HHS Public Access

Author manuscript

Clin Lung Cancer. Author manuscript; available in PMC 2025 September 01.

Published in final edited form as:

Clin Lung Cancer. 2024 September ; 25(6): 567–576.e1. doi:10.1016/j.cllc.2024.05.001.

Genomic and Immune Landscape Comparison of MET Exon 14 Skipping and MET-Amplified Non-Small Cell Lung Cancer

Rachel L. Minne[a], **Natalie Y. Luo**[a], **Anne M. Traynor**[b,c], **Minxuan Huang**[d], **Luisina DeTullio**[d], **Jen Godden**[d], **Melissa Stoppler**[d], **Randall J. Kimple**[a,b], **Andrew M. Baschnagel**[a,b,*]

[a]Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

[b]University of Wisconsin Carbone Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

[c]Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

[d]Tempus AI, Inc., Chicago, IL

Abstract

Background: Mutation or amplification of the mesenchymal-epithelial transition (MET) tyrosine kinase receptor causes dysregulation of receptor function and stimulates tumor growth in non-small cell lung cancer (NSCLC) with the most common mutation being MET exon 14 (METex14). We sought to compare the genomic and immune landscape of MET-altered NSCLC with MET wild-type NSCLC.

Methods: 18,047 NSCLC tumors were sequenced with Tempus xT assay. Tumors were categorized based on MET exon 14 (METex14) mutations; low MET amplification defined as a copy number gain (CNG) 6–9, high MET amplification defined as CNG ≥ 10, and MET other type mutations. Immuno-oncology (IO) biomarkers and the frequency of other somatic gene alterations were compared across MET-altered and MET wild-type groups.

*Corresponding author: Andrew M. Baschnagel, MD, Department of Human Oncology/Radiation Oncology, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, K4/B100-0600, Madison, Wisconsin 53792, baschnagel@humonc.wisc.edu.

Author Contributions (CRediT Authorship Statement)

Rachel L. Minne: Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Visualization.
Natalie Luo: Writing – review & editing.
Anne Traynor: Writing – review & editing.
Minxuan Huang: Methodology, Software, Formal analysis, Data Curation, Writing - Review & Editing, Visualization.
Luisina DeTullio: Resources, Data Curation, Methodology, Writing – review & editing.
Jen Godden: Resources, Data Curation, Methodology, Writing – review & editing.
Melissa Stoppler: Resources, Data Curation, Methodology, Writing – review & editing.
Randall J. Kimple: Conceptualization, Methodology, Resources, Writing – Original Draft, Writing - Review & Editing, Visualization, Supervision.
Andrew M. Baschnagel: Conceptualization, Methodology, Resources, Writing – Original Draft, Writing - Review & Editing, Visualization, Supervision.

Conflict of Interests (Disclosures)

MH, LD, JG, and MS are employed by Tempus.
RJK has a commercial research grant from BridgeBio. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Results: 276 (1.53%) METex14, 138 (0.76%) high METamp, 63 (0.35%) low METamp, 27 (0.15%) MET other, and 17,543 (97%) MET wild-type were identified. Patients with any MET mutation including METex14 were older, while patients with METex14 were more frequently female and nonsmokers. MET gene expression was highest in METamp tumors. PD-L1 positivity rates were higher in MET-altered groups than MET wild-type. METex14 exhibited the lowest tumor mutational burden (TMB) and lowest neoantigen tumor burden (NTB). METamp exhibited the lowest proportion of CD4 T cells and the highest proportion of NK cells. There were significant differences in co-alterations between METamp and METex14.

Conclusions: METex14 tumors exhibited differences in IO biomarkers and the somatic landscape compared to non-METex14 NSCLC tumors. Variations in immune profiles can affect immunotherapy selection in MET-altered NSCLC and require further exploration.

MicroAbstract

The MET oncogene can be mutated or amplified in non-small cell lung cancer. Using a large population-based database we compared the genomic and immune landscape of MET-altered lung cancer. MET-altered tumors exhibited differences in immune biomarkers and somatic mutations compared to non-MET-altered tumors. Variations in immune profiles may affect immunotherapy selection in these patients and require further exploration.

Keywords

lung cancer; MET; MET exon 14; MET amplification; immune biomarkers; cancer genomics

Introduction

The tyrosine kinase receptor mesenchymal-epithelial transition (MET) plays a key role in activating pathways involved in cell proliferation, embryogenesis, and tissue development[1,2]. Aberrant activation of MET can occur through overexpression, gene amplification, and point mutations of the receptor leading to cancer growth and metastasis[1,3,4]. In non-small cell lung cancer (NSCLC) the MET gene is amplified in 1–6%[5–7] of patients and mutated in 3–4%[6,8,9] of patients. MET exon 14 skipping mutation (METex14) is the most common MET mutation and is characterized by splice-site alterations that cause a loss of transcription of exon 14[10]. There are over 500 mutations at the genomic site that can cause MET exon 14 skipping with point mutations at the splice donor site being the most common[11]. The presence of a METex14 mutation is characterized by the deletion of the MET juxtamembrane domain which leads to impaired MET ubiquitination, decreased MET turnover, and increased signaling[12,13]. Other MET mutations in NSCLC include variants located on intron 13 and intron 14, both of which have been observed to not correlate with METex14 skipping mutations[14]. MET amplifications in NSCLC can dysregulate MET signaling through protein overexpression and constitutive receptor kinase activation[15]. Previous literature has also identified MET amplification as a mechanism for targeted therapies resistance, including those targeting EGFR[16,17]. Consequently, amplifications are not mutually exclusive with other oncogenic drivers and can occur in patients with METex14 mutations[15].

