

ORIGINAL ARTICLE

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Real-world analysis of MET exon 14 mutations in non-small cell lung cancer: a retrospective study from two Swedish hospitals

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ABSTRACT

Background: Real-World evidence on mesenchymal-epithelial transition exon 14 skipping mutations (METex14) in lung cancer remains limited. With an incidence of 3–4% across histological subtypes, METex14 is now an actionable target for MET inhibitors (METi) in advanced lung cancer, demonstrating response rates between 30–70%. Yet, its role in early stages and sensitivity to immune checkpoint inhibitors (ICIs) is still under exploration.

Material and methods: We conducted a retrospective analysis of the clinical data of lung cancer patients presenting with METex14 across all stages. These patients were treated at two Swedish University Hospitals: Karolinska and Skåne, between the years 2014 and 2022.

Results: We identified a total of 63 patients, of which 50 met the inclusion criteria. The median overall survival (OS) with corresponding 95% confidence intervals (95% CI) according to the stage was not reached (NR) for stage I, NR for stage II, 15 months (95% CI, 5.4–24.6) for stage III, and 17 months (95% CI, 9.2–NR) for stage IV. The median OS for stage IV patients who received a METi was 17 months (95% CI, 9.5–NR) vs. 10 months (95% CI, 6.2–NR) in patients without METi ($p=0.92$; Hazard Ratio [HR] = 1.07). The median OS for stage IV patients who received ICIs was 18 months (95% CI, 16.5–NR) vs. 6 months (95% CI, 2.5–NR) in patients without ICIs ($p=0.15$; HR = 0.47). The median OS for stage IV patients who received chemotherapy was 17 months (95% CI, 9.7–NR) vs. 10 months (95% CI, 4.5–NR) in patients without ($p=0.97$; HR = 0.98).

Conclusions: Our data suggest limited survival benefits from METi, ICIs, and chemotherapy for METex14 lung cancer patients. While not statistically significant, these findings underscore the need for larger trials for validation. Identifying effective treatments for this challenging lung cancer subtype remains a priority.

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Introduction

Over the last decade, advances in genomic profiling have revealed novel druggable mutations in non-small cell lung cancer (NSCLC), such as *EGFR*, *KRAS*, *BRAF* mutations, *ALK*, *ROS1*, *RET* gene rearrangements, *ERBB2* (HER2) mutations, *NTRK* mutations and *MET* alterations, which include *MET* exon 14 skipping mutations (*METex14*) [1]. *METex14* involves the c-MET protein (c-Mesenchymal-Epithelial Transition Factor), a transmembrane receptor with tyrosine kinase activity [2]. The incidence of *METex14* varies across NSCLC histological subtypes: 3–4% in adenocarcinoma, 1–2% in squamous cell carcinoma [3], 0–0.2% in small cell lung cancer

[2,4], and up to 20–30% in pulmonary sarcomatoid carcinoma [3]. However, limited data exists for earlier stages, where Next Generation Sequencing (NGS) reflex testing is not yet clinical routine, hindering the assessment of its prognostic and predictive value.

Despite the emergence of tyrosine kinase inhibitors (TKIs) targeting *METex14*, challenges persist. Approximately 20% of advanced NSCLC patients treated with epidermal growth factor receptor (EGFR) TKIs develop *MET* gene amplifications as acquired resistance to treatment, compromising the effectiveness of EGFR-targeted therapy [2]. Intrinsic resistance to METi is estimated to be present in as high as one-third of patients [5]. Nevertheless, this underscores the potential of

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METi as a therapeutic avenue. Although *METex14* is considered an actionable driver mutation, primarily mutually exclusive with other drivers [4], clinical outcomes remain pessimistic. As a result, *METex14* remains an unfavorable prognostic factor, primarily due to its tendency for distant metastases [2]; overall response rates (ORR) vary from 30–70% [6].

Exploration of appropriate therapy for metastatic *METex14*-positive patients is underway, including prospective randomized trials investigating the efficacy of various novel TKIs. The phase 3 trial PROFILE 1001 assessed crizotinib in patients with various genetic variations, including *METex14* advanced lung cancer [7]. The study reported an ORR of 32% (95% confidence interval [CI], 21%–45%) and a median duration of response (mDOR) of 9.1 months (95% CI, 6.4 months–12.7 months).

