Editorial Commentary

ATM—the gene at the moment in non-small cell lung cancer

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ATM variants in non-small cell lung cancer (NSCLC)

ATM encodes ataxia-telangiectasia mutated (ATM), a cell cycle checkpoint kinase involved in cellular response to double stranded DNA breaks that belongs to the PI3/PI4-kinase family. DNA double-strand break (DSB) recognition by the MRE11-RAD50-NBS1 (MRN) complex activates ATM which phosphorylates effectors to transduce signals that activate DNA repair, stimulate cell cycle arrest, or induce cell death (1). As such, ATM is critical for maintaining genomic integrity and correcting DNA mutations that could otherwise promote neoplastic transformation, tumor growth and cancer progression. Pathogenic germline variants (PVs) in the *ATM* gene, generally in the form of truncating variants (frameshift or nonsense), are present in 0.2–0.7% of the population and have a well-established role in conferring risk for several malignancies including breast, ovarian and pancreatic cancers (2). In fact, individuals with ataxia-telangiectasia (A-T) syndrome who carry two dysfunctional *ATM* alleles have a 20–30% lifetime risk of developing cancer (3). In lung cancer patients, the prevalence of germline *ATM* PVs appears to be only slightly higher than in the general population (up to 1.2–1.9% of patients) and is greatest in the most common type of lung cancer, lung adenocarcinoma (LUAD) (4,5). Based on a large case-control study, *ATM* has been proposed as a moderate-penetrance risk gene for LUAD (6).

In addition to germline variants, *ATM* is often somatically mutated in lung tumors. Of the DNA damage response and repair genes frequently mutated in NSCLC, *ATM* mutations are the most prevalent occurring in ~9% of LUAD and ~4% of lung squamous cell carcinoma based on The Cancer Genome Atlas (TCGA) cohorts (7,8). They are also found in ~8% of small cell lung cancers (9). Unlike commonly mutated oncogenes, *ATM* mutations are not localized to specific amino acids or functional domains, and are instead scattered throughout the *ATM* gene which spans ~150 kilobases. The seemingly random distribution of somatic mutations in *ATM* brings into question their functional significance and underlies the tendency to dismiss them as "passengers" that arise as a consequence of high tumor mutation burden (TMB) and nucleotide instability typically observed in lung cancers. However, similar to germline PVs in people with A-T syndrome, many somatic *ATM* mutations are predicted to have deleterious effects that cause protein truncation and/or loss of ATM expression which could promote lung cancer pathobiology.

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The prevalence of germline and somatic *ATM* gene variants in NSCLC emphasizes their potential to serve as prognostic biomarkers and/or molecular determinants of therapy response. *ATM* is routinely interrogated by commercial (e.g., FoundationOne CDx) and non-commercial next generation sequencing (NGS) targeted gene panels (e.g., MSK-IMPACT and OncoPanel) used to profile tumors to discover clinically informative genetic alterations. As such, *ATM* mutations can be readily detected in the clinic to inform patient care. However, besides establishing that germline *ATM* variants are associated with increased lung cancer susceptibility, the clinical significance of somatic *ATM* mutations in NSCLC has not been robustly defined. Addressing this knowledge gap, Ricciuti *et al.* recently published a study characterizing *ATM* mutations in NSCLC which was followed by a similar study led by Vokes and colleagues (10,11). Here, we briefly summarize the findings of these studies and share our perspective on pertinent questions that should be considered when interpreting the clinical relevance of *ATM* mutations as biomarkers for NSCLC.

