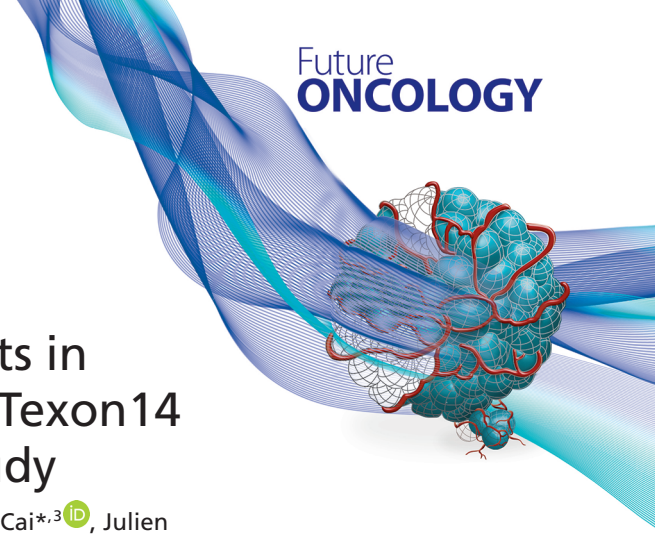
Short Communication

For reprint orders, please contact: reprints@futuremedicine.com

Future ONCOLOGY



Effectiveness of standard treatments in non-small-cell lung cancer with METexon14 skipping mutation: a real-world study

Muhammad Furqan[1], Siddharth Karanth[2], Ravi K Goyal[2], Beilei Cai*[,3], Julien Rombi[2], Keith L Davis[2], Nydia Caro[3] & Teddy Saliba[3]

[1]University of Iowa Hospitals & Clinics, Carver College of Medicine, Iowa City, IA 52242, USA

[2]RTI Health Solutions, Research Triangle Park, NC 27709, USA

[3]Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936, USA

*Author for correspondence: beilei.cai@novartis.com

Aim: To assess real-world clinical outcomes with standard therapies for advanced non-small-cell lung cancer (aNSCLC) with METexon14 skipping mutation (METex14). **Methods:** In an oncologists-led retrospective review of medical records, data were abstracted and analyzed for patients initiating first-line (1L) systemic therapy after 1 January 2017. **Results:** In total 287 aNSCLC patients with METex14, the real-world best overall response rate was 73.4% for capmatinib (n = 146), 68.8% for immunotherapy (IO) monotherapy (n = 48), 52.0% for chemotherapy (CT, n = 30), and 54.8% for IO + CT (n = 63). As compared with capmatinib, patients receiving IO (hazard ratio [HR]: 1.57; 95% CI: 0.77–3.20; p = 0.220), CT (HR: 2.41; 95% CI: 1.19–4.85; p = 0.014) and IO + CT (HR: 2.33; 95% CI: 1.35–4.04; p = 0.003) had higher rates of progression. Further, patients receiving CT (HR: 4.43; 95% CI: 1.54–12.75; p = 0.006) and IO + CT (HR: 3.53, 95% CI: 1.41-8.85; p = 0.007) had higher rates of mortality than patients receiving capmatinib. **Conclusion:** The study showed better clinical outcomes with capmatinib than other standard therapies in 1L setting for aNSCLC harboring METex14.

Plain language summary – Real-world study that investigated the outcomes of different therapies used to treat non-small-cell lung cancer patients with mesenchymal-epithelial transition exon 14 skipping mutation:

What is this article about?: A real-world study that investigated clinical outcomes in patients with diagnosis of advanced non-small-cell lung cancer (aNSCLC) with mesenchymal-epithelial transition exon 14 (METex14) skipping–a rare form of genetic mutation–who received treatment with one of the commonly used therapies for this disease: immunotherapy, chemotherapy, immunotherapy + chemotherapy combination and capmatinib, which is a highly selective inhibitor of MET tyrosine kinase protein involved in the growth of cancer cells.

What were the results?: The study showed that, in general, patients treated with capmatinib as the frontline therapy more frequently achieved a clinical response in the form of complete tumor resolution or tumor shrinkage, had a lower risk of disease worsening and lived longer than patients who were treated with immunotherapy, chemotherapy or immunotherapy + chemotherapy combination.

What do the results of the study mean?: This study suggests that capmatinib is effective in treating patients with aNSCLC with METex14 skipping who have not been treated with another anticancer therapy previously. It provides evidence to support the use of capmatinib in the frontline setting and may inform clinical decision-making in routine practice.

Tweetable abstract: This real-world study of clinical outcomes showed capmatinib to be effective in first-line treatment of patients with advanced/metastatic NSCLC with MET exon 14 skipping mutation.

First draft submitted: 11 December 2023; Accepted for publication: 6 March 2024; Published online: 17 April 2024

Keywords: capmatinib • medical chart review • non-small-cell lung cancer • real world evidence • treatment effectiveness

Taylor & Francis
Taylor & Francis Group

Lung cancer is the most common cause of cancer-related death in the USA [1]. Non-small-cell lung cancer (NSCLC) accounts for 81% of all lung cancers [2]. Mesenchymal–epithelial transition (MET) exon 14 skipping mutation (METex14) is present in 3–4% of NSCLC [3–5]. Overall, the 5-year survival for NSCLC is 26.4%; for stage IIIB, it is 17.3% and for stage IV, 5.8% [6].

Systemic therapies, such as immunotherapy (IO), chemotherapy and IO (CT + IO) and MET inhibitors (METis) are being used to treat advanced NSCLC (aNSCLC) with MET exon 14 (METex14) in the first-line (1L) setting. Program death-1 (PD1) or program death ligand-1 (PD-L1) antibodies inhibit the PD1/PD-L1 checkpoint and facilitate T-cell-mediated anticancer immune response. Nivolumab, pembrolizumab and atezolizumab are approved PD1/PD-L1 immune checkpoint inhibitors and are generally prescribed with or without CT for patients with aNSCLC. In 1L treatment, nivolumab and ipilimumab in combination with two cycles of CT showed better overall survival (OS) as compared with CT alone in the CheckMate 9LA trial (14.1 vs 10.7 months at interim analysis and 15.6 vs 10.9 months with longer follow-up time) [7]. Pembrolizumab in combination with CT in 1L showed improved OS (hazard ratio [HR]: 0.49; 95% CI, 0.38–0.64) and progression-free survival (PFS) (HR: 0.52; 95% CI: 0.43–0.64) as compared with CT and placebo in the KEYNOTE-189 trial [8]. Atezolizumab targets PD-L1 protein and when given in combination with bevacizumab and CT in 1L was shown to improve OS (19.2 vs 14.7 months) and PFS (8.3 vs 6.8 months) when compared with bevacizumab and CT [9].

