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REVIEW ARTICLE

MET-Targeted Therapies and Clinical Outcomes: A Systematic Literature Review

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Abstract

Introduction Numerous therapeutic agents specifically targeting the mesenchymal-epithelial transition (*MET*) oncogene are being developed.

Objective The aim of the current review was to systematically identify and analyze clinical trials that have evaluated MET inhibitors in various cancer types and to provide an overview of their clinical outcomes.

Methods An electronic literature search was carried out in the PubMed and Embase databases to identify published clinical trials related to MET inhibitors. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement was followed for the systematic appraisal of the literature. Data related to clinical outcomes, including progression-free survival, overall survival, objective response rate, and overall tumor response, were extracted.

Results In total, 49 publications were included. Among these, 51.02% were phase II studies, 14.28% were randomized controlled trials, three were phase III studies, two were prospective observational studies, and the remainder were either phase I or Ib studies. The majority (44.89%) of articles reported the clinical outcomes of MET inhibitors, including small molecules, monoclonal antibodies, and other agents, in patients with non-small-cell lung cancer (NSCLC) harboring *MET* alterations. *MET* amplification, overexpression, and *MET* exon 14 skipping mutations were the major *MET* alteration types reported across the included studies. Clinical responses/outcomes varied considerably.

Conclusion This systematic literature review provides an overview of the literature available in Embase and PubMed regarding *MET*-targeted therapies. *MET*-selective tyrosine kinase inhibitors (TKIs) (capmatinib, tepotinib, and savolitinib) may become a new standard of care in NSCLC, specifically with *MET* exon 14 skipping mutations. A combination of *MET* TKIs with epidermal growth factor receptor (EGFR) TKIs (osimertinib + savolitinib, tepotinib + gefitinib) may be a potential solution for *MET*-driven EGFR TKI resistance. Further, *MET* alteration (*MET* amplification/overexpression) may be an actionable target in gastric cancer and papillary renal cell carcinoma.

1 Introduction

In the past two decades, enormous advances have been made in the understanding of biological, genetic, and molecular mechanisms leading to cancer, and this has fueled the introduction of targeted therapies in cancer [1, 2]. Mesenchymal-epithelial transition (*MET*) proto-oncogene—receptor tyrosine kinase or hepatocyte growth factor (HGF) receptor—belongs to a family of receptor tyrosine kinases (RTKs) and, along with its ligand HGF (HGF/MET axis), is involved in transduction pathways and modulates essential cellular processes under normal physiological conditions [3]. Copious evidence has indicated that diverse oncogenic alterations, including mutations, *MET* amplification, *MET* overexpression, chromosomal rearrangements, and fusions, cause dysregulation of the HGF/MET axis and lead to a wide range of human cancers [4, 5]. In addition to its physiological and pathological roles, increasing evidence implicates *MET* as a common mechanism of resistance to targeted therapies (epidermal growth factor receptor [EGFR] and vascular EGFR [VEGFR] inhibitors) due to crosstalk between other RTKs [6, 7]. Based on this evidence, the HGF/MET axis has been explored as an intriguing actionable therapeutic target for drug development in different cancer types [8].

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Key Points

Mesenchymal-epithelial transition (*MET*) activity is dysregulated through diverse oncogenic alterations across a wide range of human cancers.

Several MET inhibitors targeting the hepatocyte growth factor/MET axis have been developed and used either as monotherapy or in combination therapy.

MET-selective tyrosine kinase inhibitors (TKIs) might become the new standard of care in subsets of patients with *MET* alterations and *MET*-driven epidermal growth factor receptor TKI resistance.

In the last decade, several MET inhibitors, including monoclonal antibodies, bispecific antibodies (bsAb), antibody-drug conjugate (ADC) and small molecules, have been developed and are in various phases of clinical evaluation [4, 5, 8]. These agents are used either as monotherapy or in combination therapy with other agents in various cancers [8, 9]. In March 2020, the Japanese Ministry of Health, Labour and Welfare approved tepotinib for the treatment of unresectable, advanced, or recurrent non-small-cell lung cancer (NSCLC) with *MET* exon 14 skipping mutation [10, 11]. In May of the same year, the US FDA approved capmatinib for the treatment of adult patients with NSCLC with *MET* exon 14 skipping mutation. In addition, in July 2020, the China National Medical Products Administration granted priority review status to the new drug application for savolitinib, which was then approved in June 2021 for the treatment of NSCLC with *MET* exon 14 skipping mutations. Globally, this was the first NDA filing for savolitinib and the first in China for a selective MET inhibitor [12]. These approvals not only bridge the gap in the treatment landscape for *MET*-altered NSCLS but also drive the new era of MET inhibitors. The current systematic literature review summarizes and provides an overview of the clinical outcomes with various MET inhibitors (monoclonal antibodies and small-molecule inhibitors) in different cancer types.