Similarly, the phase 2 trial, VISION, evaluated tepotinib in *METex14* or *MET*-amplified advanced lung cancer [8]. Among the 99 evaluable patients with *METex14*, the ORR was 46% (95% CI, 36%–57%), with a median progression-free survival (PFS) of 8.5 months (95% CI, 6.7 months–11.0 months). In the *MET*-amplified cohort (24 patients), the ORR was 41.7% (95% CI, 22.1%–63.4%) and the median PFS was 4.2 months (95% CI, 1.4 months–15.6 months) [9]. Another phase 2 trial with a similar population, the GEOMETRY mono-1 trial, reported an ORR of 68% (95% CI, 48%–84%) and a mDOR of 12.6 months (95% CI, 5.6 months–not estimable) in the treatment-naïve population [10]. In the previously treated population, the ORR was 41% (95% CI, 29%–53%), and the mDOR was 9.7 months (95% CI, 5.6 months–13.0 months). Regulatory approval of tepotinib and capmatinib by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) has been granted based on these results. In addition, other *MET*-targeted treatments have shown clinical efficacy in various studies [2,10–12]. Nevertheless, compared to other targeted therapies in oncogene-driven lung cancers with ORRs consistently above 60% [13], the ORRs achieved with *METex14*-targeted therapies have been more modest.

Moreover, the intracranial efficacy of METi has been limited due to the poor blood-brain barrier penetration of certain agents like crizotinib, while capmatinib and tepotinib have demonstrated better intracranial activity [10,14]. However, these findings are based on subgroup analyses with a relatively small number of patients, and patients with brain metastases in the clinical trials have only been eligible if neurologically stable on symptomatic therapy with steroids or asymptomatic. This makes treatment decisions challenging for patients with brain metastases, where either METi or chemotherapy are treatment options [15]. The effectiveness of immune checkpoint inhibitors (ICIs) has also been investigated in *METex14*-positive NSCLC, although clinical outcomes have shown conflicting results despite high programmed death-ligand 1 (PD-L1) expression [16–19].

Overall, the selection of appropriate therapy for *METex14*-positive NSCLC patients remains a clinical challenge. Real-world insights into the effectiveness of therapies in this context are limited. To address this knowledge gap and better understand the unmet clinical needs of this patient

subgroup, we conducted a retrospective data analysis of patients across all clinical stages treated at two Swedish University Hospitals, namely Karolinska University Hospital and Skåne University Hospital, between 2014 and 2022.

Methods

Patient population/study design

We retrospectively collected clinical data of lung cancer patients across all clinical stages with *METex14* mutations treated at two Swedish University Hospitals, Karolinska University Hospital and Skåne University Hospital, between May 2014 until September 2022. We identified 63 patients, of which 50 met the inclusion criteria; 14 patients were treated at Karolinska University Hospital and 36 patients were treated at Skåne University Hospital. The study design is outlined in [Supplementary Figure 1](#). Patient information was gathered from electronic medical records. Inclusion criteria comprised cytologically or histologically verified lung cancer with *METex14* mutation and ≥ 18 years of age. We excluded patients with a diagnosis other than lung cancer and a lack of verified *METex14* mutation. All treatments were administered with standard doses and schedules according to international guidelines specific to the tumor type, stage, and based on clinical judgement by the treating physician. Our study was reviewed and approved by the ethical institutional review board (Dnr. 2016/2585-32/1, 2020-00256 and 2022-00483-02).

