EGFR mutation positive non-small cell lung cancer: can we identify predictors of benefit from immune checkpoint inhibitors

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Monoclonal antibodies directed against the programmed death-1 (PD-1) receptor have demonstrated consistent survival improvement in comparison to second-line chemotherapy with docetaxel, in patients with advanced non-small cell lung cancer (NSCLC), across multiple histologic subtypes. However, this benefit is less clear in some subgroups of patients, including never smokers and patients with tumors harboring activating driver mutations, such as mutations of the epidermal growth factor receptor (*EGFR*) gene. Sub-group analyses of several phase III clinical trials comparing the immuno-oncology (IO) agents, nivolumab, pembrolizumab, or atezolizumab, with docetaxel, have failed to demonstrate superior efficacy of IO in patients with *EGFR* mutated tumors when compared to standard of care chemotherapy (1-3).

However, *EGFR* mutations are heterogeneous in nature. In treatment naive patients, differences in the type of *EGFR* mutation are known to impact on the efficacy of therapy (4). Heterogeneity also exists in the mechanisms by which tumors develop resistance to EGFR directed therapy (5). More than 50% of patients demonstrating resistance to first-line EGFR tyrosine kinase inhibitors (TKIs) develop T790M secondary mutations (6). Multiple mechanisms of resistance occur in the remaining patients including overexpression of the mesenchymal to epithelial transition (MET) and insulin-like growth factor receptor (*IGF-R*) genes and even transformation to small cell lung cancer in some patients. It is unclear how these resistance mechanisms may impact on subsequent response to IO therapy in this group of patients. It is in this context that Haratani and colleagues report on biomarker discovery research to identify predictive biomarkers for IO therapy in patients with *EGFR* mutated NSCLC (7).

The current study, reported by Haratani and colleagues, explored the impact of T790M mutation status on overall response rate (ORR) and progression free survival (PFS) from nivolumab, to identify additional potential predictive biomarkers for response to IO, in patients with *EGFR* mutated NSCLC (7). They report on a cohort of 25 NSCLC patients with activating mutations of the *EGFR* gene, previously treated with an EGFR TKI, receiving therapy with nivolumab, where T790M mutation status was known. Tissue from formalin fixed paraffin embedded (FFPE) blocks obtained following the development of EGFR TKI resistance was analyzed where available. This included assessment of immunohistochemistry (IHC) staining for PD-L1 expression, tumor-infiltrating lymphocyte (TIL) density, CD8, CD4, and FOXP3 expression, as well as whole exome sequencing (WES) in extracted DNA samples, to quantify the burden of non-synonymous tumor mutations. The analyses of these data looked at the predictive value of these putative biomarkers on ORR and PFS, according to T790M tumor mutation status. Lastly, the authors mention IHC analysis on a second cohort of 60 patients with *EGFR* mutation positive NSCLC, who did not receive therapy with nivolumab

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(cohort B).

It is important to realize that this is a very small sample of patients and statistical comparisons between groups is not particularly informative, because they are greatly underpowered. Among the 25 patients studied, eight had tumors positive for T790M mutation, which is somewhat lower than expected. The ORR to nivolumab in the entire cohort of 25 patients was 20%. The ORR was higher among patients who were T790M negative (24% in T790M negative patients, 13% in *EGFR* T790M positive patients), although this difference was not statistically different (P=1.000). Similarly, the disease control rate (DCR) was higher in patients with T790M negative tumors than T790M positive tumors (DCR, 47% *vs.* 13% respectively, P=0.182). The median PFS was 1.4 months (mos) for the entire cohort, and there was little difference between the median PFS of patients with T790M negative tumors (2.1 mos) and T790M positive tumors (1.3 mos, P=0.099). Interestingly, the hazard ratio (HR) for PFS was 0.48 [95% confidence interval (CI), 0.20–1.24] raising the potential for longer PFS among patients with T790M mutation negative tumors. Median overall survival (OS) had not been reached in the study with a median follow-up of 7.3 mos. Although it favored patients with T790M negative tumors (HR, 0.38; 95% CI, 0.09–1.65), this difference was not significant.

