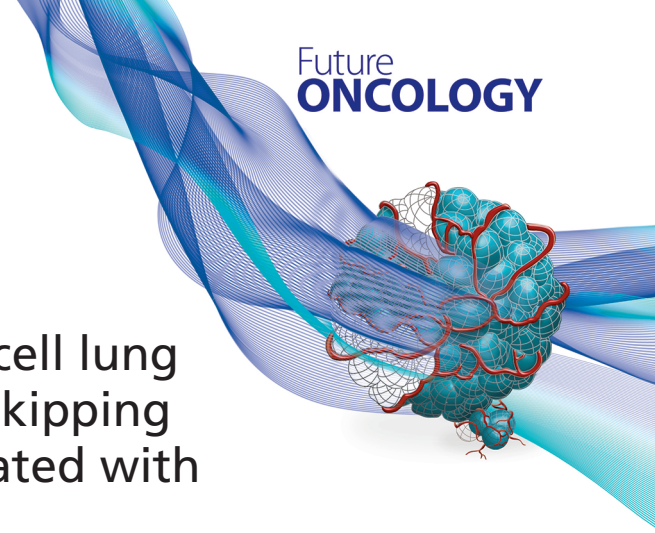
Short Communication

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



Real-world outcomes in non-small-cell lung cancer patients with MET Exon 14 skipping mutation and brain metastases treated with capmatinib

Paul K Paik[1,2], Ravi K Goyal*[,3], Beilei Cai[4], Mark A Price[3], Keith L Davis[3], Valerie Derrien Ansquer[3], Nydia Caro[4] & Teddy R Saliba[4]

[1]Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Manhattan, NY 10065, USA
[2]Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA
[3]RTI Health Solutions, 3040 E Cornwallis Road, Research Triangle Park, NC 27709, USA
[4]Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ 07936, USA
*Author for correspondence: rgoyal@rti.org

Aim: To assess real-world clinical outcomes in patients with non-small-cell lung cancer with MET exon 14 skipping mutation and brain metastases (BM) who received capmatinib, a recently approved MET inhibitor, in routine US clinical practice. **Materials & methods:** Patient data were collected using a retrospective medical record review, led by participating oncologists. Eligible patients initiated treatment with capmatinib in any line, after BM diagnosis, between May 2020 and June 2021. Data on real-world overall response rate (rwORR) and real-world progression-free survival (rwPFS) were descriptively analyzed. **Results:** 68 eligible patients were analyzed. In patients treated with first-line (1L) capmatinib (n = 55), the rwORR was 90.9% systemically and 87.3% intracranially; median systemic rwPFS was 14.1 months. Among radiation-naive patients on 1L capmatinib (n = 20), rwORR was 85.0%, both systemically and intracranially; median systemic rwPFS was 14.1 months. **Conclusion:** This study showed substantial systemic and intracranial effectiveness for capmatinib in real-world setting; findings were consistent for RT-naive patients.

Tweetable abstract: We evaluated #realworld outcomes for patients with #NSCLC with METex14 mutation and brain metastases, treated with capmatinib in clinical practice. We found substantial systemic and intracranial effectiveness with first-line capmatinib therapy.

First draft submitted: 14 November 2022; Accepted for publication: 11 January 2023; Published online: 7 February 2023

Keywords: brain metastases • capmatinib • medical chart review • non-small-cell lung cancer • treatment patterns

Lung cancer is the second leading cause of cancer worldwide and the leading cause of cancer death, accounting for over 2.2 million new cases and nearly 1.8 million deaths annually [1]. The 5-year survival rate for lung cancer in the United States is approximately 23% [1,2]. Non-small-cell lung cancer (NSCLC), the most common subtype, encompasses squamous cell carcinoma, large-cell carcinoma and adenocarcinoma and makes up 80–85% of lung cancer cases [3]. NSCLC is an aggressive disease, with poor prognosis and high likelihood of brain metastases (BM). As many as 20% of patients with NSCLC present with BM at their initial cancer diagnosis, and up to 50% of patients with NSCLC will develop BM over the course of the disease [4]. Median overall survival (OS) for patients with NSCLC with BM is low, ranging from 3 to 15 months, in part due to limited effective treatments [4]. Because many traditional cancer treatments cannot cross the blood–brain barrier and surgery may not be an option for all patients with BM, radiation therapy (RT) is commonly used to treat BM in patients with NSCLC [4].

In recent years, MET tyrosine kinase activity has been associated with oncogenesis and poor prognosis in patients with NSCLC, particularly aberrant MET activity that arises due to exon 14 skipping mutations [5,6]. Exon 14 deletion in *MET* transcription produces a highly active and dysregulated form of MET that is unique from other

mutated forms. MET exon 14 skipping mutations occur in 1–6% of patients with NSCLC and are a unique, druggable target [7,8]. Capmatinib, a small-molecule inhibitor of MET receptor, has been used to target MET exon 14 skipping mutations [5]. Clinical trial data also indicate that capmatinib is capable of crossing the blood–brain barrier [7–10]. The GEOMETRY mono-1 clinical trial is a currently active study aimed at evaluating the efficacy of capmatinib in patients with MET exon 14 skipping mutations. An *ad hoc* analysis of GEOMETRY mono-1 data indicated intracranial efficacy in patients with NSCLC with BM. Of the 13 patients with BM enrolled in the GEOMETRY mono-1 trial, seven had intracranial responses to capmatinib, including four patients who had complete resolution of all brain lesions; three of the patients with intracranial responses had prior RT [7]. In this same group, 12 of 13 patients had intracranial disease control. However, this subgroup was small, and limited conclusion could be drawn from this small cohort alone.