All patient materials were tested in clinically certified facilities. PD-L1 expression was assessed with immunohistochemistry, using the SP263-Ventana Assay (Roche Diagnostics) at the Karolinska University Hospital or the 22C3 Assay (Agilent/pharmDx) at Skåne University Hospital, respectively. Molecular genetic screening through NGS of DNA and RNA alterations in NSCLC samples was done using an S1 IonTorrent platform (Thermo Fisher Scientific), and the Oncomine Childhood Cancer Research Assay (OCA) at Karolinska University Hospital or the Oncomine Focus Assay (OFA) at Skåne University Hospital, respectively. Both the OCA and the OFA assays cover the *MET* gene on the DNA level to identify exon-junctional splice mutations, and the RNA level to detect alternate splicing of *MET*. *METex14* aberrations were classified as positive and reported if either a pathogenic splice mutation on the DNA level or a *MET* exon 13–15 splice variant was detected on the RNA level. Confirmation of *METex14* was also done in a subset of cases by NanoString sequencing (NanoString Technologies) or polymerase chain reaction (PCR) using the Idylla GeneFusion Assay (Biocartis).

The following covariates were analyzed: data on patients characteristics (age, gender, smoking status, performance status), disease characteristics (tumor histology, date of cancer diagnosis, confirmed *METex14* mutation with NGS), and treatment outcomes (including evaluation of surgical outcomes, radiotherapy, and/or systemic therapy) were retrospectively collected. The clinical stages were characterized according to the 8th edition of the TNM classification.

Outcome assessment

Radiological and clinical response evaluation was performed for patients treated with systemic therapies every three months and at each follow-up visit, respectively. DOR was defined as the duration of time of cancer response without relapse or disease progression. PFS was defined as the duration of time between treatment initiation and the development of disease progression or death. Disease progression was confirmed on planned radiological assessment or unplanned assessment after clinical deterioration observed by the treating physician, as well as overt clinical deterioration and/or death. OS was defined as the duration of time between date of diagnosis and death. Patients without disease progression or those who were alive at the time of data analysis were censored at the time of their last follow-up. Therapy response was only evaluated in the metastatic setting to avoid comparison between different stages of lung cancer, thereby avoiding an information bias (varying exposures between incomparable groups).

Statistical analysis

Descriptive statistics were used to analyze categorical and continuous variables. Statistical significance was set at $p < 0.05$ (two-sided test). The Kaplan-Meier (K-M) method was used to assess the effect of the studied variables on OS. The K-M curves were compared using the log-rank test. Patients who were alive at the time of data collection were treated as censored observations in the survival analysis. Cox regression was performed to estimate hazard ratios (HR) together with the 95% CI. Statistical analyses were performed using the SPSS version 28.00 software (IBM Corp. Armonk, NY, USA) and R version 4.3.0 software (Lucent Technologies).

Results

Patient characteristics

Patient characteristics are outlined in Table 1. Median follow-up time was 35.6 months. Mean age at diagnosis was

Table 1. Patient characteristics.

Patient Characteristics		N = 50
Mean age at diagnosis (range)		75 (47–90)
Gender (male)		20 (40%)
Smoking History	Never Smoker	17 (34%)
	Previous Smoker	30 (60%)
	Active Smoker	3 (6%)
	Adenocarcinoma	38 (76%)
Histology	Squamous Cell Carcinoma	5 (10%)
	Sarcomatoid Carcinoma/Features	3 (6%)
	NSCLC NOS/Poorly Differentiated	4 (8%)
	I	11 (22%)
Stage	II	5 (10%)
	III	7 (14%)
	IV	27 (54%)
Performance Status (ECOG)	0	23 (46%)
	1	19 (38%)
	2	5 (10%)
	3	1 (2%)
	Missing Data	2 (4%)
Brain Metastasis at Diagnosis		7 (14%)

Abbreviations: NSCLC: non-small cell lung cancer; NOS: not otherwise specified; ECOG: Eastern cooperative oncology group.

75 years. Most patients had adenocarcinoma (76%). There were 11 patients (22%) with stage I, five patients (10%) with stage II, seven patients (14%) with stage III, and 27 patients (54%) with stage IV disease. Brain metastases at diagnosis were present in seven patients (14%). Performance status (PS) was dominated by PS 0 (46%) and PS 1 (38%).

The tumor material used for *MET*ex14 analysis are summarized in Table 2. The genomic testing that identified the *MET*ex14 mutation was based on histological biopsies for 23 patients (46%), cytology in 25 patients (50%) and surgical resection material in two patients (4%). All cases were positive using NGS (100%), but samples were also tested using NanoString (18%) or PCR (2%). High PD-L1 status (PD-L1 $\geq$ 50%) was

Table 2. Description of pathology.