Capmatinib, a tyrosine kinase inhibitor, was the first targeted therapy approved by the US FDA for METex14 patients with aNSCLC in May 2020. Its approval was based on the GEOMETRY Mono-1 trial in which treatment-naive patients had an overall response rate (ORR) of 68% (95% CI: 48–84%) and a median duration or response (mDOR) of 12.6 months (95% CI: 5.6–not estimable [NE]) [10], whereas patients who were previously treated with standard CT and/or IO had an ORR of 41% (95% CI: 29–53%) and an mDOR of 9.7 months (95% CI: 5.6–13) [10]. Recent data show that among patients who were treatment naive and those who were previously treated, capmatinib provided an ORR of 68% (95% CI: 55–80%) and 44% (95% CI: 34–54%) respectively, and an mDOR of 16.6 months (95% CI: 8.4–22.1) and 9.7 months (95% CI: 5.6–13.0), respectively [11].

Capmatinib has shown significant efficacy in clinical studies; however, data on capmatinib activity in comparison with other approved therapies, particularly from the real-world settings, are limited. Additionally, based on limited real-world studies, there is no apparent consensus regarding the benefit and treatment sequencing between capmatinib and IO and/or CT when treating patients with aNSCLC harboring METex14. We aimed to review medical records of patients with METex14 in aNSCLC or metastatic NSCLC (mNSCLC) treated with capmatinib, or IO and/or CT to assess real-world clinical outcomes at various sites in the USA.

Materials & methods

Study design

A retrospective, noninterventional cohort study of patients with a confirmed diagnosis of aNSCLC harboring METex14 was conducted. The study was determined to be not research involving human subjects by RTI International's institutional review board. Data were abstracted in October–November 2022 from patient medical records by US oncologists, recruited via a nationwide panel of physicians, using an electronic case report form. The participating oncologists were the primary decision-makers regarding treatment decisions for the patients in the study. The study included all patients who were aged ≥18 years at the time of aNSCLC diagnosis, had histologically confirmed stage IIIB, IIIC or IV NSCLC harboring METex14, had initiated 1L treatment for aNSCLC between 1 January 2017, and date of data abstraction along with ≥6 months of follow-up after the initiation of 1L treatment (exception for patients who died sooner) with one of the following treatment regimens: capmatinib; IO as monotherapy (e.g., atezolizumab, pembrolizumab); CT regimen, single agent or combinations of CT agents (e.g., platinum agents, taxane agents, gemcitabine, pemetrexed) and combination regimen containing IO and CT agents (IO + CT). Excluded patients who had targetable co-alterations in the *EGFR*, *ALK*, *BRAF*, *ROS1* or *RET* genes; received targeted therapy regimens for any actionable mutations other than METex14; received treatment with other METis (e.g., crizotinib or tepotinib) or MET-targeting antibodies (such as emibetuzumab) at any time during the study period; or participated in clinical trials related to treatment for NSCLC at any timepoint. To ensure adequate representation of capmatinib and other therapies (IO and/or CT) in the sample, soft quotas were applied, with 50% of the sample being assigned to capmatinib, 10% to CT and 20% each to IO monotherapy and IO + CT regimens. The study index date was defined as the date of the first systemic therapy initiation after

aNSCLC diagnosis. Patients' prior treatment for earlier stage NSCLC was captured up to 12 months before the index date. Patient demographics, genotype mutations and biopsy methods were collected at initial NSCLC diagnosis, while clinical characteristics including comorbidities, metastatic sites and performance status were collected at aNSCLC diagnosis. Treatment characteristics included all treatments following aNSCLC diagnosis.

Study outcomes

The study outcomes consisted of real-world ORR (rwORR; patients with complete or partial response), real-world disease control rate (rwDCR; patients with complete or partial response or stable disease), time to treatment discontinuation (TTD; time from treatment initiation to discontinuation or death whichever occurred earlier), real-world PFS (rwPFS; time from start of therapy until the earliest of a systemic disease progression or death) and OS (time from start of therapy until death). Patient clinical response to treatment was evaluated by participating physicians based on a modified Response Evaluation Criteria in Solid Tumors (pseudo-RECIST) criteria (Appendix B) [12–14]. The outcomes were assessed for each of the four treatment regimens by therapy line.

Statistical analysis

Demographics and clinical characteristics were analyzed descriptively, using median and quartiles for continuous variables and proportions for categorical variables. The differences among the four treatment regimens were analyzed using the Kruskal-Wallis test for continuous variables and a chi-square test or Fisher's exact test for categorical variables. The Kaplan–Meier method was used to estimate time to event measures: TTD, rwPFS and OS. Log rank test was used to analyze the differences in survival among the four treatment regimens.

To adjust for observed imbalances in baseline characteristics, a multivariable Cox proportional hazards (PH) regression analysis was performed for TTD, rwPFS and OS. The 1L treatment category (capmatinib [reference (ref)], IO monotherapy, CT, IO + CT) was the main independent variable of interest. The other variables included age at 1L treatment initiation; female; race-ethnicity; year of 1L treatment initiation; insurance type; healthcare setting; disease stage at 1L therapy initiation; metastatic sites, including bone metastasis, brain metastasis (BM), liver metastasis and all other sites of metastasis that included adrenal glands, contralateral lung, lymph nodes, pleural/pericardial fluid and other sites; National Cancer Institute (NCI) comorbidity score; Eastern Cooperative Oncology Group (ECOG) performance status; and method of biopsy for testing METex14. Patients whose performance status was determined using the Karnofsky performance scale were converted to ECOG before regression analysis [15]. Following an unadjusted analysis, a multivariable model with backward selection was constructed by enforcing the model to retain variables with p-value ≤ 0.15 [16]. Variables of specific clinical significance (i.e., age, female) were forced to be retained in the final model. Finally, the PH assumption was checked in all models. All analyses were conducted in SAS 9.4 (SAS Institute, Inc.), and significance was assumed at $p \leq 0.05$.