ATM mutations are prevalent in NSCLC and have potential as clinical biomarkers

Ricciuti and colleagues characterized *ATM* gene variants in 5,172 tumors from NSCLC patients using either the OncoPanel (tumor-only) or MSK-IMPACT (tumor and normal tissue) NGS panels, and identified deleterious *ATM* mutations in 9.7% of cases (10). *ATM* mutations were positively associated with female sex, smoking history, non-squamous histology, TMB and PD-L1 positivity. Moreover, *KRAS*, *STK11*, *KMT2D* and *KEAP1* mutations were enriched in *ATM* mutant tumors, while *TP53* and *EGFR* mutations were negatively associated with *ATM* mutations. The subsequent study by Vokes *et al.* investigated *ATM* mutations in an even larger NSCLC cohort (N=26,857), assembled by collating data from 5 different clinicogenomic repositories (11). The Vokes group reported a comparable frequency of nonsynonymous *ATM* mutations (11.2% of cases), and confirmed that they were positively associated with *KRAS* mutations and increased TMB, negatively associated with *TP53* and *EGFR* mutations, and enriched in tumors from patients with LUAD histology and smoking history (see *Table 1*). It is worth noting that since both studies included NSCLC samples from the Memorial Sloan Kettering (MSK) Cancer Center and the Dana Farber Cancer Institute (DFCI), overlap between the patient cohorts analyzed is probable. Thus, although the extent of overlap is unclear from the sample information provided, this could contribute to similarities in the study findings. It should also be noted, however, that the survival analyses in the Vokes *et al.*'s study was limited to the FH-FMI CGDB cohort.

In an attempt to understand the phenotypic consequences of the various *ATM* mutations identified, both groups examined associations between mutations and protein expression using immunohistochemistry (Ricciuti) or data from reverse-phase protein arrays (Vokes) (10,11). As expected, ATM expression was lower in tumors with truncating mutations (nonsense, frameshift, or indels) compared to missense mutations. Finally, extensive correlative analyses were conducted in both studies to investigate associations between *ATM* mutation status and patient outcomes. Ricciuti *et al.* found that *ATM* mutations were not associated with patient survival or response to immune checkpoint inhibitor (ICI) monotherapy or chemoimmunotherapy; but patients whose tumors had concurrent *ATM*/*TP53* mutations exhibited better progression free survival after treatment with ICI. In contrast, Vokes *et al.* reported better overall survival in patients whose tumors had functionally-relevant *ATM* mutations (e.g., truncating, splice site, or curated missense) and improved survival in *ATM*-mutant patients treated with chemoimmunotherapy.

Taken together, these two large studies affirm the recurrence of somatic *ATM* mutations in the most common subtype of NSCLC, LUAD, and provide evidence that not all *ATM* mutations are functionally equivalent. The reproducible (co-)mutation patterns observed could indicate that *ATM* has functionally relevant, "epistatic" interactions with other genes commonly mutated in NSCLC. And, although the correlations reported between *ATM* status and patient outcomes were not consistent between the studies, both groups identified putative prognostic associations that warrant investigation in follow-up studies. Thus, the findings presented further emphasize the potential for *ATM* mutations to inform the clinical management of NSCLC patients, and highlight several questions that should be addressed with additional research to refine their clinical utility in NSCLC as discussed below.

How should the significance of ambiguous ATM mutations be interpreted?