Capmatinib received accelerated approval by the US FDA in May 2020 for patients with metastatic NSCLC (mNSCLC) with MET exon 14 skipping mutations. This study was developed to assess the real-world intracranial efficacy of capmatinib in patients with NSCLC and BM in light of the promising data from GEOMETRY mono-1. Using data from patients across the US who received capmatinib to treat mNSCLC, we sought to determine the best overall response rate (ORR) systemically and intracranially as well as the duration of response, time-to-treatment-discontinuation (TTD), disease control rate (DCR), and progression-free survival (PFS) in a routine clinical practice setting. Because the real-world practice setting can vary distinctly from the environment of a clinical trial, which has rigorous selection standards and optimal treatment conditions, it is important to assess clinical outcomes for real-world use of capmatinib, especially for patients with BM, who are often underrepresented in clinical trials [11,12].

Materials & methods

Study design

This was a retrospective, noninterventional cohort study of patients with a confirmed diagnosis of mNSCLC with MET exon 14 skipping mutation and BM who received treatment with capmatinib in any line in real-world practice settings. This study was deemed 'not research involving human subjects' by the Research Triangle Institute Institutional Review Board.

The study population consisted of patients with mNSCLC with MET exon 14 skipping mutations. The date of the initiation of therapy with capmatinib after the date of initial BM diagnosis at or after the initial advanced or mNSCLC diagnosis defined the study index date. The 12-month period before the study index date defined the baseline period during which baseline demographic and clinical characteristics were assessed. The index date needed to occur between 1 May 2020 (to align with the capmatinib approval) and the date of data abstraction, provided the selected patients met the requirement of a minimum of 6 months' follow-up time available after capmatinib initiation; the exceptions to this were those patients who died during this period. Supplementary Figure 1 presents a graphical overview of the study design.

Participants were included in this study if they were 18 years old or older and received capmatinib, in any line, after diagnosis with BM; they were also required to have histologically confirmed stage IIIB, IIIC or IV NSCLC with MET exon 14 skipping mutation and at least one measurable intracranial lesion at or after the initial BM diagnosis. Mutation testing was recorded by patients' physicians as documented in the medical records; methods used for the testing, however, were not captured in our data abstraction. Any patients with characterized EGFR or anaplastic lymphoma kinase (ALK) mutations or other actionable molecular alterations who might be candidates to receive alternative targeted therapies were excluded.

Data for this study were abstracted from patient medical records by physicians using a secure, online case report form. Eligible physicians specialized in hematology–oncology, medical or clinical oncology, or pulmonology; had at least 2 years' experience managing care for patients with NSCLC; treated at least five patients with NSCLC over the 12 months prior to data abstraction; and spent at least 60% of their time in patient care.

Study outcomes

Patient demographic and clinical characteristics at the study index date were gathered and analyzed. The following measures were used in this study: TTD, the number of months from treatment initiation until discontinuation or death; real-world best ORR, the proportion of patients with partial or complete responses to therapy; the real-world DCR, the proportion of patients with a complete response, partial response, or stable disease; and real-world PFS (rwPFS) and OS, in months, for each line of therapy to assess the effectiveness of treatments for NSCLC with BM.

Real-world PFS was defined as the time in months from the start of therapy to the earliest occurrence of a clinically documented disease progression or death. Patients without a progression event or death were censored at last follow-up. Systemic and intracranial clinical response were measured using the modified Response Evaluation Criteria in Solid Tumors [13] (pseudo-RECIST) (Appendix A) and the modified Response Assessment in Neuro-Oncology Criteria for BM (pseudo-RANO-BM) [14] (Appendix B) measures, respectively, or using healthcare professional assessment based on the information in patient charts. The pseudo-RECIST and pseudo-RANO-BM measures were adapted for use in real-world settings [15,16] and were applied to this study in consultation with oncologists.

Statistical analysis

Analyses were primarily descriptive and exploratory in nature. Descriptive analyses involved generation of univariate statistics, including mean, median, standard deviation, and range for continuous variables and frequency distributions for categorical variables. Study end points were analyzed by treatment regimen (capmatinib or immuno-oncology [IO]-containing therapy), and data were presented overall (any line) and by line of therapy (first line and second line). All event-time end points (including TTD, intracranial rwPFS, and real-world duration of response [rwDOR]) were analyzed using the Kaplan–Meier method. Median time to event was estimated along with 95% CIs; log-rank test was used to assess for differences between subgroups. Unadjusted differences in outcomes by treatment type (capmatinib vs IO-containing therapy) should be interpreted with caution, as these groups are not independent by design (i.e., all patients treated with an IO-containing regimen in the first line had to remain alive and have advanced to the next line of therapy to receive capmatinib). Additionally, patient characteristics and outcomes were stratified by BM presentation at initial diagnosis of BM (symptomatic vs asymptomatic). Furthermore, a subgroup analysis was performed to examine treatment discontinuation and clinical outcomes among RT-naive patients. Patients were defined as 'RT naive' if they did not receive any RT before or concurrent with the therapy line.

All analyses were conducted using SAS Studio Enterprise edition (SAS Institute, Inc).

Results

Patient demographics & clinical characteristics

Medical records were abstracted for a total of 68 patients. The median age of the study sample at capmatinib initiation was 64.6 years (range, 47.4–79.3) (Table 1). Most patients were male (n = 41, 60.3%), White (n = 54, 79.4%), and non-Hispanic (n = 55, 80.9%). Most patients were treated in an academic setting (n = 49, 72.1%). Approximately two-thirds (n = 45, 66.2%) of the patients initiated capmatinib therapy in the calendar year 2021. The median duration of follow-up was 10.3 months from the initial NSCLC diagnosis and 8.2 months from the initiation of capmatinib therapy.

Approximately 93% of all patients were diagnosed with advanced (stage IIIB) or metastatic (stage IV) disease at the time of initial NSCLC diagnosis. At the time of first BM diagnosis, the majority of patients had a symptomatic presentation (n = 39, 57.4%), and the median number of measurable intracranial legions was two (range, 1–12). Most patients (n = 62, 91.2%) had no recorded history of smoking, while only 1.5% (n = 1) were current smokers and 7.4% (n = 5) were former smokers at the time of capmatinib initiation.