Results

Demographics & clinical characteristics

Two hundred eighty-seven patient medical records were reviewed, which showed that 146 patients received capmatinib, 48 received IO monotherapy, 30 received CT and 63 received IO + CT as their 1L for aNSCLC. Clinical characteristics of patients at baseline are shown in Table 1. The study population was approximately 71% male; 49.1% were Non-Hispanic White and 58.2% received care in a healthcare facility located in an urban area. The median duration of follow-up was 11 months from aNSCLC diagnosis and 10 months from the 1L therapy initiation. Most patients (63.1%) had stage IV NSCLC at 1L therapy initiation. Among metastatic sites involved at aNSCLC diagnosis, lymph nodes (66.2%), contralateral lung (27.5%), bones (25.8%) and liver (20.9%) were the most common sites. Additionally, BM was present in 23 patients (8%), of whom four had leptomeningeal disease. Hypertension (50.2%), chronic obstructive pulmonary disease (27.2%), depression (16.4%) and diabetes (16%) were the most common comorbid conditions present at the time of 1L therapy initiation. Nearly 28% had a history of tobacco use or smoking.

Treatment patterns & characteristics

Among treatments received in 1L, 146 patients (50.9%) received capmatinib, 84 patients (29.3%) received pembrolizumab alone (n = 41, 14.3%) or in combination with CT agents (n = 43, 15.0%), 42 patients (14.6%) received carboplatin containing regimens and 41 patients (14.3%) received cisplatin containing regimens (Ap-

10.2217/fon-2023-1064

Table 1. Patient demographics and clinical characteristics.

	Overall	Capmatinib	IO monotherapy	Chemotherapy alone	IO + chemotherapy
Total patients, n (%)	287 (100.0)	146 (100.0)	48 (100.0)	30 (100.0)	63 (100.0)
Age, median (range), y†	63.4 (28.4–83.9)	64.6 (40.9–82.0)	62.4 (28.4–82.8)	62.9 (46.5–83.9)	61.9 (34.7–80.7)
Female	83 (28.9)	46 (31.5)	14 (29.2)	4 (13.3)	19 (30.2)
Race-ethnicity, n (%)					
Non-Hispanic White	141 (49.1)	76 (52.1)	25 (52.1)	14 (46.7)	26 (41.3)
Non-Hispanic Black	77 (26.8)	42 (28.8)	5 (10.4)	10 (33.3)	20 (31.7)
Hispanic	27 (9.4)	4 (2.7)	9 (18.8)	3 (10.0)	11 (17.5)
Index year, n (%)					
2017–2020	54 (18.8)	15 (10.3)	8 (16.7)	11 (36.7)	20 (31.7)
2021	117 (40.8)	59 (40.4)	20 (41.7)	14 (46.7)	24 (38.1)
2022	116 (40.4)	72 (49.3)	20 (41.7)	5 (16.7)	19 (30.2)
Insurance status, n (%)					
Commercial/private insurance	133 (46.3)	71 (48.6)	26 (54.2)	14 (46.7)	22 (34.9)
Medicare	113 (39.4)	63 (43.2)	19 (39.6)	12 (40.0)	19 (30.2)
All other and don't know	41 (14.3)	12 (8.2)	3 (6.3)	4 (13.3)	22 (34.9)
Healthcare setting, n (%)					
Academic	145 (50.5)	60 (41.1)	22 (45.8)	16 (53.3)	47 (74.6)
Community	142 (49.5)	86 (58.9)	26 (54.2)	14 (46.7)	16 (25.4)
Geographic region of healthcare setting, n (%)					
Northeast	84 (29.3)	42 (28.8)	14 (29.2)	6 (20.0)	22 (34.9)
South	115 (40.1)	54 (37.0)	26 (54.2)	10 (33.3)	25 (39.7)
Midwest	65 (22.6)	42 (28.8)	8 (16.7)	8 (26.7)	7 (11.1)
West	23 (8.0)	8 (5.5)	0 (0.0)	6 (20.0)	9 (14.3)
Disease stage, n (%)					
Stage IIIB/IIIC	106 (36.9)	40 (27.4)	24 (50.0)	16 (53.3)	26 (41.3)
Stage IV	181 (63.1)	106 (72.6)	24 (50.0)	14 (46.7)	37 (58.7)
Brain metastasis at the time of advanced NSCLC diagnosis	15 (5.2)	9 (6.2)	1 (2.1)	0 (0.0)	5 (7.9)
ECOG, n (%)‡					
0	61 (21.3)	25 (17.1)	17 (35.4)	9 (30.0)	10 (15.9)
1	138 (48.1)	77 (52.7)	16 (33.3)	11 (36.7)	34 (54.0)
2 or 3	46 (16.0)	25 (17.1)	5 (10.4)	3 (10.0)	13 (20.6)
Not recorded/don't know	42 (14.6)	19 (13.0)	10 (20.8)	7 (23.3)	6 (9.5)
National Cancer Institute comorbidity score, median (range)	1.4 (0.0–9.4)	1.4 (0.0–9.4)	1.5 (0.0–6.1)	1.6 (0.0–5.9)	1.2 (0.0–6.2)

†Age at first-line therapy initiation for advanced NSCLC (index date).
‡0: Normal activity; 1: Symptoms demonstrated, but the patient remains ambulatory and able to perform self-care; 2: Ambulatory >50% of the time and requires occasional assistance; 3: Ambulatory <50% of the time and requires nursing care.
ECOG: Eastern Cooperative Oncology Group; IO: Immunotherapy; NSCLC: Non-small-cell lung cancer.

pendix A Table 1). The median time to initiation of first-line treatment was 4 weeks for capmatinib and 3 weeks for IO monotherapy, CT and IO + CT. Radiation therapy targeted at BM was received by eight patients with BM (34.8%).

Outcomes

The rwORR was highest for capmatinib (73.4%), followed by IO monotherapy (68.8%), IO + CT (54.8%) and CT (52.0%; Table 2). Similarly, rwDCR was highest for capmatinib (95.0%), followed by IO monotherapy (87.5%), CT (84%) and IO + CT (80.7%). The differences among the four treatment regimens on the rwORR and rwDCR measures were statistically significant.