A major challenge in deciphering the significance of *ATM*

Table 1 Study comparisons

Cohort features	Ricciuti *et al.* (10)	Vokes *et al.* (11)
Number of patients for mutational analyses	5,172 patients with NSCLC: DFCI (N=3,800), MSK (N=1,372)	26,587 patients with NSCLC: AACR GENIE (N=8,576[†]), GEMINI (N=3,066), TCGA (N=1,147), ICON (N=104), FH-FMI CGDB (N=4,399)
Histology	• Non-squamous 89.2%	• Adenocarcinoma & others: 21,606 (81.3%)
	• Squamous 10.8%	• Squamous: 4,981 (18.7%)
Sequencing methodology	• DFCI: OncoPanel (tumor only)[‡]	• GENIE: OncoPanel or MSK-IMPACT
	• MSK: MSK-IMPACT (tumor/normal-matched sequencing)[§]	• GEMINI: MD Anderson Molecular Diagnostics Laboratory tissue molecular profiling[#]
		• TCGA and ICON: whole exome sequencing (tumor/normal-matched)
		• FH-FMI CGDB: FoundationOne CDx (tumor only)
PD-L1 immuno-histochemistry	• PD-L1 (clone E1L3N or 22C3)	• FH-FMI CGDB cohort: laboratory developed PD-L1 test
ATM mutation rate[$]	• 9.7% (503/5,172 samples)	• 11.2% (2,980/26,587)
Key associations reported (*ATM* mutated *vs.* wild-type)	• Association with higher TMB	• Association with higher TMB
	• More likely to be PD-L1-positive in ATM^{MUT}	• No difference in PD-L1 expression
	• Enriched for concomitant mutations in *KRAS*, *STK11*, *ARID2*	• Enriched for concomitant mutations in *KRAS*, *STK11*, *ARID1A*, *RBM10*
	• De-enriched for *EGFR* and *TP53* mutations	• De-enriched for *EGFR* and *TP53* mutations[&]
	• Putative LOH in 14.1% of ATM^{MUT} cases	• *In vitro* demonstration of *ATM* loss leading to enhanced STING signalling activation with chemotherapy
	• Association with decreased *ATM* protein expression	
Survival outcomes (*ATM* mutated *vs.* wild-type)	• No differences in OS or DFS	• Improved OS with ICI-chemotherapy (multivariate)[@]
	• No differences in response rates or survival when treated with ICI	• PFS not reported
	• Improved response rate & PFS with ICI for *ATM*/*TP53* concurrently mutated cases	

[†], capture period of January 1, 2015, and December 31, 2017 for DFCI/MSKCC patients; [‡], OncoPanel interrogates for 277 (v1, 4/2013–07/2014), 302 (v2, 07/2014–09/2016), or 447 (v3, 09/2016-ongoing) genes; [§], MSK-IMPACT interrogates 341 (v1), 410 (v2), or 468 (v3) genes; [#], 134 or 146-gene panel; [$], overall number of samples with non-synonymous *ATM* variants, either confirmed to be or suspected to be somatic; [&], *TP53* de-enrichment was identified in the largest individual cohorts (GENIE, FH-FMI CGDB, and GEMINI), but was not significant in the meta-analysis; [@], survival analysis limited to one cohort (FH-FMI CGDB dataset). NSCLC, non-small cell lung cancer; DFCI, Dana-Farber Cancer Institute; MSK, Memorial Sloan Kettering; AACR GENIE, American Association for Cancer Research Genomics Evidence Neoplasia Information Exchange; GEMINI, Genome-wide Mutational Incidence for Non-Invasive detection of cancer; TCGA, The Cancer Genome Atlas; ICON, ImmunogenomiC PrOfiling of NSCLC; FH-FMI CGDB, Flatiron Health-Foundation Medicine Clinico-Genomic Database; TMB, tumor mutation burden; PD-L1, programmed cell death ligand 1; LOH, loss-of-heterozygosity; OS, overall survival; DFS, disease-free survival; ICI, immune checkpoint inhibitor; PFS, progression-free survival.

mutations in NSCLC and other cancers has been the lack of understanding of their functional impact. This, at least in part, reflects the limited biological characterization of *ATM* variants in model systems. Many *ATM* mutations in lung tumors are likely passengers that arise as a byproduct of high TMB associated with tobacco smoking, and inclusion of such mutations in correlative studies will confound conclusions regarding the clinical significance of *ATM* variants. This emphasizes the need to distinguish inert *ATM* mutations from those that have biological consequences in