2 Methodology

2.1 Evidence Acquisition

This systematic review was conducted following PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [13]. Figure 1 summarizes the search process.

2.2 Study Selection

An electronic literature search was carried out in the PubMed and Embase databases, with the final search on 8 February 2021. The following search strings were used.

PubMed: ((*c-MET* alterations OR c-MET aberrations OR *MET* amplification OR copy number gain OR *MET* mutations OR *MET* exon 14 skipping mutation) OR (TKI resistance) AND (*c-MET* inhibitors OR *c-MET* targeted therapy OR antibody-based *c-MET* inhibitors OR *c-MET* targeted antibodies) OR *c-MET* inhibitor combination therapy OR *c-MET* inhibitor treatment regimen)).

Embase: "*c-MET* alterations" OR "*c-MET* aberrations" OR "*MET* amplification" OR "copy number gain"/exp OR "copy number gain" OR "*MET* mutations" OR "*MET* exon 14 skipping mutation" OR "TKI resistance" OR "*c-MET* inhibitors" OR "*c-MET* targeted therapy" OR "antibody-based *c-MET* inhibitors" OR "*c-MET* targeted antibodies" OR "*c-MET* inhibitor combination therapy."

2.3 Inclusion and Exclusion Criteria

As per the PRISMA statement, the inclusion criteria were prospectively defined. Articles (abstracts and full texts) were screened for eligibility independently by two reviewers. Randomized controlled trials (RCTs)/observational studies that included patients with confirmed MET alterations, reported clinical outcomes of *MET*-targeted therapies in different cancers, and were published in the English language were included. During the screening process, we excluded duplicates, non-English articles, duplicate publications from the same patient population, case reports, articles reporting insufficient/inappropriate data, therapies including only chemotherapy regimens, reviews, and meta-analyses. The remaining articles (abstracts and full text) were reviewed by two independent reviewers until consensus was reached, with any disagreements resolved by the third reviewer.

A data extraction algorithm was constructed, and the following data were extracted from each included study: (1) *MET* inhibitor, (2) cancer type, (3) study type, (4) number of patients, (5) number of patients with *MET* positivity, (6) progression-free survival (PFS), (7) overall survival (OS), (8) objective response rate (ORR), and (9) overall tumor response. We used the Jadad scale and the Newcastle–Ottawa scale to evaluate the methodological quality of included RCTs and non-RCTs, respectively. The study was prospectively registered on the PROSPERO website (CRD42021268933).

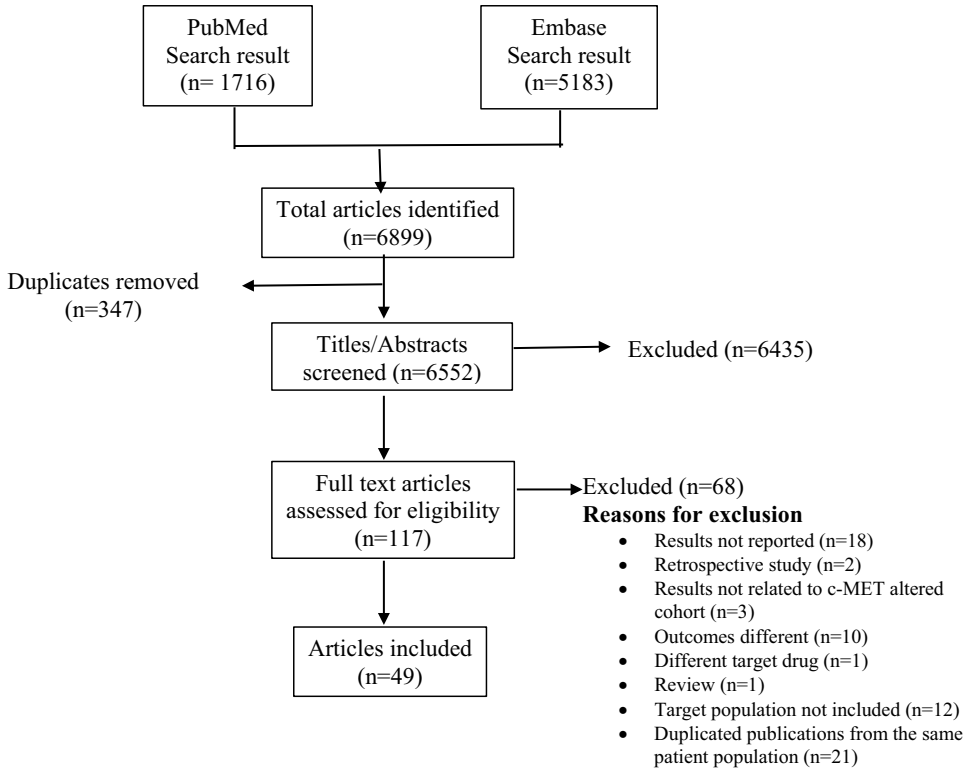

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart: Search process for study selection