Treatment characteristics

All patients received at least one line of systemic therapy for metastatic disease. The median number of total therapy lines received was one (range, 1–3). Three-fourths (n = 51, 75%) of patients received only one line of therapy, 22.1% (n = 15) received two lines, and 2.9% (n = 2) received three lines (Table 2).

Radiation therapy targeted at BM was received by 64.7% of the patients (n = 44). Among those who received RT, the most common reasons for prescribing it were reported to be palliative intent (n = 31, 66%) and tumor cell reduction (n = 24, 51.1%). At the first line, 29 patients (42.6%) were RT naive (n = 20 for first-line capmatinib and n = 9 for first-line IO-containing therapy).

For the first-line therapy after BM diagnosis, 80.9% (n = 55) received capmatinib, 16.2% (n = 11) received IO-containing regimens (pembrolizumab [n = 8] and durvalumab [n = 3] alone or in combination with chemotherapy), and 2.9% (n = 2) received chemotherapy alone. A total of 17 patients (25%) received a second line of therapy; of these, 76.5% (n = 13) received capmatinib and the remaining (23.5% [n = 4]) received an IO-containing regimen. Only two patients received one third line of therapy. In the RT-naive subgroup, 29 patients received first-line therapy (n = 20, capmatinib; n = 9, IO-containing therapy) and six patients received a second-line therapy with

Table 1. Patient demographics and clinical characteristics.

	Overall sample
Total patients, n (%)	68 (100)
Age at advanced/metastatic NSCLC diagnosis, median (range), y	64.2 (47.3–79.3)
Disease stage at initial NSCLC diagnosis, n (%)	
Stage II	3 (4.4)
Stage IIIA	2 (2.9)
Stage IIIB	6 (8.8)
Stage IV	57 (83.8)
Age at BM diagnosis, median (range), y	64.3 (47.4–79.3)
Age at capmatinib initiation, median (range), y	64.6 (47.4–79.3)
Sex, n (%)	
Female	27 (39.7)
Male	41 (60.3)
Predominant race, n (%)	
Asian, Native Hawaiian, or Other Pacific Islander	5 (7.4)
Black/African–American	9 (13.2)
White	54 (79.4)
Treatment setting, n (%)	
Academic or teaching hospital	49 (72.1)
Community or nonacademic hospital	19 (27.9)
Charlson Comorbidity Index score, mean (SD)	1.3 (1.0)
Comorbidities, n (%)	
Chronic obstructive pulmonary disease	13 (19.1)
Depression	11 (16.2)
Diabetes	11 (16.2)
Hypertension	35 (51.5)
Smoking status at capmatinib initiation, among those with history of smoking, n (%)	
Current smoker	1 (1.5)
Former smoker	5 (7.4)
Unknown (no recorded history of smoking)	62 (91.2)
Presentation of BM at BM diagnosis, n (%)	
Asymptomatic	28 (41.2)
Symptomatic	39 (57.4)
Unknown	1 (1.5)
No. of measurable (≥10 mm) intracranial lesions recorded at BM diagnosis, median (range)	2 (1–12)
Metastatic site(s) involved (other than the brain) at capmatinib initiation (index date), n (%)	
Adrenal glands	14 (20.6)
Bones	32 (47.1)
Liver	20 (29.4)
Lungs	35 (51.5)
Pleural/pericardial fluid	6 (8.8)
Lymph nodes	24 (35.3)
None	3 (4.4)
Diagnosis of COVID-19/SARS-CoV-2	
Yes – before initiating capmatinib	7 (10.3)
Yes – after initiating capmatinib	2 (2.9)
No	54 (79.4)
Unknown	5 (7.4)

BM: Brain metastases; NSCLC: Non-small-cell lung cancer; SD: Standard deviation.

Table 2. Anticancer therapies received after metastatic NSCLC diagnosis.

	Value
Total patients, N (%)	68 (100.0)
No. of systemic therapy lines received after diagnosis of advanced or metastatic NSCLC, median (range)	1 (1–3)
Type of systemic therapy regimen (any line), n (%)	
Capmatinib	68 (100.0)
Pembrolizumab	8 (11.8)
Durvalumab	3 (4.4)
Carboplatin + paclitaxel + pembrolizumab	2 (2.9)
Carboplatin + pembrolizumab + pemetrexed	2 (2.9)
Bevacizumab + carboplatin + paclitaxel	1 (1.5)
Carboplatin + paclitaxel	1 (1.5)
Carboplatin + pemetrexed	1 (1.5)
Cisplatin + pemetrexed	1 (1.5)
Composition of first-line regimens, n (%)	
Capmatinib	55 (80.9)
Pembrolizumab (monotherapy or combination)	8 (11.8)
Durvalumab monotherapy	3 (4.4)
Other	2 (2.9)
Total patients who received second-line therapy, n	17
Composition of second-line regimens, n (%)	
Capmatinib	13 (76.5)
Pembrolizumab	2 (11.8)
Carboplatin + paclitaxel + pembrolizumab	1 (5.9)
Carboplatin + pembrolizumab + pemetrexed	1 (5.9)
Total patients who received third-line therapy, n	2
Composition of third-line regimens	
Bevacizumab + carboplatin + paclitaxel	1 (50)
Carboplatin + pemetrexed	1 (50)
Received radiation therapy targeted at the BM, n (%)	
Yes (≥1 administration at any time after BM diagnosis)	44 (64.7)
No	24 (35.3)
Types of radiation therapy received, n (%)	
External beam radiation	7 (14.9)
SRT	7 (14.9)
WBRT	8 (17.0)
SRS	20 (42.6)
iMRT	3 (6.4)
Gamma knife	2 (4.3)

BM: Brain metastases; iMRT: intensity-modulated radiation therapy; NSCLC: Non-small-cell lung cancer; SRS: Stereotactic radiosurgery; SRT: stereotactic radiation therapy, WBRT: whole brain radiation therapy.

capmatinib; no patient was treated with IO-containing therapy in the second line. The median time to initiate first-line therapy following mNSCLC diagnosis was 0.7 months (range, 0.1–6.0). The median time to initiate second-line therapy following mNSCLC diagnosis was 6.9 months (range, 1.4–34.7).