In the US, three approved MET-specific tyrosine kinase inhibitors (TKI), capmatinib[13], tepotinib[18],and crizotinib[19] have shown promising results in treating METex14 NSCLC; an additional TKI, savalotinib, has also been approved in China[20]. MET-amplified tumors have shown a mixed response to MET-directed therapy[19,21,22]. Patients with a gene copy number (GCN) of less than 10 have shown limited response to capmatinib[22] while patients with a GCN of 10 or higher exhibited an overall higher response to capmatinib. It is unknown what the appropriate MET GCN threshold is for response to MET-directed therapy[7]. It is possible that patients with lower or moderate levels of MET amplification do not benefit from therapy because of the coexistence of other driver oncogenes. Also, not all patients with high-level MET amplification respond to MET-directed therapy. Similarly, non-METex14 mutated NSCLC may not respond to TKIs[14].

While these small molecule inhibitors have led to improvement in the treatment of this disease, resistance to these inhibitors eventually occurs, and thus novel treatment approaches are needed. Identifying the molecular pathways that drive these tumors could assist in developing effective therapeutic strategies and identify subsets of patients that would most benefit from MET-directed therapies.

The immune landscape of both METex14 mutated tumors and MET-amplified tumors is not well described. The efficacy of immunotherapy for MET-altered NSCLC remains unclear with some studies showing mixed responses with immune checkpoint inhibitors (ICIs), despite high programmed death-ligand 1 (PD-L1) expression[23–25]. Having better insight into the immune profile of these tumors would assist in developing rational immunotherapy combinations.

In this study, we sought to compare the genomic and immune landscape of MET-mutated and MET-amplified NSCLC using a large population-based dataset. Our objectives were to determine the association between MET mutations, MET copy number, and MET RNA expression in MET, and examine the immune landscape of MET-altered NSCLC by examining PD-L1 expression, tumor mutation burden, and distribution of immune cell subtypes by deconvolution of RNA-seq data. Given that MET amplification serves as a pivotal mechanism of resistance in patients undergoing EGFR targeted therapies, we conducted a comparative analysis between cohorts of MET amplified patients, stratified by the presence or absence of an EGFR mutation. In addition, we present somatic co-mutational frequencies between MET expression groups.

Together, these results shed critical information on the differences in the immunogenic landscape based on MET alteration. Ultimately, understanding co-alterations, molecular signatures, and immune profiles of MET-altered NSCLC, also may provide insight into mechanisms of treatment resistance and help predict sensitivity to novel combination therapies including immunotherapies.

Methods

Cohort Selection

The observational study was approved by the University of Wisconsin IRB and Tempus. De-identified records of patients with NSCLC who underwent sequencing between 2004 and 2023 were selected from the Tempus Database. Clinical, demographic, and genomics data were retrieved.

Overall, 18,047 patients with NSCLC were included in this analysis. The tumor stage was determined using information recorded within 60 days of the biopsy collection date.

Patients were classified based on their MET gene status which included high MET amplification, defined as GCN ≥ 10, low MET amplification defined as GCN 6–9, METex14 mutations, MET mutations other than METex14, and MET wild type. METex14 mutation classifications were based upon the location of the mutation on the MET gene. Single nucleotide variants (SNV) were detected at the canonical splice sites: c.3028+1/c.3028+2, c.2888–2/c.2888–1, at the non-canonical splice site: c.3028+3, and at the last nucleotide of Exon 14 (c.3028). In addition, deletions that encompassed the branch site and/or the polypyrimidine tract on Intron 13, the boundaries of Intron 13/Exon 14 or Exon 14/Intron 14, were also detected. Any MET mutations not located on MET exon 14 sites were classified as MET other mutations.

Tempus xT Panel DNA and RNA library construction and sequencing

DNA sequencing and whole-transcriptome RNA sequencing from tumor specimens were performed via Tempus Labs (xT.v2 and xT.v4), as previously described[26–28]. The assay is a targeted panel that detects variants in 596 or 648 genes (xT.v2 and xT.v4, respectively), with high sensitivity and specificity (23–24). Somatic short variants, including single-nucleotide variants (SNV) and insertion-deletion variants (indels), were reported. Copy-number variations were assessed using the Tempus copy-number algorithm[26], which utilizes sequencing coverage and variation in heterozygous germline SNVs between tumor and normal samples.

RNA analysis was performed as previously described[28]. Immune deconvolution was performed to produce super-resolution ST maps through xFuse[29] and validated using multiplex immunofluorescence via CODEX[30]. Significance was assessed using the methods of Benjamini and Hochberg after empirical Bayes moderation (function eBayes()) to better estimate gene-wise variability, and genes with a False Discovery Rate (FDR) < 5% were considered differentially expressed.

The relative proportions of immune cell subtypes were estimated using a support vector regression (SVR) model, as previously described[28].

PD-L1 Immunohistochemistry

PD-L1 status was determined by clinical Tempus testing with the 22C3 anti-PD-L1 pharmDx assay[28]. Slides were scored by a pathologist using the tumor proportion score,

which is the percentage of tumor cells with complete or partial membrane staining. PD-L1 positive is defined as a tumor proportion score of 1% or more.

Tumor Mutational Burden

As described previously[26], Tumor Mutational Burden (TMB) was determined by dividing the count of nonsynonymous mutations by the size of the panel (2.4 Mb for the panel size of xT.v2 and 1.9Mb for the panel coding region of xT.v4). All non-silent somatic coding variations including missense, indel, and stop-loss variants with coverage greater than × 100 and an allelic fraction greater than 5% were included in the count of nonsynonymous variations.

Neoantigen Tumor Burden

Neoantigen tumor burden (NTB) was performed on all non-silent mutations as previously described[27]. The binding affinities for all possible 8–11 amino-acid peptides containing the mutation of interest were predicted using MHCflurry[31]. Binding affinities of cases that lacked training data available to create an allele-specific MHCflurry model were estimated by the closest HLA allele with similar amino acid sequences. Antigenic classifications were assigned to peptides that were predicted to bind to patients' HLA alleles with a minimum binding affinity of 500 nM.