Among patients receiving 1L therapy, 29% of those receiving capmatinib, 43% receiving IO, 94% receiving CT and 75% receiving IO + CT discontinued treatment. The median TTD from Kaplan–Meier analysis (Figure 1A)

Table 2. Outcomes of first-line systemic therapy.

	Capmatinib	IO monotherapy	Chemotherapy alone	IO + chemotherapy	p-value
Total patients, n (%)	146 (100.0)	48 (100.0)	30 (100.0)	63 (100.0)	
ORR, % (95% CI)[†]	73.4 (65.2–80.5)	68.8 (53.8–81.3)	52.0 (31.3–72.2)	54.8 (41.7–67.5)	0.027
Disease control rate, % (95% CI)[‡]	95.0 (89.9–98.0)	87.5 (74.8–95.3)	84.0 (63.9–95.5)	80.7 (68.6–89.6)	0.015
TTD, median (95% CI), months	19.1 (12.4–NE)	12.6 (9.0–NE)	5.5 (4.1–5.8)	8.8 (6.6–10.0)	<0.0001
Rate of patients on therapy, % (95% CI)					
At 6 months	86.3 (79.6–90.9)	81.3 (67.1–89.8)	23.3 (10.3–39.4)	71.4 (58.6–80.9)	
At 12 months	65.5 (54.3–74.6)	50.8 (27.6–70.0)	0.0 (NE)	33.7 (21.3–46.5)	
At 18 months	51.7 (35.9–65.5)	42.3 (19.1–64.0)	0.0 (NE)	16.4 (6.9–29.5)	
PFS, median (95% CI), months	NE	12.6 (11.1–NE)	10.1 (5.9–NE)	12.0 (9–12.6)	<0.0001
PFS rate, % (95% CI)					
At 6 months	89.7 (83.2–93.8)	88.7 (74.9–95.1)	70.0 (48.8–83.7)	82.2 (70.2–89.7)	
At 12 months	80.6 (70.6–87.4)	57.7 (30.9–77.3)	38.4 (17.9–58.7)	47.4 (32.5–60.9)	
At 18 months	68.0 (51.9–79.7)	48.1 (21.2–70.8)	38.4 (17.9–58.7)	29.9 (15.5–45.8)	
OS, median (95% CI), months	NE	NE (14.3–NE)	17.6 (10.9–NE)	29.9 (20.20–32.10)	0.003
OS rate, % (95% CI)					
At 6 months	97.2 (92.8–99.0)	100.0 (100.0–100.0)	96.6 (77.9–99.5)	96.8 (87.9–99.2)	
At 12 months	92.6 (84.9–96.5)	88.4 (66.9–96.3)	70.4 (47.1–84.9)	78.2 (63.7–87.5)	
At 18 months	92.6 (84.9–96.5)	77.4 (43.8–92.3)	48.3 (23.1–69.7)	69.3 (52.9–81.0)	

[†]Includes complete response and partial response.
[‡]Disease control rate includes complete response, partial response and stable disease.
IO: Immunotherapy; NE: Not estimable; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation.

was 19.1 months (95% CI: 12.4-NE) for capmatinib, 12.6 months (95% CI: 9-NE) for IO monotherapy, 5.5 months (95% CI: 4.1–5.8) for CT and 8.8 months (95% CI: 6.6–10) for IO + CT (Table 2). The outcomes of second-line systemic therapy by treatment categories are in Appendix A, Table 2. The unadjusted HRs of variables for 1L therapy are in Appendix A, Table 3. In the multivariable Cox PH analysis for TTD for the 1L therapy (Table 3), patients receiving CT (HR: 9.12; 95% CI: 5.26–15.79; $p < 0.0001$) and IO + CT (HR: 2.27; 95% CI: 1.46–3.54; $p < 0.001$) had higher rate of treatment discontinuation than those receiving capmatinib. Patients on Medicare as compared with commercial/private insurance (HR: 0.49; 95% CI: 0.30–0.79; $p = 0.003$) and patients with stage IV disease as compared with stage IIIB/IIIC (HR: 0.58; 95% CI: 0.40–0.84; $p = 0.003$) had lower rates of treatment discontinuation. Patients with ECOG scores of 1 (HR: 1.74; 95% CI: 1.06–2.84; $p = 0.027$) and 2/3 (HR: 2.70; 95% CI: 1.50–4.86; $p = 0.001$) had higher rates of treatment discontinuation than patients with an ECOG score of 0.The median systemic rwPFS was not reached for capmatinib therapy, while it was 12.6 months for IO monotherapy, 10.1 months for CT, and 12.0 months for IO + CT. Per Kaplan–Meier analysis, rwPFS rate at 18 months from 1L therapy initiation was 68% (95% CI: 51.9–79.7%) for capmatinib, 48.1% (95% CI: 21.2–70.8%) for IO monotherapy, 38.4% (95% CI: 17.9–58.7%) for CT and 29.9% (95% CI: 15.5–45.8%) for IO + CT (Figure 1B). The unadjusted difference in rwPFS was statistically significant among the four treatment regimens. In multivariable Cox PH analysis for the 1L therapy, patients receiving CT (HR: 2.41; 95% CI: 1.19–4.85; $p = 0.014$) and IO + CT (HR: 2.33; 95% CI: 1.35–4.04; $p = 0.003$) had significantly higher rates of progression than those receiving capmatinib; IO monotherapy (HR: 1.57; 95% CI: 0.77–3.20; $p = 0.220$) had a higher rate of progression than capmatinib, but the difference was not statistically significant (Table 3). Among other variables in the model, receiving care in the community or a nonacademic hospital had significantly lower rate of progression than care received in an academic or teaching hospital (HR: 0.56; 95% CI: 0.32–0.96; $p = 0.036$). The median OS was NE for patients receiving capmatinib and IO monotherapy regimens in 1L (Figure 1C), while it was 17.6 months for CT and 29.9 months for IO + CT. Kaplan–Meier analysis showed that at 18 months since 1L therapy initiation, the OS rate was 92.6% (95% CI: 84.9%–96.5%) for patients receiving capmatinib, 77.4% (95% CI: 43.8–92.3%) for IO monotherapy, 69.3% (95% CI: 52.9–81%) for IO + CT, and 48.3% (95% CI: 23.1–69.7%) for CT. The difference in OS was statistically significant among the four treatment regimens. The multivariable Cox PH analysis showed that patients receiving CT (HR: 4.43; 95% CI: 1.54–12.75; $p = 0.006$) and IO + CT (HR: 3.53, 95% CI: 1.41–8.85; $p = 0.007$) had a statistically significantly higher rate