Time-to-treatment-discontinuation

For patients receiving capmatinib, treatment discontinuation was observed in 18.2% (n = 10) for the first line and 23.1% (n = 3) for the second line. The majority of treatment discontinuation was due to disease progression (n = 9, 90%). From Kaplan–Meier analyses, the estimated median TTD was 13.2 months (95% CI, 13.2-not estimable [NE]) for first-line capmatinib therapy (Figure 1A). Of patients treated with capmatinib in the first line, an estimated 73.6% were still on therapy at 12 months after treatment initiation. For patients who received

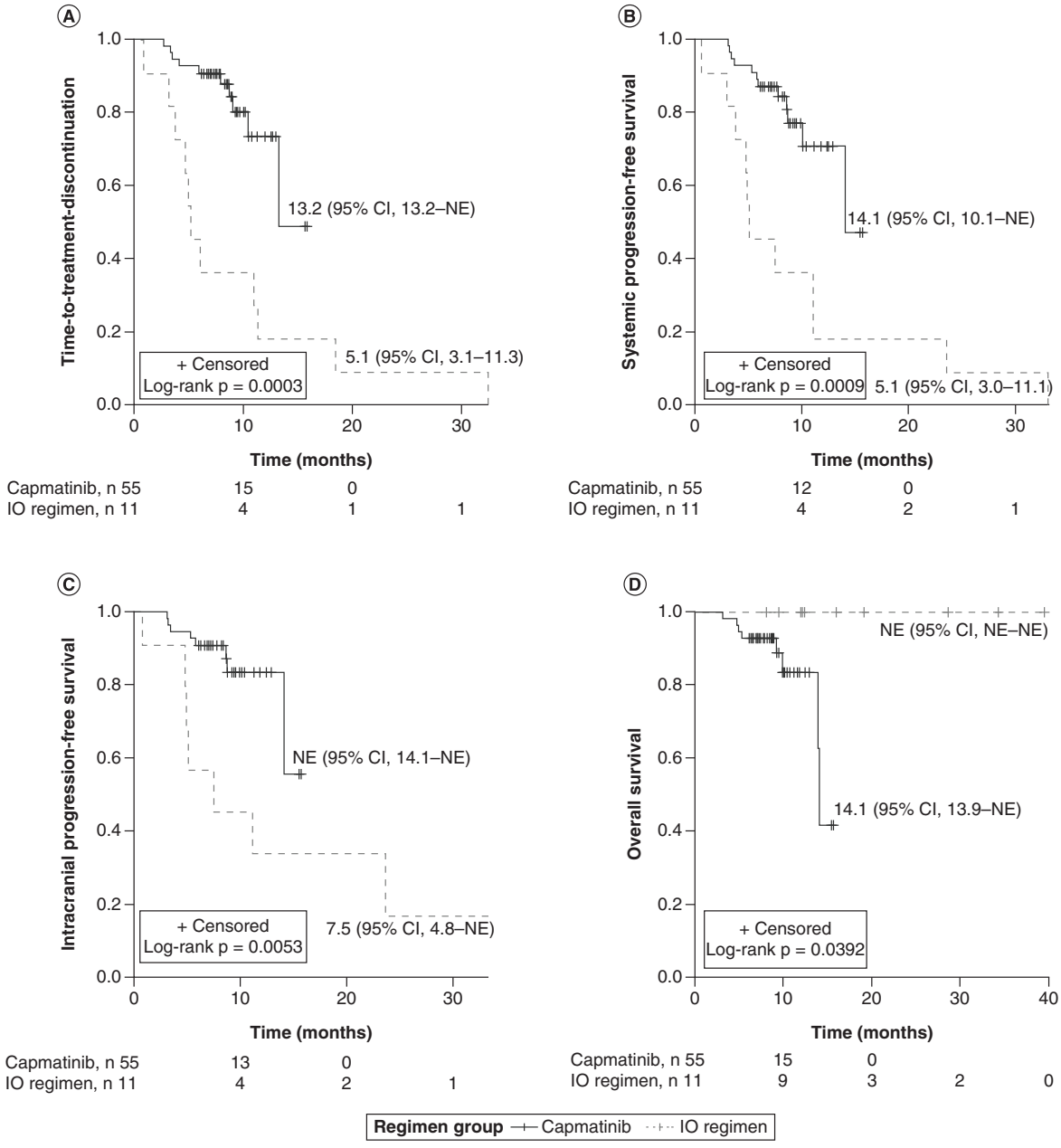


Figure 1. Treatment outcomes with first-line therapy (all patients). (A) Time-to-treatment discontinuation. **(B)** Systemic progression-free survival. **(C)** Intracranial progression-free survival. **(D)** Overall survival.
Note: The treatment categories are not necessarily independent because, as required by design, all patients treated with an IO-containing regimen in the first line (n = 11) had to remain alive and advance to the next line of therapy to receive capmatinib for study eligibility (suggesting that patients treated with first-line IO in this analysis may be healthier than those treated with first-line IO in general practice).
IO: Immune-oncology; NE: Not estimable.

first-line IO therapy, the TTD was 5.1 months (95% CI, 3.1–11.3) (Figure 1A). Among those treated with an IO-containing therapy in first line, 18.2% were still on therapy after 12 months.

In RT-naive patients, median TTD was 13.2 months (95% CI, NE) for first-line capmatinib and 6 months (95% CI, 0.8–18.4) for first-line IO-containing regimens (Figure 2A). At 12 months, 95% of patients treated with first-line capmatinib and 22.2% of those treated with first-line IO-containing therapy were still on therapy.