Statistical Analysis

Statistical differences between groups were assessed by chi-squared/Fisher's exact tests or Kruskal-Wallis tests. The prevalence of gene alterations was compared with false-discovery correction for multiple testing. All analyses were two-sided with statistical significance evaluated at the 0.05 alpha level or 0.05 q level in the case of false-discovery correction. Analyses were performed in R version 4.2.0.

Results

The incidence of any MET mutation was 1.7% including 276 (1.5%) patients with METex14 and 27 (0.15%) patients with non METex14 mutations. The most common type of mutation leading to METex14 was a SNV at the splice donor site (N=87), or a SNV at the last nucleotide of exon (N=82). MET amplification was seen in 201 tumors including 138 (0.76%) with high METamp and 63 (0.35%) with low METamp. Patients with METex14 were older, and more likely to be women and nonsmokers than those with MET-amplified or wild-type (METwt) MET tumors (Table 1 and Figure 1, $P < .001$). While MET RNA expression was found to be higher in METex14 tumors compared to METwt tumors, MET RNA expression was the highest in high METamp and low METamp tumors (Figure 1, $P < .001$).

METwt showed significantly lower PD-L1 gene expression (2.22) compared to METex14 (2.44), high METamp (2.39), and low METamp (2.65, $P < .001$). Similarly, METwt had lower PD-L1 IHC positivity rates than METex14, high METamp, and low METamp (Figure 2).

METex14 showed significantly lower median TMB (2.6) relative to high METamp (5.4), low METamp (5.2), and METwt (4.6, $P < .001$). Similarly, METex14 showed significantly less neoantigen load than METamp high, METamp low, or METwt tumors ($P < .001$, Figure 2).

Immune cell profiling revealed CD4 cell concentration to be lowest and natural killer (NK) cell concentrations to be highest in both high METamp and low METamp NSCLC compared to METwt and METex14 ($P < .001$). Similar values of CD4 and NK cell concentration were reported for METwt and METex14. B cell concentrations were lower in METex14, high METamp, and low METamp compared to METwt ($P < .001$). No differences were seen in CD8, macrophage, or total immune cell populations (Figure 3).

Of the 196 METamp patients, 58 (28%) had an EGFR alteration, 43 (74%) with high METamp and 15 (26%) with low METamp. PD-L1 expression and positivity were lower in METamp groups with an EGFR alteration (2.3% and 74.0%, P = 0.015). TMB was lower in EGFR altered METamp patients (2.9) compared to high METamp (6.5) and low METamp (6.1) patients with EGFR wild type (P<.001). Similarly, neoantigen tumor burden was lower in EGFR-altered METamp patients (Figure 4). No significant differences were observed in immune cell populations between METamp groups (Supplemental 1).

METex14 tumors harbored significantly fewer co-occurring alterations and METex14 skipping variants were largely mutually exclusive with other known driver mutations and amplifications, compared to METamp and METwt tumors (Figure 5A). High MET-amplified tumors had an increased prevalence of mutations compared to METex14 in TP53 (80% vs. 36%), EGFR (23% vs. 1.1%), KEAP1 (14% vs. 0.7%), CDKN2A (9.4% vs. 3.3%), and STK11(8.0% vs. 1.1%). Mutations in KRAS and STK11 were higher in METwt compared to groups with altered MET expression (Figure 5A).

The co-occurring GCN alterations differed significantly between METex14 and METamp tumors. Compared to high METamp, METex14 harbored significantly higher co-occurring gene amplification of MDM2 (15% vs. 4.3%) and lower EGFR (0.4% vs. 9.4%). YEATS4 and FRS2 also had high co-occurring amplifications with METex14 tumors (14% and 12%). Tumors with high MET amplification had significantly higher co-amplification of TFEC, CFTR, and WNT2 compared with low MET amplification (Figure 5B). Additionally, copy number loss of CDKN2A, CDKN2B, and MTAP was higher in METamp than in METex14 tumors (Figure 5C).

Discussion

In this large, real-world patient study, the genomic and immune landscape of 18,047 patients with NSCLC were assessed based on MET alterations. Overall, we found significant differences between TMB, neoantigen load, PD-L1, CD4, and NK cell concentrations, based on the presence of MET mutation or MET amplification. Subdivision of METamp patients according to the presence of EGFR alterations revealed notable variances in PD-L1, TMB, and neoantigen profiles. In addition, the incidence of mutations and amplifications in other genes appear to be significantly different between MET-mutated and MET-amplified tumors. METex14 tumors had more frequent gene amplifications in MDM2, UGT1A1, FRS2, and

YEATS4. High METamp and low METamp tumors showed a higher prevalence of mutations in TP53, EGFR, and KEAP1 and higher prevalence of copy number loss in CDKN2A, CDKN2B, and MTAP.

There is conflicting data regarding the efficacy of ICIs in MET-altered NSCLC. Multiple retrospective studies of patients with METex14 mutations have demonstrated a limited response to ICIs regardless of PD-L1 positivity[24,32–34]. In patients with MET amplification, the results are more mixed with most studies showing low responses to anti-PD-L1 immunotherapy regardless of high PD-L1 expression[35–37]. In a study of 81 patients with MET amplification that excluded ALK-positive and EGFR-altered patients, non-responsiveness to ICIs was associated with high (>5) MET copy numbers[37]. Another study comparing the efficacy of nivolumab in METamp and METwt NSCLC found no significant differences in progression-free survival between the two groups[36]. A third retrospective series examined both patients with METex14 (n=59) and METamp (n=278) NSCLC and found that patients with MET-amplified NSCLC with GCN ≥10 had a survival benefit with immunotherapy whereas those with METex14-mutated NSCLC did not[35]. Most of these studies examined ICIs in the monotherapy setting and therefore there is limited data on the efficacy of chemotherapy-ICI or TKI-ICI combinations in these patients, and prospective data are needed. A recent study has suggested a significant immunosuppressive effect associated with the overexpression of the HGF/MET cell pathway as HGF has been reported to enhance the population of T reg cells, reduce CD8+ T cells, and induce the production of other immunosuppressive cytokines[38]. Furthermore, HGF/MET signaling has been shown to lead to up-regulation of PD-L1 through the PI3K pathway[38]. The recognition of MET as a tumor-associated antigen by CD8 cytotoxic T-cells highlights its potential as an immune response target[39], suggesting that inhibiting MET could be a strategy to overcome immune response evasion in cancer therapy. Combination treatment may be a potential therapeutic strategy, as preclinical studies have shown that inhibition of MET can inhibit the recruitment of immunosuppressive neutrophils and lead to improved efficacy of cancer immunotherapies by activating the STING protein[40].