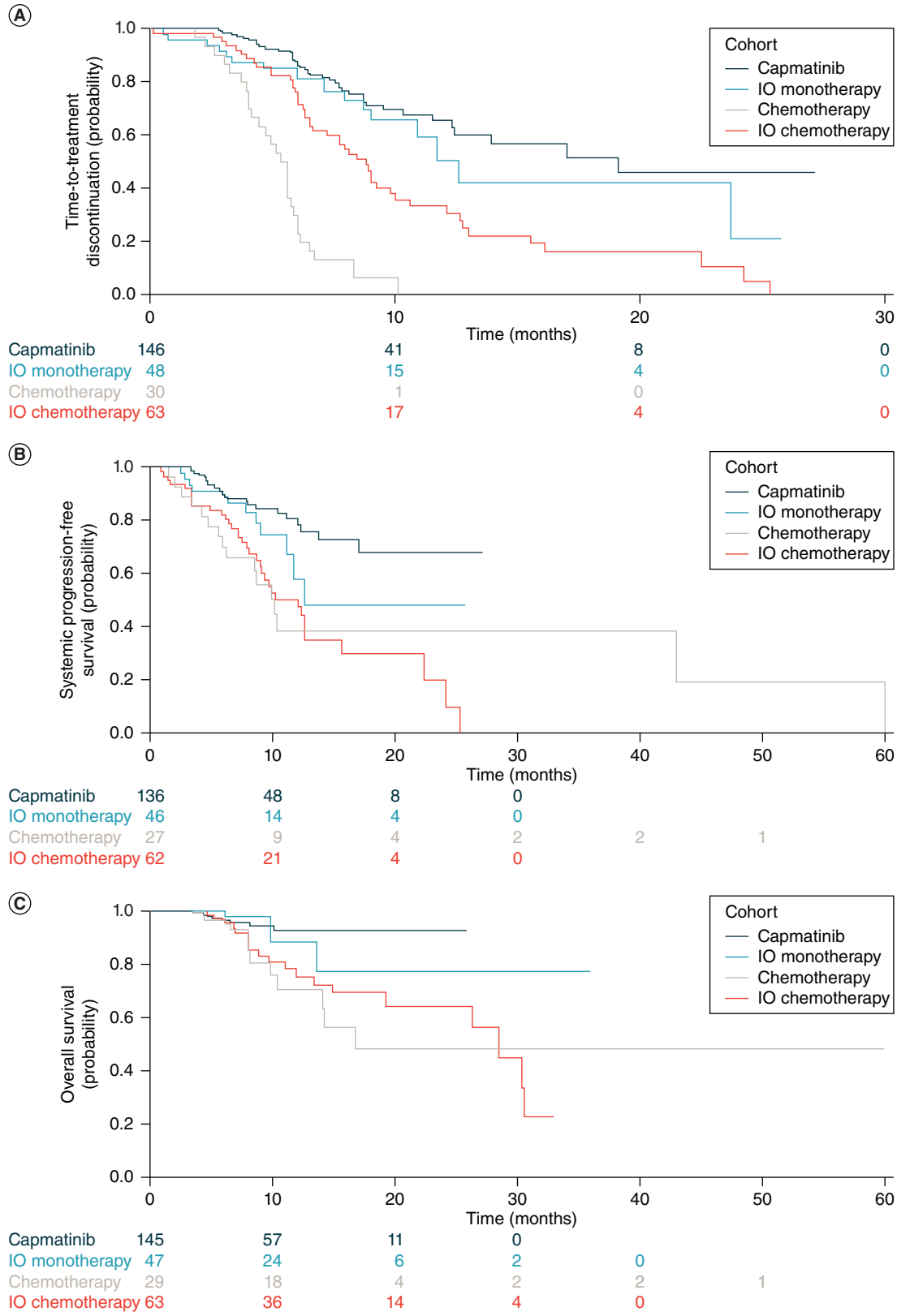


Figure 1. Treatment outcomes for first-line systemic therapy. (A) Time to treatment discontinuation, **(b)** systemic progression-free survival and **(c)** overall survival.
IO: Immunotherapy.

Table 3. Multivariable cox proportional hazards regression analysis of first-line systemic therapy outcomes†.

Variable	TTD		Systemic PFS		OS	
	HR (95% CI)	Pr >ChiSq	HR (95% CI)	Pr >ChiSq	HR (95% CI)	Pr >ChiSq
First-line therapy (reference: capmatinib)						
IO monotherapy	1.39 (0.78–2.48)	0.259	1.57 (0.77–3.20)	0.220	1.46 (0.40–5.29)	0.564
Chemotherapy alone	**9.12 (5.26–15.79)**	**<0.0001**	**2.41 (1.19–4.85)**	**0.014**	**4.43 (1.54–12.75)**	**0.006**
IO + chemotherapy	**2.27 (1.46–3.54)**	**0.000**	**2.33 (1.35–4.04)**	**0.003**	**3.53 (1.41–8.85)**	**0.007**
Age (continuous)	1.00 (0.98–1.02)	0.952	1.01 (0.98–1.03)	0.666	1.02 (0.98–1.06)	0.319
Female (reference: no)						
Yes	0.77 (0.51–1.15)	0.196	0.89 (0.55–1.45)	0.653	0.67 (0.30–1.46)	0.310
Index year (reference: 2017–2020)						
2021	1.31 (0.85–2.03)	0.218	N/A‡		0.72 (0.31–1.67)	0.445
2022	0.74 (0.42–1.31)	0.297			2.17 (0.68–6.94)	0.194
Insurance status (reference: commercial/private)						
Medicare	**0.49 (0.30–0.79)**	**0.003**	N/A‡		1.16 (0.47–2.86)	0.751
All other and don't know	0.86 (0.52–1.43)	0.569			**2.64 (1.08–6.49)**	**0.034**
Healthcare setting type (reference: academic or teaching hospital)						
Community or nonacademic hospital	N/A‡		**0.56 (0.32–0.96)**	**0.036**	N/A‡	
Disease stage (reference: stage IIIB/ IIIC)						
Stage IV	**0.58 (0.40–0.84)**	**0.003**	N/A‡		**3.92 (1.78–8.65)**	**0.001**
National Cancer Institute comorbidity score (reference: ≤1.35)						
>1.35	1.44 (0.99–2.09)	0.054	N/A‡		**2.34 (1.10–4.99)**	**0.027**
ECOG (reference: 0)						
1	**1.74 (1.06–2.84)**	**0.027**	0.96 (0.50–1.83)	0.892	3.10 (0.86–11.18)	0.083
2 or 3	**2.70 (1.50–4.86)**	**0.001**	2.05 (0.99–4.25)	0.054	**8.64 (2.31–32.41)**	**0.001**
Not recorded/don't know	1.13 (0.60–2.14)	0.708	0.73 (0.30–1.74)	0.475	**7.41 (1.80–30.50)**	**0.006**