Pathology		N = 50
<i>MET</i> Mutation	<i>MET</i> ex14	48 (96%)
	Concomitant <i>MET</i> amp	2 (4%)
Other concomitant genetic aberrations*	Total	13 (26%)
	<i>MDM2</i> amplification	4 (8%)
	<i>TP53</i>	4 (8%)
	<i>GLI1</i> amplification	2 (4%)
	<i>CDK4</i> amplification	2 (4%)
	<i>EGFR</i> (probably not pathogenic)	1 (2%)
	<i>NF1</i>	1 (2%)
	<i>CCND1</i> amplification	1 (2%)
	<i>RB1</i>	1 (2%)
	<i>NOTCH1</i>	1 (2%)
	<i>HARS</i>	1 (2%)
	<i>KRAS</i> (amplification)	1 (2%)
	<i>MYC</i>	1 (2%)
	<i>FGFR4</i>	1 (2%)
	<i>ERBB3</i>	1 (2%)
	<i>ATRX</i>	1 (2%)
	<i>ALK</i>	1 (2%)
	Other <i>MET</i> mutation	1 (2%)
Type of Material for <i>MET</i> Analysis	Biopsy	23 (46%)
	Cytology	25 (50%)
	Surgery	2 (4%)
Assay for <i>MET</i> Analysis	NGS	50 (100%)
	PCR	1 (2%)
	Other (NanoString)	9 (18%)
PD-L1 Status	<1%	12 (24%)
	1–49%	10 (20%)
	$\geq$ 50%	22 (44%)
	Not Analyzed	6 (12%)

Abbreviations: *MET*ex14: *MET* exon 14 skipping mutations; *MDM2*: mouse double minute 2 homolog; *TP53*: tumor protein P53; *GLI1*: glioma-associated oncogene; *CDK4*: cyclin-dependent kinase 4; *EGFR*: epidermal growth factor receptor; *NF1*, Neurofibromin 1; *CCND1*, Cyclin D1; *RB1*, Retinoblastoma protein 1; *NOTCH1*: neurogenic locus notch homolog protein 1; *HARS*: histidyl-tRNA synthetase; *KRAS*: kirsten rat sarcoma virus; *FGFR4*: fibroblast growth factor receptor 4; *ERBB3*: ERB-B2 receptor tyrosine kinase 3; *ALK*: anaplastic lymphoma kinase; *MET*: mesenchymal-epithelial transition; *MET*amp: *MET* amplification; NGS: new generation sequencing; PCR: polymerase chain reaction, PD-L1: programmed death-ligand 1.

*Note that multiple mutations can be present in the same patient.

Table 3. Total lines of treatment.

Total Lines of Treatment		N = 50
All Lines of Treatment	0 (Curative Surgery/Radiotherapy)	14 (28%)
	0 (BSC)	11 (22%)
	1	12 (24%)
	2	9 (18%)
	3	2 (4%)
	4	1 (2%)
	5	1 (2%)

Abbreviations: BSC: best supportive care.