We observed no statistically meaningful differences in TTD when stratifying by BM presentation (symptomatic vs asymptomatic) (Supplementary Figure 2). For patients treated with first-line capmatinib, the median TTD was

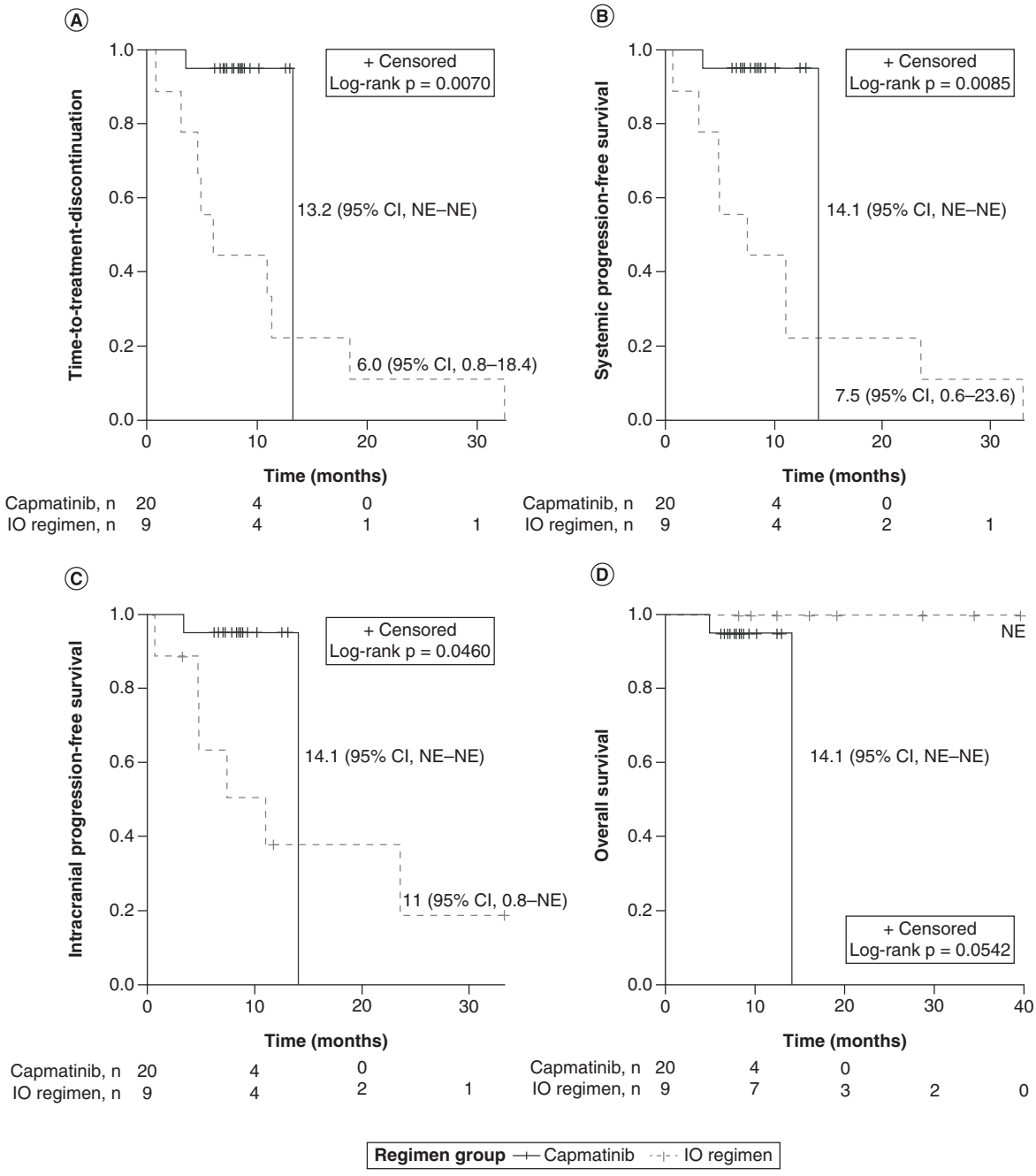


Figure 2. Treatment outcomes with first-line therapy (RT-naive patients). (A) Time-to-treatment discontinuation. **(B)** Systemic progression-free survival. **(C)** Intracranial progression-free survival. **(D)** Overall survival.
Notes: The treatment categories are not necessarily independent because, as required by design, all patients treated with an IO-containing regimen in the first line (n = 11) had to remain alive and advance to the next line of therapy to receive capmatinib for study eligibility (suggesting that patients treated with first-line IO in this analysis may be healthier than those treated with first-line IO in general practice). The Kaplan–Meier curves for capmatinib drop to zero because the last observation (patient with longest follow-up) in this treatment category represents an event, with no subsequent observations available for censoring – a common phenomenon in Kaplan–Meier analyses when sample sizes are small.
IO: Immune-oncology; NE: Not estimable.

10.2217/fon-2022-1133

Table 3. Outcomes of systemic therapy.

	Capmatinib			IO-containing therapy[†]		
	Any line	1st line	2nd line	Any line	1st line	2nd line
Total patients, n (%)	68 (100.0)	55 (100.0)	13 (100.0)	15 (100.0)	11 (100.0)	4 (100.0)
Best systemic response, total sample, % (95% CI)						
Overall response rate[‡]	85.3 (74.6–92.7)	90.9 (80.1–97.0)	61.5 (31.6–86.1)	53.3 (26.6–78.3)	72.7 (39.0–94.0)	0.0 (0.0–0.0)
Disease control rate[§]	94.1 (85.6–98.4)	96.4 (87.5–99.6)	84.6 (54.6–98.1)	73.3 (44.9–92.2)	81.8 (48.2–98.7)	50.0 (6.8–93.2)
Best intracranial response, total sample, % (95% CI)						
Overall response rate	80.9 (69.5–89.4)	87.3 (75.5–94.7)	53.8 (25.1–80.8)	20.0 (4.3–48.1)	27.3 (6.0–61.0)	0.0 (0.0–0.0)
Disease control rate	92.6 (83.7–97.6)	96.4 (87.5–99.6)	76.9 (46.2–95.0)	46.7 (21.3–73.4)	45.5 (16.8–76.6)	50.0 (6.8–93.2)
Radiation therapy-naive patients, n (%)	26 (100)	20 (100)	6 (100)	9 (100)	9 (100)	0 (0)
Best systemic response in radiation therapy–naive patients, % (95% CI)						
Overall response rate	80.8 (60.7–93.5)	85.0 (62.1–96.8)	66.7 (22.3–95.7)	66.7 (29.9–92.5)	66.7 (62.1–96.8)	0.0 (0.0–0.0)
Disease control rate	92.3 (74.9–99.1)	95.0 (75.1–99.9)	83.3 (35.9–99.6)	77.8 (40.0–97.2)	77.8 (75.1–99.9)	0.0 (0.0–0.0)
Best intracranial response in radiation therapy–naive patients, % (95% CI)						
Overall response rate	80.8 (60.7–93.5)	85.0 (62.1–96.8)	66.7 (22.3–95.7)	11.1 (0.3–48.3)	11.1 (0.3–48.3)	0.0 (0.0–0.0)
Disease control rate	92.3 (74.9–99.1)	95.0 (75.1–99.9)	83.3 (35.9–99.6)	33.3 (7.5–70.1)	33.3 (7.5–70.1)	0.0 (0.0–0.0)