Consistent with previous studies[41–43], PD-L1 expression and positivity were significantly higher for MET-altered NSCLC tumors compared to METwt NSCLC tumors in our large patient cohort. Also as reported previously[34,36,43], TMB was lowest in the METex14 tumors while MET-amplified tumors had TMB levels similar to METwt tumors. Neoantigen tumor burden was lowest in METex14 tumors compared to MET-amplified and METwt tumors. The lower TMB and neoantigen tumor burden seen in METex14 tumors is most likely due to the oncogene-dependent nature of these tumors. This is similar to what is seen in EGFR- and ALK-driven NSCLC tumors which also show lower TMB and neoantigen load compared to non-oncogene-driven tumors[44]. This is likewise supported by the lower frequency of gene alterations in the METex14 cohort and consistent with previous literature that has identified METex14 as a primary oncogenic driver[39]. MET-amplified tumors can be genomically heterogeneous and while present, MET signaling may not be the predominant oncogenic driver for many of these tumors.

While we did not see a difference in total immune cell populations between the groups, we did find that MET-amplified tumors had a lower proportion of CD4+ cells and a higher

proportion of NK+ cells compared to METex14 tumors. There was no difference in CD8+ cells among the groups. The proportion of positive B-cells was lower in both METex14 and METamp compared to METwt. These findings contrast with a recent study that found decreased CD8+ T cells and NK cells in patients with MET amplification compared with those with METwt, and this decrease correlated with poor response to ICI[37]. Others have found baseline CD4+ and NK cell concentrations to be identified as independent predictors of immunotherapy response in patients with NSCLC[45]. While the results of our study suggest that METamp tumors have an immune landscape that is unique from METex14 and METwt, more insight into these differences and the effect of CD4+ and NK cell population on ICI response is needed.

Consistent with previous findings[46], there was a significant co-occurrence of MET amplification and EGFR alterations. Approximately 28% of MET-amplified patients in this study had an EGFR alteration. Our findings showed that TMB as well as PD-L1 positivity and expression was lower in METamp patients with altered EGFR than METamp patients with EGFR wild type. While we cannot comment on whether these EGFR-altered patients developed MET amplification as a result of EGFR targeted therapies, it is clear that these tumors have a significantly different immune landscape than MET-amplified tumors with wild type EGFR. Analyses from clinical trials have demonstrated that patients with EGFR exon 19 deletions or exon 21 L858R mutations have less benefit to ICI[47,48]. Subsequent investigations may benefit from assessing both MET and EGFR status in trial evaluating ICIs. Consistent with previous findings, MET-amplified tumors had significantly more alterations in the GCN of CDKN2A[49]. Our results also demonstrated that MET-amplified tumors are more likely to harbor gene deletions of CDKN2B and MTAP. Similarly, CDKN2A and CDKN2B have co-occurring GCN alterations due to sharing a similar chromosomal location and the loss of the CDKN2 cluster is associated with centrosome amplification[50]. Recent studies have demonstrated that deletions of CDKN2A and MTAP (9p21 loss) are frequently co-occurring and associated with an immunosuppression phenotype consisting of a reduced abundance of tumor-infiltrating leukocytes and lower PD-L1 positivity as well as a poor response to immunotherapy in multiple tumors including NSCLC[50,51]. TFEC, CFTR, and WNT2 all share a cytogenic location with MET at 7q31.2 on human chromosome 7 and their co-occurring frequency with MET amplification is most likely because of their proximity to each other.

METex14 has a higher expression of MDM2 and lower expression of TP53 compared to the other groups. These results are consistent with other findings, demonstrating MDM2 as a negative regulator of P53 and MDM2 co-amplification mutually exclusive to TP53 mutations[43,52]. METex14 also had a higher expression of altered YEATS4, a protein identified as a P53 pathway inhibitor[53,54], compared to the other groups. Gene copy number alterations of FSF2, an adaptor protein that plays a critical role in FGFR signaling[55], also has higher co-occurrences in METex14 than other MET expression groups. However, it is unclear whether the amplification of FSF2 expression is contributing to the inhibition of the P53 pathway or rather due to the fact it is located near MDM2 and YEATS4 on chromosome 12q13–15.

Conclusion

We provide evidence of significant differences in the genomic and immune landscape between METex14 and MET-amplified NSCLC. The results of our study yield hypothesis-generating variance between immunologic biomarkers, such as PD-L1, TMB, neoantigen burden, CD4+ and NK+ immune cell concentrations, in METamp and METex14 tumors which may have a potential impact on the efficacy of immunotherapy. Furthermore, the dissimilarity of co-occurring gene mutations, gene copy number amplifications, and deletions between METex14 and METamp tumors shed light on the different mechanisms driving their tumorigenesis and targetability. While METex14 and MET amplification drive oncogenesis through the overexpression of MET, they give rise to significantly different genomic and immune profiles which could translate to unique disease behavior and treatment response. Further investigations and prospective studies will be needed to elucidate the clinical benefit of ICIs in MET-dysregulated tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank James P. Zacny, Ph.D. for manuscript preparation and formatting assistance.