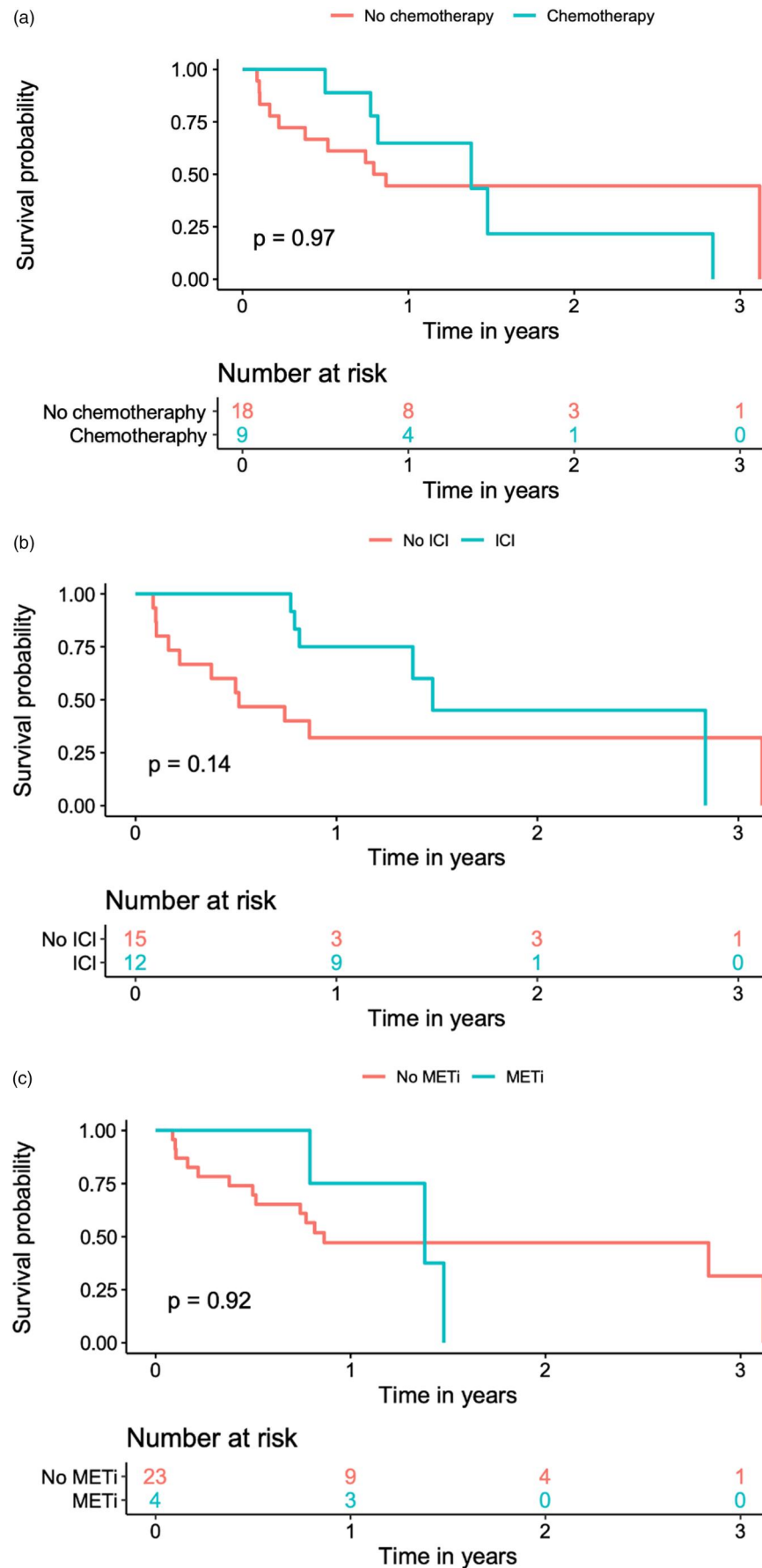


Figure 1. a: Kaplan-Meier Estimate of Overall Survival with Chemotherapy. b: Kaplan-Meier Estimate of Overall Survival with Immune checkpoint inhibitors. c: Kaplan-Meier Estimate of Overall Survival with MET Inhibitors. Abbreviations: ICI: immune checkpoint inhibitor. METi: MET inhibitor.

Table 4. Survival outcomes.

Survival outcomes		N = 50	N = 27
Death		26 (52%)	
Median OS by Stage	I	NR	
	II	NR	
	III	15 months (95% CI, 5.4–24.6)	
	IV	17 months (95% CI, 9.2–NR)	
Median OS (stage IV, Platinum-Based Regimen)	Overall		17 months (95% CI, 9.2–NR; $p = 0.97$; HR = 0.98).
	No Chemotherapy		10 months (95% CI, 4.5–NR)
Median OS (stage IV, ICI)	Chemotherapy		17 months (95% CI, 9.7–NR)
	Overall		17 months (95% CI, 9.2–NR; $p = 0.15$; HR = 0.47)
	No ICI		6 months (95% CI, 2.5–NR)
	ICI		18 months (95% CI, 16.5–NR)
Median OS (stage IV, METi)	Overall		17 months (95% CI, 9.2–NR; $p = 0.92$; HR = 1.07)
	No METi		10 months (95% CI, 6.2–NR)
	METi		17 months (95% CI, 9.5–NR)

Abbreviations: OS: overall survival; CI confidence interval; NR: not reached; HR: hazard ratio; ICI: immune checkpoint inhibitor; METi: MET inhibitor.

present in 22 patients (44%), 10 patients (20%) had PD-L1 1%–49% and 12 patients (24%) had PD-L1 < 1%.