Bold values indicate statistically significant results.
‡Variable was not retained in the final model estimated via backward selection process.
HR: Hazard ratio; N/A: Not applicable; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation.

of mortality than those receiving capmatinib, while IO monotherapy (HR: 1.46; 95% CI: 0.40–5.29; p = 0.564) had a numerical but not statistically significantly higher rate of mortality (Table 3). The multivariable model also showed that stage IV (HR: 3.92; 95% CI: 1.78–8.65; p = 0.001) patients had significantly higher rate of mortality than stage IIIB/IIIC. Similarly, patients with an NCI comorbidity score >1.35 (HR: 2.34; 95% CI: 1.10–4.99; p = 0.027) and ECOG score of 2/3 (HR: 8.64; 95% CI: 2.31–32.41; p = 0.001) had higher rate of mortality.

Discussion

This retrospective study provided insight into the real-world patient characteristics, treatment patterns, clinical outcomes and survival of patients diagnosed with aNSCLC/mNSCLC with METex14 who initiated treatment with capmatinib and other standard of care therapies in the USA. The study showed that capmatinib in aNSCLC with MET exon 14 had higher rwORR and longer TTD, rwPFS and OS compared with other standard of care therapies. Cox PH regression analyses further showed that after controlling for demographic and clinical characteristics, patients receiving CT alone or IO + CT had significantly higher rate of treatment discontinuation, disease progression and death than patients treated with 1L capmatinib for aNSCLC. Patients treated with 1L IO monotherapy agents had a numerically higher rate of treatment discontinuation, disease progression and death than patients treated with capmatinib, but this difference was not statistically significant, likely because of the smaller sample size of the IO monotherapy patients. Further, our data show that patients treated in the community or nonacademic hospitals had lower rate of progression than those treated in academic or teaching hospitals; this may be related to a possible concentration of sicker patients in academic hospitals [17] or to practice variations such

as a greater application of objective assessment criteria (hence more frequent CT scans, for instance) in academic hospitals [18].

The GEOMETRY mono-1 and VISION trials included treatment-naive and pretreated aNSCLC patients with METex14. Both capmatinib and tepotinib were effective in controlling cancer irrespective of line of therapy. However, outcomes were better for patients receiving capmatinib when they received it in the 1L setting compared with later lines. In the GEOMETRY mono-1 trial, ORR was 68% in treatment-naive patients, with a PFS of 12.4 months, whereas the ORR and PFS for patients receiving capmatinib as their second or later line of therapy were 41% and 5.4 months, respectively [10]. Capmatinib has also shown intracranial efficacy in the GEOMETRY Mono-1 trial, wherein of the 13 patients with BM, 12 (92%) had intracranial disease control and seven (54%) had an intracranial response [10]. However, the VISION trial did not show such difference in outcomes based on line of treatment [19]. Nonetheless, the FDA approved both of these drugs irrespective of line of therapy in aNSCLC with METex14, leaving treating providers the option to choose between IO alone or chemoimmunotherapy or targeted agents for their patients. In the absence of randomized data, it is difficult to conclude whether one option is better than the other. This is an important issue for patients with aNSCLC, as a significant proportion of these patients may not receive any subsequent line of systemic therapy [20,21]. In addition, prior studies have shown that immune checkpoint inhibitors have modest efficacy in this patient population who may often express high amount of PD-L1 [22].

Therefore, sequencing of effective therapy options is an important consideration when making treatment decisions. Few investigators did make an attempt to study this issue. For example, Lau SCM, Perdrizet K, Giffoni de Mello Morais Mata D *et al.* [23] reviewed the charts of 43 patients with aNSCLC with METex14. Those who received IO did better than those who received a METi (median OS: 48.3 vs 13.6 months); however, they did not control for other prognostic factors and most of the patients received older generations of MET tyrosine kinase inhibitors (crizotinib or cabozantinib [n = 17/18]) [23]. In contrast, a multicenter, retrospective analysis of 148 patients with NSCLC with METex14 reported significantly longer median OS in patients who ever initiated a METi (24.6 months) compared with patients who never used METis (8.1 months) [24]. A similar METi OS benefit was observed in a chart review study [25]. An external comparator study comparing 1L capmatinib clinical trial patients to real-world patients with NSCLC with METex14 in an oncology electronic health record database who received 1L CT or IO indicated that 1L capmatinib conferred longer PFS compared with 1L IO and/or CT (12.0 vs 6.2 months after weighting) [26]. A chart review of 70 patients with aNSCLC with METex14 reported that METi patients had better ORR than non-METi patients in the 1L setting (40.0 vs 23.1%); however, in the second-line setting, METi patients had a lower ORR than non-METi patients (25.0 vs 33.3%) [27]. A multicenter retrospective study of 81 patients with aNSCLC with METex14 from several countries showed that 37 patients who received capmatinib in 1L had an ORR of 68% and median PFS of 9.6 months [28]. Another recent chart review of 68 patients with NSCLC with METex14 and BM who were treated with capmatinib (any line) in routine practice, the systemic ORR and median PFS were 85.0% and 14.1 months, respectively, for 1L capmatinib [29]. Additionally, patients treated with 1L IO-containing regimen had a systemic ORR and median PFS of 66.7% and 7.5 months, respectively. That study also showed that capmatinib had intracranial efficacy (intracranial ORR: 87.3% for 1L) [29]. The current study provides further evidence that capmatinib yields better clinical outcomes than CT and IO + CT (and possibly also better than IO monotherapy) in patients with aNSCLC with METex14.