Funding Sources

This project was supported in part by the University of Wisconsin Carbone Cancer Center Support Grant (P30 CA014520), University of Wisconsin Lung Disease-Oriented Team, donor funds from John Hallick and the MET Crusaders (https://metcrusaders.org).

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Clinical Practice Points

- The immune landscape of MET-altered non-small cell lung cancer (NSCLC) is not well described.
- The efficacy of immunotherapy for MET-altered NSCLC remains unclear with some studies showing mixed responses with immune checkpoint inhibitors, despite high programmed death-ligand 1 expression.
- In our study, we found significant differences between tumor mutation burden, neoantigen load, PD-L1, CD4, and natural killer cell proportions, based on MET mutation or MET amplification status.
- The incidence of mutations and amplifications in other genes appear to be significantly different between MET-mutated and MET-amplified tumors.
- Variations in immune profiles may affect immunotherapy selection in MET-altered NSCLC and require further exploration.

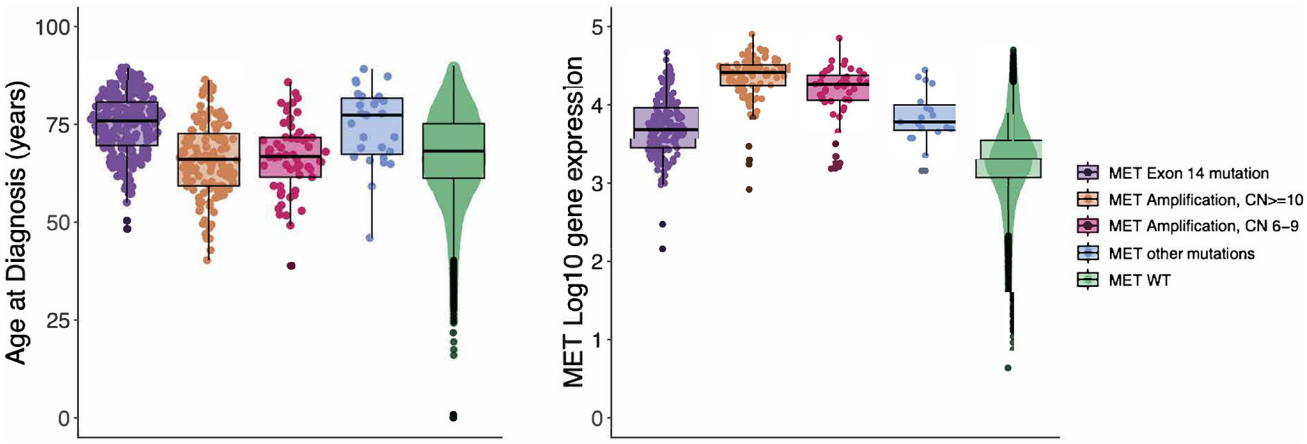

Figure 1.

Age at diagnosis in the full NSCLC cohort (Left) and overall MET log10 gene expression in the full NSCLC cohort (right). Data are represented as box plots showing median values (center line), with upper and lower quartiles.