3 Results

The electronic literature search retrieved 6552 references; after duplicates were removed, 49 were considered for final review: three were phase III studies, 25 were phase II studies, seven were RCTs, two were prospective observational studies, and the remainder were phase I or phase Ib studies (Table 1). The finalized studies were grouped according to cancer type: NSCLC (44.89%), papillary renal cell carcinoma (PRCC) (12.24%), gastric cancers (16.32%), and other cancers (26.53%) (Tables 2, 3, 4, 5).

3.1 Non-Small Cell Lung Cancer (NSCLC)

A total of 22 studies reporting the clinical outcomes of various *MET* inhibitors in NSCLC harboring different *MET* alterations were included. Four (18.18%) studies included patients with *MET* exon 14 skipping mutations (Table 2), and the remaining studies included patients with *MET* amplification or overexpression or *MET* exon 14 skipping mutation/*MET* amplification (Table 3). In total, 12 (52.17%) studies reported on monotherapy and ten (45.45%) reported on combination therapy. The majority of the studies reported on monotherapy involving crizotinib (41.66%).

3.1.1 *MET*-Targeted Therapy in NSCLC Harboring *MET* Exon 14 Skipping Mutation

MET exon 14 skipping mutation is believed to be an independent driver mutation in NSCLC and is usually mutually exclusive from other drivers (e.g., EGFR, anaplastic lymphoma kinase [ALK], c-ros oncogene 1 [ROS1]) and associated with a poor prognosis. Further, comprehensive studies conducted by Awad et al. [14] and Tong et al. [15] reported that *MET* exon 14 skipping mutations represent a clinically unique molecular subtype of NSCLC and aid in patient stratification for personalized therapy. Many advances in targeted therapy for *MET* exon 14 skipping mutations in NSCLC are being reported.

3.1.1.1 Crizotinib Monotherapy Crizotinib is a multitargeted small-molecule tyrosine kinase inhibitor (TKI) specifically targeted to ALK, ROS1 and *MET*. However, it is also a potent inhibitor of ALK and ROS1. It competitively inhibits ALK phosphorylation and alters downstream signal transduction, which leads to G1/S-phase cell cycle arrest and apoptosis [16]. The efficacy of crizotinib against tumors with *MET* exon 14 skipping alterations or *MET* amplification has not been reported in a large population. Drilon et al. [17] conducted the phase I PROFILE 1001 study ($n=69$) and reported the efficacy of crizotinib (median PFS [mPFS] 7.3 months; objective response rate [ORR] 32%) in patients with advanced stage NSCLC harboring *MET* exon 14 skip-