A total of 25 patients (50%) received no systemic treatment (curative surgery/radiotherapy in 14 patients [28%] and best supportive care in 11 patients [22%]), 12 patients (24%) received first-line systemic therapy for advanced disease, nine patients (18%) received second-line therapy, and four patients (8%) received third line and beyond (Table 3). Platinum-based chemotherapy was administered in 20 patients (40%) with an ORR of 20% in the subset of patients with available response data ($N = 16$) (Supplementary Table 1). ICI was administered in 16 patients (32%) with an ORR of 12% in a subset of patients with available response data ($N = 14$) (Supplementary Table 2). METi was administered in 13 patients (26%); 8% received capmatinib and 18% received crizotinib. For patients with available response data ($N = 12$), 6% had partial response and 14% had stable disease (Supplementary Table 3).

Survival outcomes

K-M estimates of median OS with corresponding 95% CI according to stage were not reached (NR) for stage I, NR for stage II, 15 months (95% CI, 5.4–24.6) for stage III, and 17 months (95% CI, 9.2–NR) for stage IV. Systemic therapy evaluation was limited to stage IV patients to avoid comparison between lung cancer stages ($N = 27$). Median OS for stage IV patients who received platinum-based regimen was 17 months (95% CI, 9.7–NR) vs. 10 months (95% CI, 4.5–NR) in patients without chemotherapy ($p = 0.97$; HR = 0.98) (Figure 1a). Median OS for stage IV patients who received ICI was 18 months (95% CI, 16.5–NR) vs. 6 months (95% CI, 2.5–NR) in patients without ICI ($p = 0.14$; HR = 0.47) (Figure 1b). Median OS for stage IV patients who received a METi was 17 months (95% CI, 9.5–NR) vs. 10 months (95% CI, 6.2–NR) in patients without METi ($p = 0.92$; HR = 1.07) (Figure 1c, Table 4).

Discussion

There is a lack of real-world evidence describing lung cancer patients with *METex14* mutations in all clinical stages. We conducted a retrospective observational cohort study at two independent Swedish University Hospitals to provide further evaluation of this patient subgroup. Based on our results, the

OS advantage of METi, ICIs, and chemotherapy is limited for patients with advanced disease. Although our results did not achieve statistical significance, our study provides valuable insights into the treatment outcomes of this patient subgroup in everyday clinical practice, further emphasizing the unmet clinical needs in these patients.

The survival advantage of METi is currently being evaluated in clinical trials, with several small-molecule TKIs under investigation [4]. According to the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines, METi have been approved as first- (FDA) and second-line therapies (EMA) for patients with *METex14* lung cancer based on promising results from pivotal prospective clinical trials [4,19]. In contrast to these studies, our research was unable to provide evidence of prolonged OS with METi, which could be attributed, in part, to poorly characterized mechanisms of intrinsic or acquired resistance to METi. Therefore, gaining a further understanding of the molecular underpinnings of therapeutic sensitivity and resistance remains a primary objective in cancer care to optimize the efficacy of METi [13]. Moreover, it is worth noting that the patient characteristics in our study differ from those in prospective clinical trials, potentially influencing the treatment outcomes.

The close association between *METex14* splicing alterations and concomitant mutations in *MDM2*, *CDK4* and *TP53* has previously been reported [20], with similar observations in our cohort. On the contrary, concomitant mutations with other oncogenic drivers are almost mutually exclusive [21], which our study further validates. Regardless, it has been hypothesized that combination of METi with an added targeted therapy such as a CDK 4/6 or MDM2 inhibitor could prove useful in patients with *MDM2* or *CDK4* co-amplification [22], presenting an interesting avenue of research in the coming years.