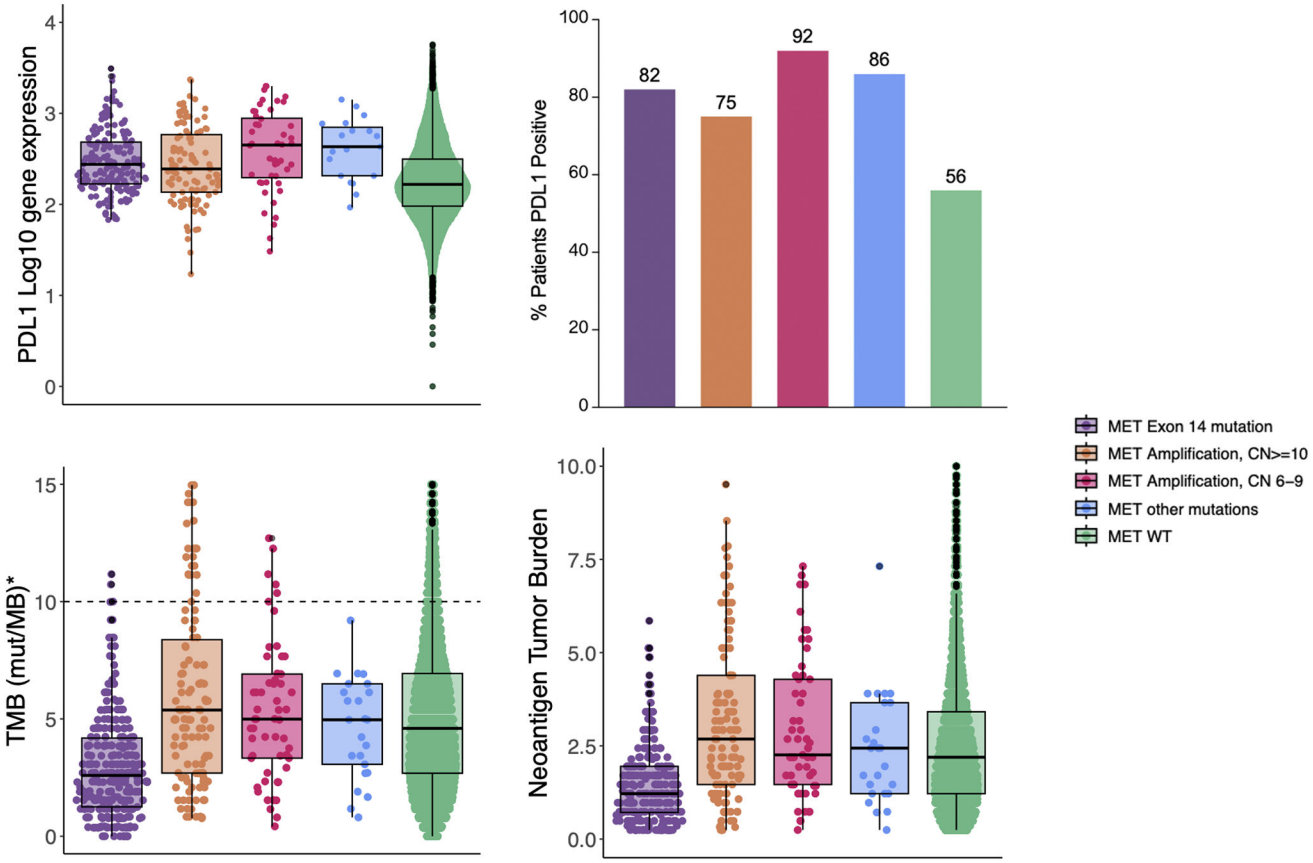

Figure 2.

Overall PD-L1 gene expression (top left) and PD-L1 positivity rate (top right) were determined by IHC for the entire patient cohort. Data are represented as box plots showing median values (center line), with upper and lower quartiles. TMB (bottom left) and Neoantigen tumor burden (bottom right) for the entire patient cohort. Dashed line indicator for cut off for high TMB. CN = copy number; PD-L1 = programmed death-ligand 1; TMB = tumor mutation burden.

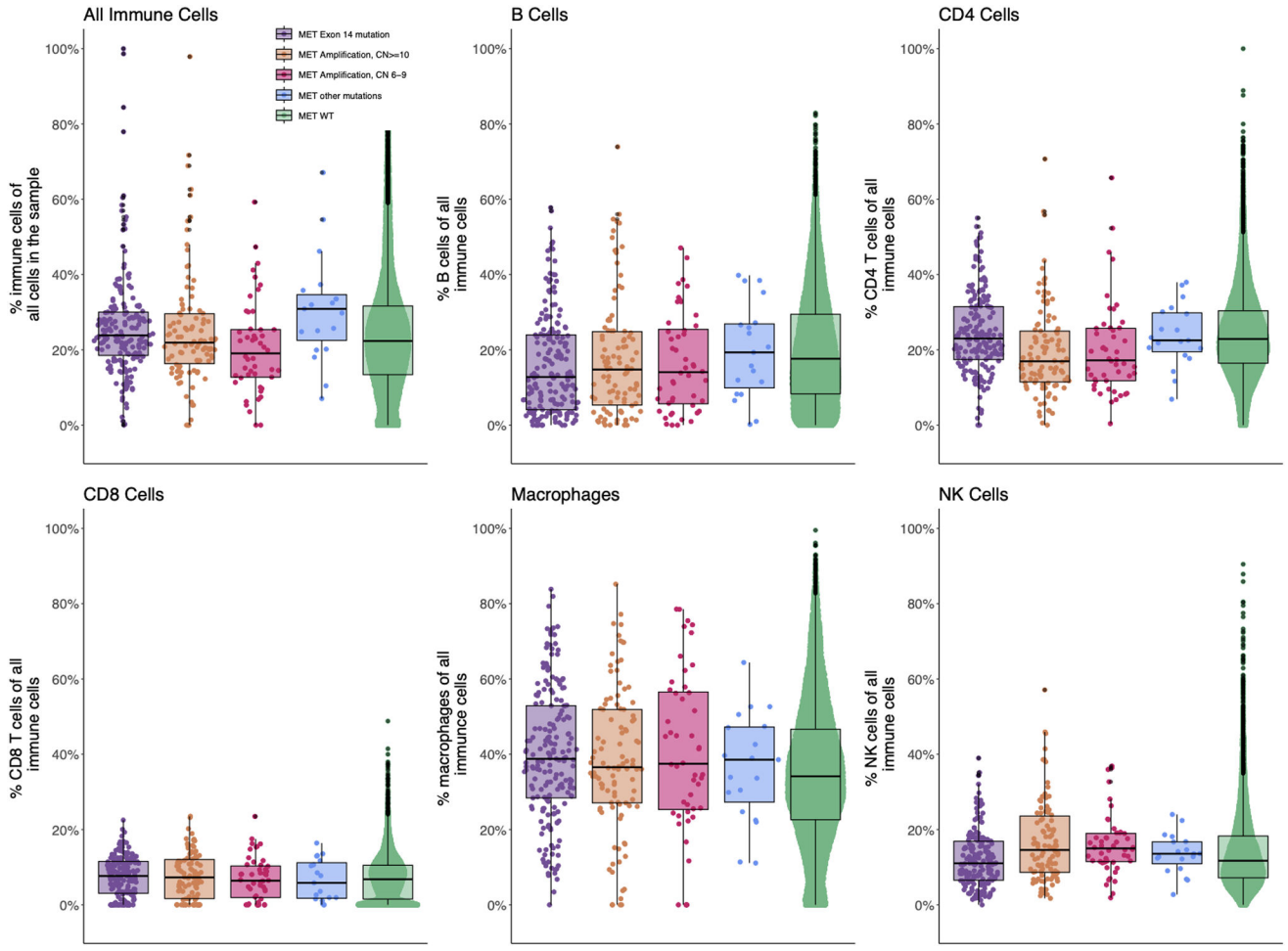

Figure 3.

Comparison of immune cell concentrations which are restricted to patients with RNAseq (N = 13,192). METamp high expression (N =102), METamp low expression (N = 49), METex14 (N = 187), MET other mutations (N = 19), and METwt (N=12,836). Percentages are representative of the proportion relative to all immune cells. Data are represented as box plots showing median values (center line), with upper and lower quartiles.