Table 1 Summary of identified studies

Study no.	Study	Study design	Cancer type	Diagnostic platform	*MET* alteration type	*MET* positivity criteria	Quality assessment
1	Paik et al. [19]	Phase II	NSCLC (advanced/metastatic)	NGS	*MET* exon 14 SM	–	4
2	Lu et al. [23]	Phase II	PSC and other NSCLC	–	*MET* exon 14 SM	–	3
3	Drilon et al. [17]	Phase I (NCT00585195) (PROFILE 1001)	NSCLC	NGS	*MET* exon 14 SM	–	3
4	Wolf et al. [85]	Phase II	NSCLC (stage IIIB/IV)	–	*MET* exon 14 SM	–	3
5	Wu et al. [33]	Phase Ib/II	NSCLC	FISH, IHC	*MET* amp	*MET* GCN ≥ 5, *MET*/CEP7 ratio ≥ 2.0, or *MET* OE; ≥ 50% of tumor cells with IHC 3+ or IHC 2+ with *MET* GCN > 5 and then to 50% of tumor cells with IHC 3+ or *MET* GCN > 4	4
6	Sequist et al. [32]	Phase Ib	NSCLC (locally advanced or metastatic)	FISH, NGS, IHC	*MET* amp	*MET* GCN ≥ 5 or *MET*/CEP7 ratio ≥ 2; IHC (MET +3 expression in ≥ 50% of tumor cells), or NGS (≥ 20% tumor cells, coverage of ≥ 200 × sequencing depth and ≥ 5 copies)	4
7	Camidge et al. [42]	Phase I	NSCLC (advanced)	–	*MET* amp	*MET*/CEP7 ratios ≥ 1.8	3
8	Yang et al. [37]	Phase Ib study	NSCLC (advanced)	FISH	*MET* amp	*MET*/CEP7 ratio 2, *MET* gene number 5	3
9	Li et al. [86]	Prospective observational	NSCLC (advanced)	FISH, IHC	*MET* OE	*MET*/CEP7 ratio > 5 copies or *MET*/CEP7 ratio ≥ 1.8 (low ≥ 1.8 to ≤ 2.2, intermediate > 2.2 to < 5, high ≥ 5)	3
10	Nishio et al. [38]	Phase I	NSCLC	IHC, SISH	*MET* OE	IHC 2+ or 3+	3
11	McCoach et al. [39]	Phase I	Lung adenocarcinoma	IHC, FISH, RT-PCR, NGS	*MET* expression	–	3
12	Park et al. [87]	Observational study	NSCLC (stage IIIB/IV)	–	*MET* OE/MET amp	IHC 2+ or 3+ defined as positivity	3
13	Wu et al. [30]	Phase Ib/II	NSCLC (advanced or metastatic)	IHC, ISH (FISH)	*MET* OE or MET amp	IHC 2+ or 3+, GCN ≥ 5, *MET*/(CEP7) ratio of ≥ 2:1	3

Table 1 (Continued)

Study no.	Study	Study design	Cancer type	Diagnostic platform	*MET* alteration type	*MET* positivity criteria	Quality assessment
14	Schuler et al. [80]	Phase I	NSCLC (stage IIIB or IV)	IHC, FISH, NGS	*MET* amp, *MET* OE	*MET* H-score ≥ 150 or *MET*/centromere ≥ 2.0, or *MET* GCN ≥ 5, or ≥ 50% of tumor cells, IHC score 2+ or 3+	3
15	Camidge et al. [36]	Phase Ib	NSCLC	IHC	*MET* amp/*MET* exon 14 SM	IHC H-score ≥ 150	3
16	Landi et al. [88]	phase II	NSCLC (locally advanced or metastatic)	FISH, Sanger sequencing	*MET* exon 14 SM/MET amp	*MET*/CEP7 ratio > 2.2	5
17	Moro-Sibilot et al. [89]	Phase II	NSCLC (locally advanced or metastatic)	IHC, FISH, NGS	*MET* amp and mutation (exons 14 and 16–19)	IHC 2+ or 3+, *MET* amp threshold ≥ 6 copies, *MET*/CEP7 ratio: high polysomy (< 1.8 c-*MET*/centromere), low (≥ 1.8–≤2.2), intermediate (> 2.2–< 5.0), and high (≥ 5.0) amps	5
18	Seto et al. [90]	Phase II GEOMETRY mono-1 study (NCT02414139)	NSCLC (stage IIIb or IV)		*MET* exon 14 SM and *MET* amp	GCN ≥ 10; GCN ≥ 6 and < 10; GCN ≥ 4 and < 6; GCN < 6	4
19	McCoach et al. [91]	Phase I/II (NCT01911507)	NSCLC (advanced/metastatic)	FISH, RT-PCR, IHC	*MET* amp, *MET* exon 14 SM	IHC 2–3+, CNG	3
20	Wolf et al. [21]	Phase II	NSCLC		*MET* amp and *MET* exon 14 SM	GCN ≥ 10; GCN 6–9; GCN 4 or 5; GCN < 4, *MET* exon 14 SM and any GCN ≥ 10; *MET* exon 14 SM and any GCN	3
21	Felip et al. [92]	Phase Ib/II (NCT02335944)	NSCLC (stage IIIB/IV)		–	IHC 3+ and/or GCN ≥ 4	2
22	Camidge et al. [40]	Phase II	NSCLC stage IV	IHC	–	IHC: ≥ 10% of cells ≥ 2+	1
23	Van Cutsem et al. [50]	Phase II	Gastric/GEJ/esophageal, and other solid tumors	FISH (IQ FISH)	*MET* amp	*MET*/CEN-7 ratio ≥ 2.0	4
24	Kang et al. [51]	Phase I	Advanced GEC	FISH	*MET* amp	*MET*/CEP7 ratio > 2 in ≥ 20%	3
25	Shah et al. [52]	Phase II	Gastric cancer (metastatic)	FISH	*MET* amp	–	3
26	Aparicio et al. [54]	Phase II	Esogastric adenocarcinoma	FISH, IHC	*MET* amp	IHC scores ≥ 2+, GCN > 6 MET copies, whatever the *MET*/CEN7 ratio	3
27	Shah et al. [56]	Phase III	Advanced gastroesophageal adenocarcinoma	IHC	*MET* OE	IHC 1+, 2+, or 3+	5