Regarding ICIs, the evidence supporting their use in *METex14*-positive patients is limited and conflicting [16–18]. However, it has been observed that *METex14*-positive lung cancer often exhibits a high PD-L1 expression, which may be attributed to adaptive immune resistance and activated MET signaling, leading to the upregulation of various immune checkpoints through Janus Kinase 2 (JAK2)-independent pathways [8,23]. This rationale provides a basis for

considering the use of ICIs in this patient group. Nonetheless, PD-L1 expression does not appear to be a predictive biomarker in this setting [16,24]. Our study further contributed to the evidence that this type of oncogene-driven lung cancer does not result in improved OS, despite a high overall PD-L1 expression in our cohort (44% of patients had PD-L1 $\geq$ 50%).

Chemotherapy continues to be an important treatment strategy in *METex14*-positive cases [25], which our data also shows. Although METi is recommended as a first- (NCCN) and second line (ESMO) therapy, the treating physician should consider chemotherapy as part of the treatment arsenal [25]. Our results further reinforce the notion that *METex14* mutation is a poor prognostic factor due to its aggressive clinical trajectory and resistance to therapy.

The incidence of *METex14* mutations in earlier stages of lung cancer remains unclear due to a lack of diagnostic testing. Consequently, the role of therapy in the neoadjuvant and adjuvant settings is limited and remains an understudied area. A study by Schrock et al. provided a descriptive overview of the clinical and molecular characteristics of *METex14* mutations, analyzing genomic profiling data from 11,205 lung cancer patients, among whom 298 (2.7%) were found to be *METex14*-positive [26]. However, unlike our study, clinical response and follow-up data were not the focus and thus not provided.

To the best of our knowledge, this is the first study to comprehensively analyze lung cancer patients with *METex14* mutations across all stages and provide follow-up data in a real-world setting. Previous retrospective studies [16,17,24], prospective studies [10–13,21], as well as current guidelines [7,25] have primarily focused on therapeutic management in the metastatic setting, leaving the prognostic value of this established oncogenic driver in earlier stages uncertain.

However, it is important to acknowledge several limitations of our study. First, its retrospective design introduces inherent biases and limitations. Furthermore, reflex testing of *METex14* mutations has not been available for all patients, leading to limited data about this patient subgroup. In addition, not all patients received METi due to regulatory approval constraints, leading to a selection bias (heterogeneous population with a resultant immortal time bias) and a potential information bias. The small sample size of our study limits its internal validity and may contribute to the lack of statistical significance observed. Small retrospective cohort trials are prone to type 1 and type 2 errors, particularly type 2 errors, which are directly influenced by sample size. Although we included all eligible patients from two independent University Hospitals, larger prospective and observational trials are warranted to provide a more comprehensive overview of this patient subgroup and improve the external validity of our results.

Moving forward, the focus of future research should be on addressing these limitations and expanding our understanding of the optimal management of lung cancer patients with *METex14* mutations. Prospective studies with larger sample sizes and randomized designs are needed to confirm our findings and provide more robust evidence. Also, studies

are needed that include patient groups not usually included in prospective registration studies, including patients with active brain metastases, poorer PS or substantial comorbidities. Moreover, efforts should be directed toward elucidating the mechanisms of resistance to METi and identifying potential predictive biomarkers that can guide treatment decisions in this patient subgroup. In addition, investigating the role of *METex14* mutations and targeted therapies in the neoadjuvant and adjuvant settings is crucial to optimize treatment strategies and improve outcomes.

In conclusion, our study adds valuable real-world evidence regarding lung cancer patients with *METex14* mutations across all clinical stages. Despite limitations, we provide insights into the limited efficacy of METi and ICIs in this patient subgroup. Our findings emphasize the need for further research to enhance our understanding of the molecular mechanisms underlying therapeutic response and resistance, as well as the exploration of alternative treatment strategies. By addressing these challenges, we can strive to meet the unmet clinical needs of patients with *METex14*-positive lung cancer and improve their outcomes.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings in this study are available from the corresponding author, SE, upon reasonable request.

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