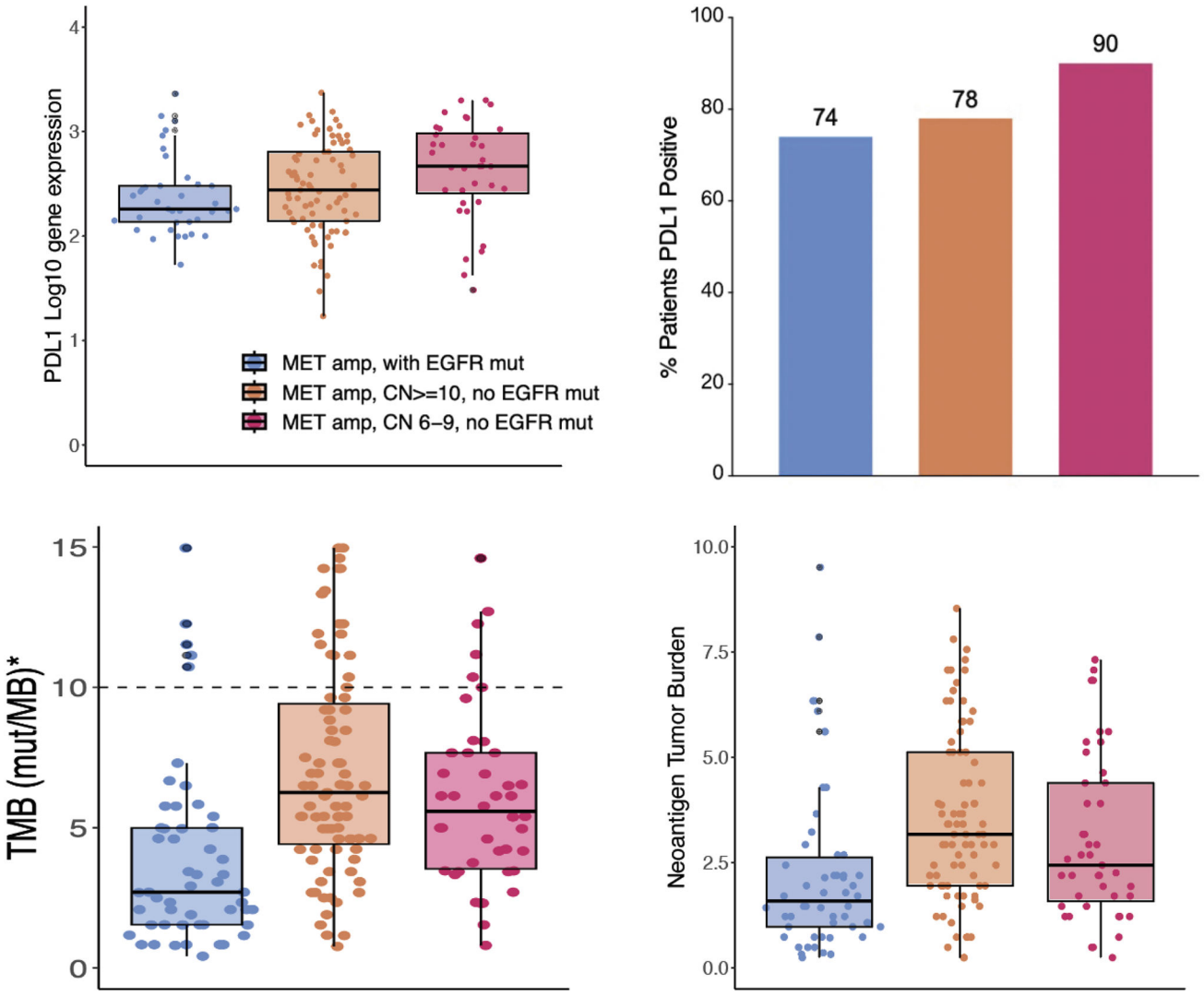

Figure 4.

Comparison of PD-L1 gene expression (top left), PD-L1 positivity rate (top right), TMB (bottom left), and Neoantigen tumor burden (bottom right) for patients with MET amplification and EGFR alteration (N= 23), high MET amplification and EGFR wild type (N = 69), and low MET amplification and EGFR wild type (N= 30). Dashed line indicator for cut off for high TMB. CN = copy number; PD-L1 = programmed death-ligand 1; TMB = tumor mutation burden.