Table 1 (Continued)

Study no.	Study	Study design	Cancer type	Diagnostic platform	*MET* alteration type	*MET* positivity criteria	Quality assessment
28	Iveson et al. [55]	Phase Ib (NCT00719550)	Advanced or metastatic gastric or esophagogastric junction adenocarcinoma	FISH	*MET* OE (FISH)	*MET* probe to centromere probe of > 2; as ≥ 15 *MET* gene copies in 10% of tumor cells; or as four or more *MET* gene copies in 40% of tumor cells; 25% tumor membrane staining cutoff	2
29	Lee et al. [53]	Phase II NCT02299648: savolitinib monotherapy (biomarker D, NCT02449551); savolitinib + docetaxel (biomarker D, NCT02447406), savolitinib + docetaxel (biomarker E, NCT02447380)	Metastatic and/or recurrent gastric adenocarcinoma	NGS, IHC	*MET* amp/*MET* OE	*MET* OE by IHC 3+	4
30	Kim et al. [70]	Phase I	GC, melanoma, sarcoma, rectal cancer	IHC, FISH	*MET* OE/*MET* amp	*MET*/CEP7 ratio > 2.0	3
31	Catenacci et al. [93]	Phase III (NCT01697072)	Locally advanced or metastatic gastric or GEJ adenocarcinoma	IHC	–	IHC (defined as ≥ 25% of tumor cells with membrane staining of ≥ 1+ intensity)	3
32	Schöffski et al. [58]	Phase II	PRCC (type I)	FISH	*MET* mutation exons (16–19)/ MET amp	*MET*/CEP7 ratio ≥ 2	4
33	Choueiri et al. [59]	Phase II	PRCC (type I and II)	–	*MET*/HGF GCN gain	–	3
34	Gan et al. [94]	Phase I	PRCC	–	*MET* copy number increase	–	3
35	Choueiri et al. [95]	Phase II	PRCC (advanced)	–	Germline *MET* mutation ($n = 11$), somatic mutation ($n = 5$), gain of chromosome 7= ($n = 18$), MET amp ($n = 2$)	–	4
36	Choueiri et al. [57]	Phase III (NCT03091192)	Metastatic papillary renal cancer	–	*MET* amp, chromosome 7 gain	–	2
37	Suarez Rodriguez et al. [60]	Phase I/II (NCT02819596)	Metastatic papillary renal cancer	–	*MET* expression		3

Table 1 (Continued)

Study no.	Study	Study design	Cancer type	Diagnostic platform	*MET* alteration type	*MET* positivity criteria	Quality assessment
38	Angevin et al. [68]	Phase I	Solid tumors	IHC, FISH	*MET* amp	IHC: *MET* (t-MET) protein expression (>/= 50% of tumor cells with 2+ or 3+ positive, *MET* amp (≥ 10% of cells with > 4, t-MET/CEP7 ratio ≥ 2, *MET* positivity (H-score 15)	3
39	Shitara et al. [69]	Phase I	Solid tumors (GC, colorectal, lung. kidney)	FISH, IHC	*MET* amp	*MET*-amplified if ≥ 10% of cells had GCN > 4, *MET*:CEP7 ratio ≥ 2. IHC > 50% of tumor cells with IHC 2+ or 3+	3
40	Bang et al. [67]	Phase I	Solid tumors	FISH, IHC	*MET* OE	*MET* H-score ≥ 150 or *MET*/centromere ratio ≥ 2.0, *MET* GCN ≥ 5, IHC ≥ 50% of tumor cells with score 2+ or 3+; for HCC and GBM, a *MET* H-score ≥ 50 or a ratio of *MET*/centromere ≥ 2.0 or *MET* GCN ≥ 5	3
41	Bang et al. [65]	Phase I	Solid tumors (advanced)	FISH, IHC	–	–	3
42	Strickler et al. [66]	Phase I	Advanced solid tumors (lung, GC, esophageal, ovarian, and colorectal cancer)	FISH, NGS	*MET* amp	*MET*/CEP7 ratio ≥ 2 in ≥ 20% of cells	4
43	Schöffski et al. [64]	Phase II (NCT01524926)	Advanced or metastatic clear-cell sarcoma	FISH	–	–	3
44	Van den Bent et al. [62]	Phase Ib/II	Glioblastoma	FISH, IHC, NGS	MET amp	*MET*-amplified GCN > 5	3
45	Hu et al. [96]	Phase I (NCT02978261)	Gliomas (high grade)		ZM fusion and/or *MET*ex14	–	2
46	Jia et al. [61]	Phase I/II	Metastatic colorectal cancer	–	*MET* amp	–	3
47	Decaens et al. [63]	Phase II	HCC (advanced)	IHC, ISH	*MET* amp	*MET*/CEP7 ratio ≥ 2 or GCN ≥ 5, IHC, moderate (2+) or strong (3+)	3
48	Banck et al. [71]	Phase I	RCC, HCC, NSCLC	IHC	*MET* OE	IHC: ≥ 50% of cells ≥ 2+	3