This study has some limitations. The data represent a sample of patients with aNSCLC/mNSCLC with METex14 from participating physicians, which may affect its generalizability to the broader population. Information on PD-L1 expression was not collected in the study, and patients with co-mutations such as *EGFR*, *ALK*, *ROS1*, *RET*, *NTRK*, *BRAF* or *KRAS* were excluded from the study. The study relied on participating physicians to provide data that were extracted only from the patient's medical records. The assessment of clinical response was not standardized; physicians may have used their clinical judgment, although they were encouraged to use pseudo-RECIST criteria. Also, there was insufficient follow-up to perform a detailed analysis of patients receiving capmatinib beyond 1L for aNSCLC.

Despite these limitations, given the rarity of aNSCLC cases with METex14s, a key strength of this study is that it is one of the first comparative studies across targeted therapy, IO regimen and chemotherapy regimens using a relatively large sample size of 287 patients. Further, due to the relatively larger sample size compared with a previous study by Paik *et al.* [29], this study was able to control for baseline differences using multivariable analyses, which offered a stronger validation of the results. This study assessed the therapeutic effectiveness among broader METex14 patients, while the previous study by Paik *et al.* [29] looked only at METex14 patients with BMs. Also,

this study's results are more informative to physicians who are looking for an optimal treatment choice among patients with METex14 NSCLC in the 1L setting.

Conclusion

This real-world study showed capmatinib to be effective in 1L treatment of patients with aNSCLC/mNSCLC with MET exon 14 skipping mutation. It provides evidence to support the use of capmatinib in this setting and may inform clinical decision-making in routine practice.

Summary points

- Capmatinib, a tyrosine kinase inhibitor, was the first targeted therapy approved by the US FDA for METex14 patients with advanced non-small-cell lung cancer (aNSCLC).
- Capmatinib has shown significant efficacy in clinical studies; however, data on capmatinib activity in comparison with other standard therapies when treating patients with aNSCLC harboring METex14, particularly from the real-world settings, are limited.
- This study conducted a medical record review to assess real-world clinical outcomes of patients with METex14 in aNSCLC treated with capmatinib, or immunotherapy (IO) and/or chemotherapy (CT) at various sites in the USA.
- Study reviewed 287 patient charts, of whom 146 patients received capmatinib, 48 received IO monotherapy, 30 received CT and 63 received IO + CT as their first-line (1L) for aNSCLC.
- The study population was approximately 71% male; 49.1% were Non-Hispanic White, with a median duration of follow-up of 11 months from aNSCLC diagnosis and 10 months from the 1L therapy initiation, and most patients (63.1%) had stage IV NSCLC at 1L therapy initiation.
- Capmatinib in aNSCLC with MET exon 14 had higher real-world overall response rate (73.4% [95% CI: 65.2–80.5%]) and longer time to treatment discontinuation (median- 19.1 months [95% CI: 12.4–not estimable (NE)]), real-world progression-free survival (Median–NE) and overall survival (Median–NE) compared with other standard of care therapies.
- Multivariable cox regression models indicated that after controlling for demographic and clinical characteristics, 1L CT and IO + CT versus capmatinib had significantly higher rates of treatment discontinuation, progression and mortality.
- This study provides evidence to support the use of capmatinib in 1L treatment of patients with aNSCLC/mNSCLC with MET exon 14 skipping mutation.

Author contributions

M Furqan: methodology, supervision. S Karanth: conceptualization, methodology, investigation, formal analysis, data curation, project administration. RK Goyal: conceptualization, methodology, investigation, formal analysis, data curation, project administration. B Cai: conceptualization, methodology, supervision. KL Davis: conceptualization, methodology, investigation, formal analysis. J Rombi: investigation, data curation, project administration. N Caro: conceptualization, methodology, supervision. TRS: conceptualization, methodology, supervision. All authors contributed to the writing of this manuscript.

Financial disclosure

Novartis Pharmaceuticals Corporation provided the financial support for the study. RTI Health Solutions, an independent nonprofit research organization, received funding under a research contract with Novartis Pharmaceuticals Corporation to conduct this study and provide publication support in the form of manuscript writing, styling, and submission. M Furqan is a full-time employee of University of Iowa Hospitals and Clinics; serves on advisory boards for AbbVie, Pfizer, AstraZeneca, Beigene, Mirati; is a consultant for Novartis and Omega Therapeutics; and has received clinical research funding (institutional) from AbbVie, Amgen, Aprea, AstraZeneca, Beigene, Bristol Meyer, Elicio, GSK, Genmab, Gilead, Genentech, Immunocore, Inbrix, Incyte, Jacobio, Lilly, Merck, Mirati, Novartis, Poseida, Pfizer, Sophia Deep and Tempus. S Karanth, RK Goyal, J Rombi and KL Davis are full-time employees of RTI Health Solutions, an independent nonprofit research organization, which was retained by Novartis Pharmaceuticals Corporation to conduct the research that is the subject of this manuscript. Their compensation is unconnected to the studies on which they work. B Cai, N Caro and T Saliba are employees of and stock/shareholders in Novartis Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

The authors would like to thank John Forbes of RTI Health Solutions for editing assistance. Novartis Pharmaceuticals Corporation provided funding for publication support in the form of grammar and spelling checks, reference formatting and styling.

Ethical conduct of research

RTI International's institutional review board reviewed the study and determined that the study was not research involving human subjects (RTI IRB ID for the study: STUDY00022147). Due to the retrospective design of the study, and RTI IRB determination for the study, written informed consent was not required.

