated tumours
Down-regulated CD4+/CD8-Tcells (muted immune response)	*STK11* mutations	
Tumoural PD-L1	Most elevated immune marker in smokers	
High	*TP53* mutations	
Low	*PIK3CA*	*ADCY8, PIK3CA* (also associated with downregulated peri-tumoural PD-1 expression)
Upregulated CD57 and Granzyme B (augmented NK cell infiltration)	*TP53* or *KEAP1*	–
Upregulated CD45ro	–	*PIK3CA*

WES, whole exome sequencing; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; CNV, copy number variation; LOH, loss of heterozygosity; RFS recurrence free survival.

prognostic or predictive power. Also, since not every case was analysed for immune molecules, there is a possibility of selection bias, so it would be informative to know whether the cases were consecutive or a convenience sample, to judge the risk of such bias. Nonetheless, these data provide a rational basis for validation studies.

In summary, these companion papers report high quality data in modestly sized lung cancer subsets and add to the pivotal data generated by TCGA. They report some new gene candidates, and potentially useful biomarkers predictive of response to therapy. Furthermore, there were correlations with immune IHC biomarkers, some of which are known to differentially affect responses to emerging immunotherapies. The future addition of multi-omic comparison, e.g., epigenomics, RNA-Seq, proteomic, as well as multi-region sampling would add further value to these data helping to better understand the increasingly recognised complexities of intra- and inter-tumoural genomic heterogeneity (3-5).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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