Table 1 (Continued)

Study no.	Study	Study design	Cancer type	Diagnostic platform	*MET* alteration type	*MET* positivity criteria	Quality assessment
49	Harding et al. [72]	Phase Ib/II (NCT02082210)	GC ($n=16$), HCC ($n=45$), RCC ($n=15$), NSCLC ($n=15$)	IHC	*MET* OE	*MET* expression of 2+ staining intensity in ≥ 50% or < 50% of their tumor cells	3

The Jadad scale was used to assess the randomized controlled trials, and the Newcastle–Ottawa Scale was used to assess the quality of the non-randomized studies

amp amplification, *CEP7 Chromosome 7 centromere, FISH* fluorescence in-situ hybridization, *GBM* glioblastoma, *GC* gastric cancer, *GCN* gene copy number, *GEC* gastric or esophageal cancer, *GEJ* gastroesophageal junction, *HCC* hepatocellular carcinoma, *HGF* hepatocyte growth factor, *IHC* immunohistochemistry, *IQ FISH* interphase quantitative FISH, *ISH* in situ hybridization, *MET* mesenchymal-epithelial transition, *NGS* next-generation sequencing, *no.* number, *NSCLC* non-small-cell lung cancer, *OE* overexpression, *PRCC* papillary renal cell carcinoma, *PSC* pulmonary sarcomatoid carcinoma, *RCC* renal cell carcinoma, *RT-PCR* reverse transcriptase polymerase chain reaction, *SISH* silver in situ hybridization, *SM* skipping mutation

ping alteration and showed that *MET* inhibition with crizotinib remains a treatment option for NSCLCs with *MET* exon 14 alterations (Table 2) [17].

3.1.1.2 Tepotinib Monotherapy Tepotinib is a selective MET inhibitor that disrupts the MET signal transduction pathway and exhibits potential antineoplastic activity [18]. Only one of the studies included in this analysis reported the use of tepotinib monotherapy in patients with *MET* exon 14 altered NSCLC. VISION was a phase II trial by Paik et al. [19] that evaluated the durable clinical activity of tepotinib 500 mg once daily (OD) in 152 patients with *MET* exon 14 altered NSCLC, 99 of whom were followed for at least 9 months. The authors reported that tepotinib was associated with a partial response in approximately half the patients, with an overall response rate of 46% (95% confidence interval [CI] 36–57) by independent review committee (IRC) review and of 56% (95% CI 45–66) by investigator assessment. PFS and OS were 8.5 and 17.1 months, respectively (Table 2). These findings led to the regulatory approval of tepotinib in *MET* exon 14 skipping mutations in March 2020 in Japan [19].

3.1.1.3 Capmatinib Monotherapy Capmatinib is a selective small-molecule MET inhibitor that prevents activation of downstream effectors in the *MET* signaling pathway by blocking *MET* phosphorylation [20]. Wolf et al. [21] conducted a phase II study (GEOMETRY mono-1 study) involving patients with NSCLC harboring *MET* exon 14 skipping mutations who were assigned to cohorts according to previous lines of therapy. The authors reported that patients with NSCLC with a *MET* exon 14 skipping mutation who had already received one or two lines of therapy receiving capmatinib 400 mg tablet twice daily (BID) exhibited an overall response of 41% (28/69) and a mPFS of 5.2 months. Treatment-naïve patients exhibited an overall response and PFS of 68% (19/28) and 12.4 months, respectively (Table 2) [21].