Data sharing statement

Data will be made available upon reasonable request. Please contact Ravi Goyal at rgoyal@rti.org.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J. Clin.* 73(1), 17–48 (2023).
2. American Cancer Society. Cancer facts & figures 2023 (2023). www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf
3. Frampton GM, Ali SM, Rosenzweig M *et al.* Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. *Cancer Discov.* 5(8), 850–859 (2015).
4. Hong L, Zhang J, Heymach JV, Le X. Current and future treatment options for MET exon 14 skipping alterations in non-small-cell lung cancer. *Ther. Adv. Med. Oncol.* 13, 1758835921992976 (2021).
5. Tong JH, Yeung SF, Chan AW *et al.* MET amplification and exon 14 splice site mutation define unique molecular subgroups of non-small-cell lung carcinoma with poor prognosis. *Clin. Cancer Res.* 22(12), 3048–3056 (2016).
6. Ganti AK, Klein AB, Cotarla I, Seal B, Chou E. Update of incidence, prevalence, survival, and initial treatment in patients with non-small-cell lung cancer in the US. *JAMA Oncol.* 7(12), 1824–1832 (2021).
7. Paz-Ares L, Ciuleanu TE, Cobo M *et al.* First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, Phase III trial. *Lancet Oncol.* 22(2), 198–211 (2021).
8. Gandhi L, Rodriguez-Abreu D, Gadgeel S *et al.* Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N. Engl. J. Med.* 378(22), 2078–2092 (2018).
9. Socinski MA, Jotte RM, Cappuzzo F *et al.* Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N. Engl. J. Med.* 378(24), 2288–2301 (2018).
10. Wolf J, Seto T, Han JY *et al.* Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N. Engl. J. Med.* 383(10), 944–957 (2020).

•• **This paper is of considerable interest as it is based on GEOMETRY Mono-1 trial which led to Capmatinib's US FDA approval.**

11. Novartis Pharmaceuticals Corporation. Efficacy of TABRECTA (2023). www.hcp.novartis.com/products/tabrecta/met-exon-14-skipping-mutation-nsclc/efficacy/
12. Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* 45(2), 228–247 (2009).
13. Feinberg BA, Bharmal M, Klink AJ, Nabhan C, Phatak H. Using response evaluation criteria in solid tumors in real-world evidence cancer research. *Future Oncol.* 14(27), 2841–2848 (2018).
14. Izano MA, Tran N, Fu A *et al.* Implementing real-world RECIST-based tumor response assessment in patients with metastatic non-small-cell lung cancer. *Clin. Lung Cancer* 23(3), 191–194 (2022).
15. ESMO. Performance scales: Karnofsky & ECOG scores. https://oncologypro.esmo.org/oncology-in-practice/practice-tools/performance-scales
16. Butcher B, Smith BJ. Feature engineering and selection: a practical approach for predictive models. *Am. Statist.* 74(3), 308–309 (2020).
17. Ayanian JZ, Weissman JS. Teaching hospitals and quality of care: a review of the literature. *Milbank Q* 80(3), 569–593; v (2002).
18. Spinu-Popa EV, Cioni D, Neri E. Radiology reporting in oncology-oncologists' perspective. *Cancer Imag.* 21(1), 63 (2021).
19. Le X, Sakai H, Felip E *et al.* Tepotinib efficacy and safety in patients with MET exon 14 skipping NSCLC: outcomes in patient subgroups from the VISION study with relevance for clinical practice. *Clin. Cancer Res.* 28(6), 1117–1126 (2022).
20. Davies J, Patel M, Gridelli C, de Marinis F, Waterkamp D, McCusker ME. Real-world treatment patterns for patients receiving second-line and third-line treatment for advanced non-small-cell lung cancer: a systematic review of recently published studies. *PLOS ONE* 12(4), e0175679 (2017).

21. Lazzari C, Bulotta A, Ducceschi M *et al.* Historical evolution of second-line therapy in non-small-cell lung cancer. *Front. Med. (Lausanne)* 4, 4 (2017).

22. Sabari JK, Leonardi GC, Shu CA *et al.* PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. *Ann. Oncol.* 29(10), 2085–2091 (2018).

23. Lau SCM, Perdrizet K, Giffoni de Mello Morais Mata D *et al.* Sequencing of systemic therapies in advanced NSCLC with MET exon 14 skipping mutation: a multicenter experience. *J. Clin. Oncol.* 39, e21123–e21123 (2021).

• **The following references are of interest as they involved patients with non-small-cell lung cancer (NSCLC) with METex14.**

24. Awad MM, Leonardi GC, Kravets S *et al.* Impact of MET inhibitors on survival among patients with non-small-cell lung cancer harboring MET exon 14 mutations: a retrospective analysis. *Lung Cancer* 133, 96–102 (2019).

• **The following references are of interest as they involved patients with NSCLC with METex14.**

25. Wolf J, Baik C, Heist RS *et al.* Natural history, treatment (tx) patterns, and outcomes in MET dysregulated non-small-cell lung cancer (NSCLC) patients (pts). *Euro J. Cancer* 103, e23–e147 (2018).

• **The following references are of interest as they involved patients with NSCLC with METex14.**

26. Wolf J, Neal JW, Mansfield AS *et al.* 1346P Comparison of clinical outcomes of patients with METΔex14 NSCLC treated with first-line capmatinib in the GEOMETRY mono-1 study with those of a cohort of real-world patients. *Ann. Oncol.* 31, S863 (2020).

• **The following references are of interest as they involved patients with NSCLC with METex14.**

27. Bittoni M, Yang JC, Shih JY *et al.* Real-world insights into patients with advanced NSCLC and MET alterations. *Lung Cancer* 159, 96–106 (2021).

• **The following references are of interest as they involved patients with NSCLC with METex14.**

28. Illini O, Fabikan H, Swalduz A *et al.* Real-world experience with capmatinib in MET exon 14-mutated non-small-cell lung cancer (RECAP): a retrospective analysis from an early access program. *Ther. Adv. Med. Oncol.* 14, 17588359221103206 (2022).

29. Paik PK, Goyal RK, Cai B *et al.* Real-world outcomes in non-small-cell lung cancer patients with MET Exon 14 skipping mutation and brain metastases treated with capmatinib. *Future Oncol.* 19(3), 217–228 (2023).

•• **This is of considerable interest as this study was on a similar population METex14 NSCLC patients, but with brain metastasis.**