studies focused on understanding their clinical implications. It is not surprising that nonsense, frameshift, and indel mutations are associated with loss of ATM expression, as they encode premature termination codons that can lead to nonsense-mediated mRNA decay (12). The functional impact of these "truncating" mutations is also evident from the cancer predisposition of individuals with A-T syndrome who carry them (3). However, multiple studies have established that most *ATM* variants in NSCLC are missense mutations, for which functional consequences are more challenging to predict (10,11). This makes missense *ATM* mutations difficult to interpret with respect to their biological significance and associated clinical relevance. Therefore, implementation of companion tests to measure ATM expression in tumors with ambiguous mutations would be useful for interpreting their implications. Moreover, functional genomics studies in preclinical models could also be done to define the biological consequences of missense mutations with unknown significance, such as their impacts on ATM-mediated signaling pathways and DSB repair. Such studies would provide much-needed insights into the relevance of *ATM* mutations which would facilitate interpretations of their clinical significance.

What is the prognostic and predictive value of ATM mutations?

To date, the clinical relevance of *ATM* mutations has largely been prognostic for various cancer types, with *ATM* mutations typically associated with inferior outcomes (1). The Ricciuti and Vokes studies described found that *ATM* mutations represent putative biomarkers of better overall survival and enhanced response to ICI monotherapy and chemoimmunotherapy; however, these associations were only identified by one of the two groups. The disparate findings may be attributable to differences in patient cohorts examined, strategies for stratifying patients based on *ATM* status, and/or sample size between the studies. Nevertheless, the individual associations are supported by additional published reports, raising enthusiasm for the prognostic significance of somatic *ATM* mutations in NSCLC. For instance, *ATM*-mutant tumors and tumors with concurrent *ATM*/*TP53* mutations were previously associated with favorable responses to ICI in NSCLC patients (13,14). To resolve the generalizability of the associations identified, granular dissection of patient populations by treatment sequences (especially for chemoimmunotherapy), doses and durations used, specific ICIs employed, and other relevant factors is required. Thus, multi-institute studies with sample sizes large enough to stratify patients on treatment variables and mutational profiles are needed to robustly decipher the prognostic value of *ATM* mutations.

With respect to the response-predictive potential of *ATM* mutations in NSCLC, preclinical lung cancer models with *ATM* deficiency were found to be sensitive to etoposide, poly (ADP-Ribose) polymerase (PARP) and ataxia-telangiectasia and Rad3-related protein (ATR) inhibitors that directly impair DSB repair, but not to platinum-based chemotherapy that induces DNA damage (15). Others have demonstrated that pharmacologic inhibition of ATM sensitizes lung cancer models to DNA damage induced by radiation therapy, findings that may be relevant to tumors with ATM loss-of-function (16). While these *in vitro* studies suggest that *ATM* mutations could be useful for predicting NSCLC treatment response, results from clinical trials are needed to confirm whether they are robust indicators of response to DNA damaging treatments like radiotherapy and targeted inhibitors of DNA repair (e.g., PARP inhibitors) in patients. Accumulating clinical evidence suggests *ATM* mutations may be biomarkers of olaparib response in castration-resistant prostate cancer patients (17,18). Ongoing trials evaluating PARP inhibitor response in patients stratified by *ATM* mutation status will determine whether the same is true for NSCLC.

What biological mechanisms underlie the clinical relevance of ATM mutations in NSCLC?

Understanding how *ATM* mutations contribute to and/or promote lung tumor biology would provide additional rationale for their use as prognostic and predictive biomarkers to inform the clinical management of NSCLC. The co-mutation and mutual exclusivity patterns of *ATM* mutations identified by the Ricciuti and Vokes groups are concordant with data from several prior studies (7,13,14), and could indicate that *ATM* mutations interact with other genetic events to influence tumor biology. For example, while *ATM* and *TP53* mutations are both enriched in NSCLC tumors with high TMB, tumors with truncating *ATM* mutations rarely have *TP53* mutations. This could reflect functional redundancy or synthetic lethality due to the roles of both proteins in maintaining genomic integrity and the dependence of mutant tumors on DNA repair mechanisms (1). If synthetic lethality were the underlying mechanism explaining the rarity of *ATM*/*TP53* co-mutations, NSCLC patients with co-mutated tumors could

be hypersensitive to DNA damaging therapies or drugs targeting DNA repair.