Information was missing for many patients in the biomarker discovery analysis. PD-L1 status was known in only 15 of 25 patients and only 14 of 25 patients had evaluable TIL density scores. Only 9 of 25 patients had material available for WES. There appears to be an association between the likelihood of response to therapy and tumor PD-L1 expression. ORR increases as PD-L1 expressions increase from ≥1%, to ≥10%, to ≥50%, corresponding to ORR of 38% (n=8), 75% (n=4), and 100% (n=2) respectively. PFS also favored patients with tumors showing any PD-L1 positivity ≥1% (2.1 *vs.* 1.3 mos; HR, 0.37). In cohort B (n=60), the proportion of patients whose tumors demonstrated any PD-L1 positivity was similar between T790M mutation negative and positive tumors. However, there appears to be an association between higher levels of PD-L1 expression and T790M mutation negative tumors. A higher proportion of tumors demonstrated staining for PD-L1 ≥10% and ≥50%, in T790M negative than T790M positive patients.

Biomarker analysis of TIL density was also explored. Of the three immunotypes assessed, only the CD8 positive TIL counts were higher in nivolumab responders when compared to non-responders (P=0.024), whereas CD4 positive and FOXP3 positive TIL densities were similar in both groups. PFS assessments based on differences in TIL densities did not yield any statistically significant results in this study. Among the nine patients assessed with WES, the three patients with response to IO demonstrated a significantly higher non-synonymous mutation rate compared to the six who did not respond (P=0.038). This did not differ by T790M status (P=0.710).

The findings by Haratani and colleagues shed light on the efficacy of IO agents in NSCLC patients with *EGFR* mutations. Data from randomized trials comparing nivolumab, pembrolizumab, or atezolizumab with docetaxel have failed to show a survival improvement in patients with an *EGFR* mutation receiving the IO agent (8,9). However, these findings are not entirely consistent across studies. The ORR and PFS seen in this trial with nivolumab are comparable to those observed with IOs in randomized trials of NSCLC patients in the second line setting (1-3). Interestingly in this study, both ORR and DCR is numerically higher in the T790M negative population, than the T790M positive population. Therefore, the mechanism of secondary resistance to EGFR directed therapy may provide some insight into the apparent lower efficacy of IO agents in NSCLC patients harboring *EGFR* mutations. OS data in this trial was immature. However, the data suggest that survival in T790M mutation negative patients treated with nivolumab may be greater than T790M mutation positive patients. Variability in the rate of T790M mutations in the second-line randomized trials of IO, might be implicated in the difference in efficacy of IO agents in *EGFR* mutated NSCLC. This hypothesis requires further exploration in prospective studies where T790M mutation status is known.

The data on PFS is more difficult to interpret. The observed PFS in the data from Haratani *et al.* (7) is reflective of published data from randomized trials (1-3). The majority of the patients progressed early, with a median PFS of 1.5 mos, independent of T790M status. However, actuarial analysis of PFS suggested longer PFS among patients with T790M mutation negative tumors (HR, 0.48; 95% CI, 0.20–1.21). It may be more informative in future research to look at PFS at 6 or 12 mos to identify the EGFR mutation positive patients who respond to IO, and determine factors associated with durable response to therapy.

There is some preclinical work to support the findings from Haratani and colleagues. Mullerian and cell-line studies suggest increases in PD-L1 staining correspond

to increased response to IO in *EGFR* mutation positive patients (10,11). There was a trend towards higher ORR with increased PD-L1 expression in this study, although the small sample size of the study limits the power to confidently demonstrate this. The expected distribution of PD-L1 expression in unselected NSCLC patients is around 50–60% PD-L1 positive, and 30% of all NSCLC are highly positive, as defined by PD-L1 staining of ≥50% of tumor cells. In the current study by Haratani *et al.* (7), we see a slightly lower rate of any PD-L1 expression ≥1% among patients with *EGFR* mutations, with much fewer patients than expected, demonstrating high PD-L1 expression ≥50% (2/9 in the T790M negative group, and 0/6 in the T790M positive group). Since higher PD-L1 staining tends to correlate with better response to IO, this may provide a glimpse into the mechanism behind lower response to IO in this population of *EGFR* mutated NSCLC.