[†]IO-containing therapy includes pembrolizumab and durvalumab (alone or in combination with chemotherapy).
[‡]Overall response rate includes complete response and partial response.
[§]Disease control rate includes complete response, partial response and stable disease.
IO: Immune-oncology.

13.2 months (95% CI, 10.4-NE) for patients with asymptomatic BM, but was NE for patients with symptomatic BM. Approximately two-thirds (65.1%) of patients with asymptomatic BM and 79% of patients with symptomatic BM who were treated with capmatinib for first-line therapy were still on therapy at 12 months.

Systemic response

Response to therapy was determined with the use of pseudo-RECIST criteria (Appendix A) for most patients (86.8%).

During capmatinib therapy (first line [n = 55]), the systemic real-world ORR (rwORR), the proportion of patients who had complete or partial responses to therapy, was achieved in 90.9% (n = 50) of the patients (Table 3). Additionally, the real-world DCR (rwDCR) was 96.4% (n = 53). The median rwDOR to capmatinib therapy (in any line) was 11.1 months (95% CI, 7.8-NE); the rwDOR for any line of IO therapy was 6.7 months (95% CI, 1.8–23.3). The rwDOR for patients treated with capmatinib in the first line was NE, and the rwDOR for patients treated with first-line IO therapy was 6.7 months.

In RT-naive patients (n = 26), the systemic rwORR and rwDCR during first-line capmatinib therapy (n = 20), were 85% and 95%, respectively. The median rwDOR for the capmatinib therapy was estimated to be 11.1 months (95% CI, 9.4-NE) for any line, and it was NE for the first line. Median rwDOR for first-line IO-containing therapy was estimated to be 7.1 months (95% CI, 1.8-NE).

In assessing systemic response by BM presentation (symptomatic vs asymptomatic), among patients treated with first-line capmatinib, those who presented with asymptomatic BM appeared to have a better systemic rwORR (95.2%) as compared with those who presented with symptomatic BM (87.9%); the difference, however, was not statistically significant (Supplementary Table 1).

Intracranial response

Intracranial response assessments were performed with the use of pseudo-RANO-BM criteria for 89.7% of patients. During first-line capmatinib therapy (n = 55), intracranial rwORR was 87.3% and intracranial DCR was 96.4%. The median rwDOR to capmatinib therapy was NE for any line, owing to low rates of progression (<15%). Similarly, median rwDOR was NE for the IO-containing therapy group, owing to low frequency of patients who met either complete or partial response.

In the subgroup of RT-naive patients receiving first-line capmatinib therapy (n = 20), the intracranial rwORR and rwDCR were 85.0% and 95.0%, respectively. The median rwDOR for the capmatinib therapy was estimated

to be 11.1 months (95% CI, 9.4-NE) for any line, but was NE for the first line. Median rwDOR for IO-containing therapy was NE for the first line.

In patients treated with first-line capmatinib, those who presented with asymptomatic BM appeared to have a better intracranial rwORR (100%) as compared with those who presented with symptomatic BM (78.8%); the difference, however, was not statistically significant (Supplementary Table 1).

PFS & OS

The median systemic rwPFS was 14.5 months (95% CI, 14.1-NE) from the start of capmatinib therapy (in any line) and 14.1 months (95% CI, 10.1-NE) from the start of first-line capmatinib therapy (Figure 1B). The median intracranial rwPFS was NE from the start of capmatinib in the first-line therapy (Figure 1C), but was 14.5 months (95% CI, 14.1-NE) in any line. The intracranial PFS rates were 90.9% at 6 months and 83.5% at 12 months (Supplementary Figure 3). In RT-naive patients treated with first-line capmatinib, the systemic and intracranial PFS were 14.1 months (95% CI, NE-NE) (Figure 2B & C). For RT-naive patients treated with first-line IO, the systemic PFS was 7.5 months (95% CI, 0.6–23.6), and the intracranial PFS was 11 months (95% CI, 0.8-NE) (Figure 2B & C). In assessing intracranial rwPFS by BM presentation (symptomatic vs asymptomatic), among patients treated with first-line capmatinib, those who presented with asymptomatic BM appeared to have a better intracranial rwPFS rate at 12 months (90.5%) as compared with those who presented with symptomatic BM (79.6%); the difference, however, was not statistically significant (Supplementary Figure 3).

For IO-containing therapy, the median systemic rwPFS was 5.1 months (95% CI, 3.0–11.1) from the start of therapy in the first line (Figure 1B). The median intracranial rwPFS was 7.5 months (95% CI, 4.8-NE) from the start of therapy in the first line (Figure 1C).

The median OS for first-line capmatinib therapy was 14.1 months (95% CI, 13.9-NE) (Figure 1D). In RT-naive patients treated with first-line capmatinib, the median OS was 14.1 months (95% CI, NE-NE) (Figure 2D). The median OS for IO-containing therapy was not estimable.