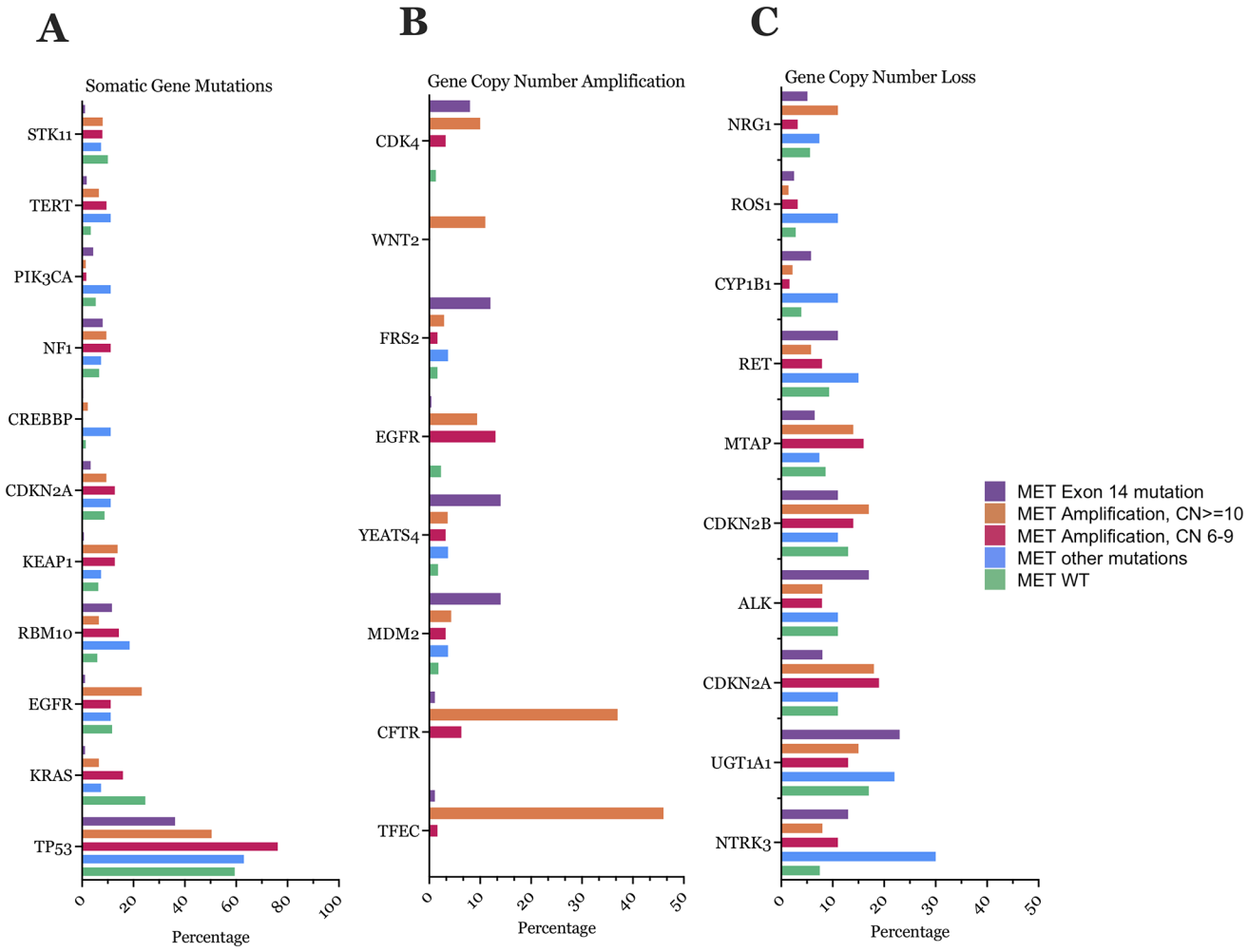

Figure 5.

Somatic co-mutational landscape (A), gene copy number amplifications (B), and gene copy number loss (C) between groups. Somatic alterations include short variant pathogenic/likely pathogenic mutation and copy number alterations (loss or amplification, copy number 0 or ≥ 10 respectively). The figure is only showing significant gene alteration differences between the five groups and found to be 10% of patients or more.

Table 1.

Patient Characteristics of the 18,047 Non-small Cell Lung Tumors

Characteristic	MET Exon 14 mutation, (N = 276)	High MET Amplification, (N = 138)	Low MET Amplification, (N = 63)	MET other mutations, (N = 27)	MET WT, (N = 17,543)
Age at Diagnosis					
Median (IQR)	76 (70, 81)	66 (59, 73)	67 (62, 72)	77 (67, 82)	68 (61, 75)
Gender					
Male	110 (40%)	78 (57%)	33 (52%)	18 (67%)	8,795 (50%)
Female	166 (60%)	60 (43%)	30 (48%)	9 (33%)	8,748 (50%)
Race					
White	154 (55%)	71 (51%)	36 (57%)	15 (55%)	9,402 (54%)
Black or African-American	20 (7.2%)	10 (7.2%)	9 (14%)	3 (11%)	1,436 (8.2%)
Asian	10 (3.6%)	6 (4.3%)	4 (6.3%)	1 (3.7%)	488 (2.8%)
Other	5 (1.8%)	2 (1.4%)	0 (0%)	1 (3.7%)	513 (3.9%)
Unknown	87 (32%)	49 (36%)	14 (22%)	7 (26%)	5,704 (33%)
Ethnicity					
Not Hispanic or Latino	113 (41%)	50 (36%)	32 (51%)	12 (44%)	6,884 (39%)
Hispanic or Latino	5 (1.8%)	2 (1.4%)	2 (3.2%)	0 (0%)	440 (2.5%)
Unknown	158 (57%)	86 (62%)	29 (46%)	15 (56%)	10,219 (58%)
Smoker status					
Current/former smoker	160 (58%)	105 (76%)	52 (83%)	23 (85%)	13,301 (75%)
Never smoker	89 (32%)	18 (13%)	9 (14%)	2 (7.4%)	2,316 (13%)
Unknown	27(9.8%)	15 (11%)	2 (3.2%)	2 (7.4%)	1,926 (11%)
Histology					
Adenocarcinoma	201 (73%)	103 (75%)	52 (83%)	17 (63%)	11,286 (64%)
Squamous cell carcinoma	39 (14%)	14 (10%)	5 (7.9%)	4 (15%)	4,440 (25%)
Others	30 (11%)	18 (13%)	6 (9.5%)	5 (19%)	1,473 (8.4%)
Large cell	0 (0%)	2 (1.4%)	0 (0%)	1 (3.7%)	271 (1.5%)
Sarcomatoid	6 (2.2%)	1 (0.7%)	0 (0%)	0 (0%)	73 (0.4%)
Stage					
Stage 1	25 (9.1%)	5 (3.6%)	7 (11%)	1 (3.7%)	1,242 (7.1%)
Stage 2	16 (5.8%)	2 (1.4%)	1 (1.6%)	1 (3.7%)	977 (5.6%)
Stage 3	27 (9.8%)	13 (9.4%)	4 (6.3%)	5 (19%)	2,411 (14%)
Stage 4	123 (45%)	71 (51%)	39 (62%)	15 (56%)	8,347 (48%)
Unknown	85 (31%)	47 (34%)	12 (19%)	5 (19%)	4,566 (26%)