3.1.1.4 Savolitinib Monotherapy Savolitinib is an inhibitor of the *MET* receptor that inhibits activation of *MET* by disrupting the *MET* signal transduction pathway in an adenosine triphosphate-competitive manner, resulting in cell growth inhibition in tumors [22]. Recently Lu et al. [23] conducted a multicenter phase II trial to evaluate the efficacy and safety of savolitinib 600 and 400 mg in Chinese patients with *MET* exon 14 altered NSCLC ($n=70$). Of these patients, 25 had pulmonary sarcomatoid carcinoma (PSC), which is a rare aggressive NSCLC subtype, and 45 had other histologies of NSCLC. The primary endpoint was ORR (assessed by IRC), assessed in the tumor response evaluable set, with a sensitivity analysis done in the full analysis set. Savolitinib showed an encouraging ORR in patients with *MET* exon 14 positive NSCLC, both in the tumor response evaluable set ($N=61$; ORR 49.2% [95% CI 36.1–62.3]) and in the full analysis set ($N=70$; ORR 42.9% [95% CI 31.1–55.3]). Savolitinib demonstrated similar tumor responses regardless of pathological subtype (ORR 44.4% in other NSCLC vs. 40.0% in PSC) or prior line of treatment (ORR 40.5% in later line vs. 46.4% in treatment-naïve patients). A post hoc analysis found that savolitinib also resulted in adequate control of brain metastases (Table 2) [23]. Overall, *MET* exon 14 skipping mutations define a special genomic subtype of NSCLCs, and existing evidence suggests that MET-selective TKIs have the potential to deliver better clinical outcomes than nonselective TKIs.

3.1.2 MET-Targeted Combination Therapies in *MET*-Amplified Post Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Resistance in NSCLC

MET activation negatively affects the effectiveness of TKIs because of crosstalk between MET and RTK (EGFR) signaling pathways, as the activation of EGFR leads to increased *MET* activation and vice versa [24, 25]. *MET* amplification promotes downstream signal transduction through bypass activation to evade cell death by EGFR TKIs. Therefore, *MET* amplification is an important resistance mechanism of EGFR TKI, with a prevalence of 5–21% after firstline/secondline EGFR TKI resistance, ~15% after first-line therapy, and ~19% after later line osimertinib resistance [26, 27]. Moreover, it is conceivable that *MET* activation could differ between patients who developed MET amplification after EGFR TKI treatment and treatment-naïve patients [28]. Therefore, the use of MET inhibitors in patients with acquired resistance to EGFR TKIs may require a different strategy than in treatment-naïve patients [28]. At this juncture, the combination of *MET* TKI and EGFR TKI may be the solution for *MET*-driven EGFR TKI resistance.

3.1.2.1 Tepotinib Plus Gefitinib Combination Gefitinib is a selective EGFR TKI that inhibits the EGFR signaling transduction pathway by blocking the autophosphorylation receptor [29]. Wu et al. [30] documented a phase Ib/II multicenter randomized trial (INSIGHT) involving EGFR-mutant NSCLC with *MET* overexpression (immunohistochemistry [IHC] 2+ or 3+) or *MET* amplification having acquired resistance to EGFR inhibition. The phase II part of the study included 55 patients, 31 of whom received tepotinib 500 mg daily plus gefitinib 250 mg, and 24 received chemotherapy (pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin). They reported that phase II survival outcomes were similar between the groups, with a mPFS of 4.9 and 4.4 months, respectively. However, survival outcomes were better with tepotinib plus gefitinib than with chemotherapy in patients with *MET* IHC 3+ (median OS 37.3 vs. 17.9 months; mPFS 8.3 vs. 4.4 months) and in patients with *MET* amplification (median OS 37.3 vs. 13.1 months; mPFS 16.6 vs. 4.2 months), suggesting improved activity for tepo-

Table 2 Clinical outcomes of MET inhibitors in non-small-cell lung cancer with *MET* exon 14 skipping mutation