Discussion

This retrospective study provides an assessment of the clinical use of capmatinib, including patient characteristics, treatment patterns, clinical outcomes, and survival in patients with NSCLC with MET exon 14 skipping mutations and BM in real-world US clinical settings. We examined the effectiveness of capmatinib in patients who had not been treated with RT, a common treatment for BM, to rule out confounding of effect due to radiation. Our analysis found that capmatinib maintains its effectiveness regardless of whether patients received RT. Moreover, we found very little difference in response to therapy for patients with symptomatic BM compared with those with asymptomatic BM. The real-world treatment outcomes in this study indicate that capmatinib is effective at treating NSCLC patients with MET exon 14 skipping mutations and BM, as patients in this study treated with capmatinib in the first line had a median systemic rwPFS of 14.1 months, regardless of whether they had been treated with RT. The systemic and intracranial rwORR were both observed to be higher with the first-line use of capmatinib (90.9% and 87.3%, respectively) as compared with when they were used in the second line (61.5% and 53.8%, respectively); however, these differences may be related to prognostic variations at the start of the two therapy lines. Intracranial effectiveness of first-line capmatinib therapy was high, with a 90.9% rwPFS rate at 6 months and 83.5% at 12 months. The intracranial rwPFS rates were slightly higher in RT-naive patients (95% at 6 and 12 months). At 12 months, the OS rates for patients treated with first-line capmatinib was 83.5% for the overall cohort and 95% for RT-naive patients. In our analysis, the subgroup of patients who were treated with an IO-containing regimen in the first-line setting were found be in line with other real-world studies of first-line IO in NSCLC. The rwPFS for patients on first-line IO-containing therapy in our study was 5.1 months (95% CI, 3.0–11.1), similar to the 6.4 months (5.4–7.8) reported previously [17]. These estimates of rwPFS for IO patients is substantially lower than that found for patients treated with first-line capmatinib in this study (14.1 months [95% CI, 10.1-NE]).

The clinical outcomes described in this study are in line with or better than the systemic and intracranial outcomes reported in the GEOMETRY mono-1 clinical trial. The ORR in the GEOMETRY mono-1 trial was 41% for previously treated patients and 68% for treatment-naive patients [7]. In the current study, we observed systemic rwORRs of 61.5% in patients receiving 1 prior line of therapy and 91% in patients who were previously untreated (i.e., first-line capmatinib). These differences could be related, at least in part, to the dissimilarity in median ages between the two study populations (71 years in the GEOMETRY mono-1 trial and 64 years in the current study). Of the 13 patients with BM in the GEOMETRY mono-1 trial, 12 (92.3%) were found to have intracranial disease

control, as determined by a neuroradiological assessment. Additionally, seven patients (53.8%) had an intracranial response, including four patients (30.7%) with a complete intracranial response [7]. In the present study, we found that the rwDCR was 92.6%, nearly identical to that in the GEOMETRY mono-1 trial. Our findings confirm that the benefits of capmatinib are maintained or even improved with real-world use compared with rigorous clinical trial settings and that it was effective in improving patient outcomes irrespective of prior or concurrent radiation therapy.

There are some limitations associated with this study. The sample size used was small because of the rarity of NSCLC with MET exon 14 skipping mutations. We captured a convenience sample of patients with mNSCLC with MET exon 14 skipping mutation and BM treated with capmatinib from participating physicians; the sample, therefore, may not be generalizable to the broader population. Mutation testing and detection of measurable intracranial lesions were ascertained by participating physicians based on the information documented in medical records, using techniques available and applicable at their respective sites and practices, but details of these methods were not captured as part of this study. This study lacked source data verification by independent reviewers owing to the study design; however, extensive logic checks were instituted within the online case report form to prevent illogical data entries. Additional quality reviews were performed during and after the data collection to ensure consistency of responses. The differences in clinical outcomes between patients treated with first-line capmatinib versus those treated with first-line IO-containing therapies should be interpreted with caution for two reasons: first, this study was not designed to compare the two treatment groups, and hence, the groups may be different in their baseline characteristics; second, since all patients treated with first-line IO-containing therapies were required, by design, to be alive and advance to a future line of therapy involving capmatinib, the two treatment groups lack statistical independence. Because of the latter condition, the first-line IO group in this study possibly represents a healthier set of patients than what may otherwise be observed, introducing survival bias. Nevertheless, we believe that the observed differences between these groups are helpful in contextualizing the considerable efficacy benefits with capmatinib that may be present in the real-world settings. Furthermore, because data were extracted by participating physicians, the data were limited to what information was available in patient records that were accessible to the participating physician. Additionally, while we used pseudo-RECIST or pseudo-RANO-BM in an attempt to standardize response rates, a small fraction of physicians preferred not to use them (due to time burden, reliance on clinical judgement, or lack of application for the requested purpose, as reported) and favored recording response measures based on documented clinical assessments. However, while these criteria for standardizing response assessments are not as stringent as those used in clinical trials, they are a significant strength for real-world studies.

Conclusion

This study shows substantial systemic and intracranial effectiveness associated with first-line capmatinib use in patients with advanced or mNSCLC with MET exon 14 skipping mutations and BM in the real-world setting. The findings from the RT-naive subgroup confirm that capmatinib is an effective treatment option with substantial benefits, regardless of whether patients received prior RT. This study also confirms the findings of capmatinib intracranial efficacy initially reported in the GEOMETRY mono-1 trial. In this patient population, the small subgroup of patients who received first-line IO-containing therapy were found to be associated with relatively poor clinical outcomes. Because the effectiveness of capmatinib in this population is so promising, in both clinical trial and real-world cohorts, this research may indicate a need for early biomarker testing for patients with mNSCLC in order to provide them with appropriately targeted therapies in a timely manner.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2022-1133

Author contributions

PK Paik: methodology, supervision. RK Goyal: conceptualization, methodology, investigation, formal analysis, data curation, project administration. B Cai: conceptualization, methodology, supervision. MA Price: conceptualization, methodology, investigation, formal analysis. KL Davis: conceptualization, methodology, investigation, formal analysis. VD Ansquer: investigation, data curation, project administration. N Caro: conceptualization, methodology, supervision. TR Saliba: conceptualization, methodology, supervision. All authors contributed to the writing of this manuscript.