NSCLC with *ATM* mutations apparently have better outcomes after treatment with ICI (10,11,13,14), indicating that *ATM* might influence anti-tumor immune responses. This association could simply be explained by the positive correlation between *ATM* mutation and TMB, which itself has been linked to enhanced tumor immunogenicity and subsequently, susceptibility to anti-tumor immunity (3). Alternatively, some preclinical evidence suggests a more direct role for ATM in modulating the tumor immune microenvironment, for instance, through ATM-dependent regulation of PD-L1 via interferon, and/or cGAS/STING signaling pathways (3). Based on these observations, functional studies to characterize the effects of *ATM* mutations on PD-L1 expression and anti-tumor immunity in NSCLC models are warranted as they could establish a biological rationale for treating *ATM*-mutant tumors with ICI.

Is it important to distinguish germline from somatic ATM variants to guide lung cancer management?

Understanding the origin of *ATM* variants detected in lung tumor tissues is important for clinical decision-making for multiple reasons. First, germline-derived variants may cause patients to experience systemic toxicities to standard of care therapies (3). Several studies have demonstrated adverse effects of chemotherapy and radiation therapy in A-T patients, including lung injury and pneumonitis, as well as hypersensitivity to these DNA damaging treatments in cell models derived from A-T patients (3). Second, the presence of *ATM* PVs could indicate that additional clinical action is necessary. For example, individuals who carry cancer-predisposing germline PVs are managed using specific strategies to reduce cancer risk. These strategies include enhanced cancer screening and risk-reducing surgeries depending on the anatomical sites at risk, such as oophorectomy and mastectomy for ovarian and breast cancers. Moreover, clinical follow-up often extends beyond the individual carrying the PV, with cascade testing done to identify family members who are also at risk. Recent reports that 4–15% of lung cancers harbor PVs not only in *ATM* but also in *BRCA1*, *BRCA2*, and *CHEK2* (5,19,20) emphasize that studies to understand the clinical significance of these variants are also warranted since they could inform the clinical management of patients.

Since tumor-only sequencing remains the prominent workflow in cancer genetics laboratories, detection of germline variants can be challenging especially because constitutional DNA samples are not always accessible. However, in recognition of their clinical implications, analytical methods to confidently identify germline PVs from tumor only sequencing data are emerging (19,21,22). Ricciuti *et al.* inferred putative germline *ATM* variants in 5% of 3,800 NSCLC cases based on targeted NGS of tumor DNA. This frequency was higher than what has been reported for germline *ATM* variants in lung tumors by previous studies (0.5–1.9%), although they were not restricted to NSCLC (5,6,19,20). One approach for differentiating germline from somatic variants is to utilize variant allele fraction (VAF) and copy number status since high VAF and loss-of heterozygosity may flag putative germline alleles (19). Although standardized bioinformatic methods for identifying germline variants from tumor NGS data would be clinically useful, germline sequencing remains the gold standard and should be performed to confirm suspected germline *ATM* PVs.

In summary, recent studies and previous literature provide ample evidence that *ATM* mutations have potential clinical relevance with respect to overall survival and therapeutic response in NSCLC patients. However, given that the clinical associations reported in the literature are not unanimous across studies, the utility of *ATM* mutations in NSCLC remains unclear and further studies are required to robustly define their clinical implications. Since the significance of *ATM* PVs is well established, differentiating germline from somatic *ATM* variants is clinically important. Review of clinical and molecular data, including VAF and family cancer history may be helpful for guiding further testing to inform clinical decisions in patients with *ATM*-mutant tumors. Genetic testing coordinated by oncologists rather than genetic counselors or clinical geneticists may be helpful in this regard, especially in places where access to genetic counseling may be limited.

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Footnote

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