Data on non-synonymous mutation burden (NMB) in this study is very limited but is consistent with other data in NSCLC. Earlier studies suggested that the NMB is associated with improved objective response rates, and durable clinical benefit, thus this study provides support to existing knowledge in the area (12). In general, NSCLC has on average a NMB of 6.86 per megabase (Mb), or 200 NMBs per tumor sample with a wide range of 11 to 1,192 NMB per sample (12,13). The samples in the current study had both a much lower NMB/sample, and NMB/Mb than data from unselected populations of NSCLC patients, likely as a reflection of the different molecular profiles between *EGFR* mutation positive tumors *vs.* smoking associated lung cancers.

The current study suggests that *EGFR* mutated NSCLC tumors have lower levels of PD-L1 expression and NMB. Since both tumor mutational burden and higher PD-L1 levels have potential predictive value for response to IO, this study may highlight a key reason underlying the poorer efficacy to IO observed among patients with *EGFR* mutated, compared to non-*EGFR* mutated NSCLC in previous phase III trials. In the second-line setting, some inconsistency has been observed between studies in the association of PD-L1 expression and improved OS from IO compared with docetaxel (1,2). Therefore, PD-L1 expression should generally not be used to select patients for IO in the second-line setting. However, given the findings by Haratani and colleagues, PD-L1 expression may prove useful in selecting patients with *EGFR* mutated NSCLC for IO *vs.* second-line chemotherapy, although this requires validation in prospective trials in these populations.

The observations on TILs in this study is thought provoking, but requires additional research. TILs may be a prognostic factor in multiple cancers independent of treatment, and is one of multiple biomarkers being actively assessed in conjunction with PD-L1 expression. Thus, the significance of higher CD8+ve TIL count in nivolumab responders than non-responders may guide further research for predictive biomarker testing. In addition to TIL density, including other potentially predictive biomarkers such as T-cell receptor clonality, or neoantigen burden, may also yield interesting hypotheses for further research in an *EGFR* mutation positive population (14).

Overall, this study highlights several interesting hypotheses involving *EGFR* mutation positive NSCLC patients and IO which are in need of further exploration. The lack of survival benefit from IO therapy compared with docetaxel, among patients with *EGFR* mutated NSCLC, has led some to suggest that these patients may not benefit from IO therapy. We would not agree with this view, but think that factors such as the presence or absence of T790M mutation, PD-L1 expression, and tumor mutation burden may all help to refine the selection of *EGFR* mutation positive NSCLC patients, for therapy with IO agents. Although we cannot use the information presented in this study to direct therapy for these patients, it does provide promising avenues of research for prospective trials that may help shed light on the area. The multiple emerging concepts in lung cancer diagnostics such as TIL density, tumor mutation burden assessment, and PD-L1 testing in this unique population are all areas requiring further clinical validation.

The combination of numerically higher ORR, and PFS as well as supporting exploratory biomarker assessment helps one hypothesize that EGFR TKI resistance in the absence of a T790M mutation may be due to a higher burden of molecular abnormalities, and these patients may potentially benefit more from IO therapy than patients with a T790M mutation. Thus, trials assessing the outcomes of responses to IO in patients with EGFR activating mutations, especially in those who do not harbor further targetable resistant mutations such as in the T790M, MET, and HER2 populations, should receive the highest priority.

Acknowledgements

Footnote

Conflicts of Interest: Dr. P Ellis has received honoraria for

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