Acknowledgments

The authors thank SA Egloff and M Frost as employees of both Sarah Cannon and the HCA Healthcare Research Institute for their assistance in defining the pseudo-RECIST and pseudo-RANO-BM measures used in this study to facilitate retrospective response assessment with real-world data. The authors also thank S Musetti Jenkins and J Forbes of RTI Health Solutions for medical writing and editing assistance, respectively.

Financial & competing interests 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. 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.

Novartis Pharmaceuticals Corporation provided funding for publication support in the form of manuscript writing, styling and submission.

Ethical disclosure

This study was deemed 'not research involving human subjects' by the RTI Institutional Review Board.

Data sharing statement

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

Summary points

- Capmatinib, a highly selective MET inhibitor, is approved for patients with metastatic non-small-cell lung cancer (NSCLC) with MET exon 14 skipping mutations.
- Capmatinib showed efficacy against brain metastases in the pivotal GEOMETRY mono-1 trial.
- This medical chart review examined real-world treatment outcomes on capmatinib in patients with brain metastases (BM).
- Subgroup analyses were performed to determine intracranial efficacy and determine patient outcomes if radiotherapy was received prior to capmatinib.
- Data were abstracted from 68 eligible patient charts; 60.3% were male, 83.3% were *de novo* metastatic.
- Capmatinib showed substantial intracranial response, with a real-world overall response rate (ORR) of 87.3% and a median progression-free survival (PFS) of 14.5 months across all lines of therapy.
- The systemic real-world ORR to capmatinib was 90.9%; the median systemic real-world PFS was 14.5 months (95% CI, 14.1-not estimable) from the start of capmatinib therapy (in any line) and 14.1 months (95% CI, 10.1-not estimable) from the start of first-line capmatinib therapy.
- This study shows a substantial systemic and intracranial effectiveness associated with first-line capmatinib use in patients with advanced or metastatic NSCLC with MET exon 14 skipping mutations and BM in the real-world setting, and the findings from the radiation therapy (RT)-naive subgroup confirm that capmatinib is an effective treatment option with substantial benefits, regardless of whether patients received prior RT.

References

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

1. Sung H, Ferlay J, Siegel RL *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 71(3), 209–249 (2021).
2. Surveillance Epidemiology and End Results Program (SEER). Cancer stat facts: lung and bronchus cancer. https://seer.cancer.gov/statfacts/html/lungb.html (Accessed 20 July 2022).
3. Fois SS, Paliogiannis P, Zinellu A, Fois AG, Cossu A, Palmieri G. Molecular epidemiology of the main druggable genetic alterations in non-small-cell lung cancer. *Int. J. Mol. Sci.* 22(2), 612 (2021).

4. Khalifa J, Amini A, Popat S, Gaspar LE, Faivre-Finn C. International Association for the Study of Lung Cancer Advanced Radiation Technology C. Brain metastases from NSCLC: radiation therapy in the era of targeted therapies. *J. Thorac. Oncol.* 11(10), 1627–1643 (2016).
5. Vansteenkiste JF, Van De Kerkhove C, Wauters E, Van Mol P. Capmatinib for the treatment of non-small-cell lung cancer. *Expert Rev. Anticancer Ther.* 19(8), 659–671 (2019).
6. Huang C, Zou Q, Liu H *et al.* Management of non-small-cell lung cancer patients with MET exon 14 skipping mutations. *Curr. Treat. Options Oncol.* 21(4), 33 (2020).
7. 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).

- **Provides the outcomes of capmatinib use in patients with MET exon 14 mutated non-small-cell lung cancer (NSCLC).**

8. Garon EB, Heist RS, Seto T *et al.* CT082 - Capmatinib in METex14-mutated (mut) advanced non-small-cell lung cancer (NSCLC): results from the phase II GEOMETRY mono-1 study, including efficacy in patients (pts) with brain metastases (BM). Presented at: *AACR Annual Meeting 2020.* (2020). Virtual.

- **Provides the initial subgroup analyses indicating capmatnib has intracranial efficacy in patients with NSCLC and brain metastases (BM).**

9. Wolf J, Seto T, Han J-Y *et al.* Capmatinib (INC280) in METΔex14-mutated advanced non-small-cell lung cancer (NSCLC): efficacy data from the phase II GEOMETRY mono-1 study. *J. Clin. Oncol.* 37(Suppl. 15), 9004–9004 (2019).
10. Klempner SJ, Borghei A, Hakimian B, Ali SM, Ou SI. Intracranial activity of cabozantinib in MET exon 14-positive NSCLC with brain metastases. *J. Thorac. Oncol.* 12(1), 152–156 (2017).

- **Reports of additional small molecule inhibitors with intracranial efficacy in patients with MET exon 14 mutated NSCLC and BM.**

11. Page S, Milner-Watts C, Perna M *et al.* Systemic treatment of brain metastases in non-small-cell lung cancer. *Eur. J. Cancer* 132, 187–198 (2020).

- **Useful overview of systemic treatments for NSCLC with BM.**

12. US Food and Drug Administration. Cancer clinical trial eligibility criteria: brain metastases guidance for industry (2020). www.fda.gov/media/121317/download

- **Provides US FDA guidelines for BM clinical trials.**

13. 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).
14. Lin NU, Lee EQ, Aoyama H *et al.* Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol.* 16(6), e270–e278 (2015).
15. 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).
16. 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).
17. Velcheti V, Hu X, Piperdi B, Burke T. Real-world outcomes of first-line pembrolizumab plus pemetrexed-carboplatin for metastatic nonsquamous NSCLC at US oncology practices. *Sci. Rep.* 11(1), 9222 (2021).