Study	Study design	Cancer type	Study, population (*MET* +)	*MET* alteration type	Therapy	ORR, %	mPFS, months	OS, months
Drilon et al. [17]	Phase I (NCT00585195) PROFILE 1001	NSCLC	69 (65 evaluable)	*MET* exon 14 alteration	Crizotinib 250 mg BID in continuous 28-d cycles	32 (95% CI 21–45)	7.3 (95% CI 5.4–9.1)	20.5 (95% CI 14.3–21.8)
Paik et al. [19]	Phase II (NCT02864992) VISION study	NSCLC (advanced/metastatic)	169 (152 received treatment)	*MET* exon 14 SM	Tepotinib 500 mg OD	Independent review 46%; investigator assessment 56%	Combined biopsy 8.5; liquid biopsy 8.5; tissue biopsy 11.0	17.1
Wolf et al. [21]	Phase II (NCT02414139)	NSCLC (stage IIIB/IV)	97 (cohort 4: 69 pts; cohort 5b: 28 pts)	*MET* exon 14 SM	Capmatinib 400 mg BID	Cohort 4: 41%; cohort 5b: 68%	BIRC 5.4 and 12.4 for cohorts 4 and 5b	NR
Lu et al. [23]	Phase II (NCT02897479)	PSC, NSCLC	593 (70 [60 evaluable; 25 PSC, 45 other NSCLC])	*MET* exon 14 SM	Savolitinib 600 and 400 mg	Tumor response evaluable set: 49.2 (95% CI 36.1–62.3); FAS 42.9 (95% CI 31.1–55.3)	Overall 6.8 (95% CI 4.2–9.6); PSC 5.5 (95% CI 2.8–6.9); other NSCLC 6.9 (95% CI 4.2–13.8)	12.5 (95% CI 10.5–23.6)

BID twice daily, *BIRC* blinded independent review committee, *CI* confidence interval, *FAS* full analysis set, *mPFS* median progression-free survival, *NR* not reported, *NSCLC* non-small-cell lung cancer, *OD* once daily, *ORR* objective response rate, *OS* overall survival, *PSC* pulmonary sarcomatoid carcinoma, *pts* patients, *SM* skipping mutation

tinib plus gefitinib compared with standard chemotherapy in patients with *MET* amplification/overexpression (Table 3) [30]. Although the INSIGHT study was a small trial (*MET*+ [$n=31$], *MET* 3+ [$n=19$], and *MET* amplification [$n=12$]) and was terminated early because of enrollment difficulties, it did shed light on the benefit of combination therapy versus chemotherapy in *MET* IHC 3+ or *MET*-amplified populations with acquired resistance to EGFR inhibition.

3.1.2.2 Osimertinib Plus Savolitinib Combination Therapy Osimertinib is a third-generation EGFR TKI that binds irreversibly to certain mutant forms of EGFR (exon 19 deletion, and double mutants containing T790M) and inhibits several downstream pathways, such as rat sarcoma/rapidly accelerated fibrosarcoma/mitogen activated protein kinase (RAS/RAF/MAPK) and phosphoinositide 3 kinase/protein kinase B (PI3K/AKT), which regulate various cellular process [31]. A phase Ib trial by Sequist et al. [32] assessed osimertinib plus savolitinib in two global expansion cohorts (parts B and D) of the TATTON study. Part B consisted of three cohorts of patients: those previously treated with a third-generation EGFR TKI (subcohort B1; $n=69$) and patients not previously treated with a third-generation EGFR TKI who were either Thr790Met negative (subcohort B2; $n=51$) or Thr790Met positive (subcohort B3; $n=18$). Part D enrolled patients with *MET*-amplified, EGFR mutation-positive NSCLC who had received previous treatment with first-generation or second-generation EGFR TKIs but no previous treatment with third-generation EGFR TKI and were Thr790Met negative (cohort D; $n=36$). They reported a higher proportion of responses in patients in subcohort B3 and part D (ORR 67 vs. 64%) and mPFS (11 vs. 9.1 months) and a poorer response (ORR 30%, PFS 5.4 months) in patients with prior third-generation EGFR TKI therapy. The authors concluded that osimertinib plus savolitinib might be a potential treatment option for patients with *MET*-driven resistance to EGFR TKIs (Table 3) [32].

3.1.2.3 Capmatinib Plus Gefitinib Combination Therapy One phase Ib/II study reported capmatinib plus gefitinib combination therapy in NSCLC [33]. Wu et al. [33] reported data from another combination (capmatinib 400 mg plus gefitinib 250 mg) in a phase Ib/II trial in patients with *MET*-amplified and EGFR-mutated NSCLC for whom EGFR inhibitor therapy had failed ($n=100$). The phase II results showed an ORR of 29% and PFS of 5.5 months with the capmatinib plus gefitinib combination. A subgroup analysis based on *MET* gene copy number (GCN) and IHC categories revealed that patients with GCN ≥ 6 and IHC 3+ had better ORRs (47 and 32%, respectively) (Table 3) [33].

3.1.2.4 Other Combination Therapies Studies reporting the clinical evidence of combination therapies including small-molecule inhibitors and monoclonal antibodies, such as capmatinib plus gefitinib [33, 34], telisotuzumab plus erlotinib [35, 36], savolitinib plus gefitinib [37], onartuzumab plus erlotinib [38], capmatinib plus erlotinib [39], and emibetuzumab plus erlotinib [40], in patients with NSCLC with *MET* alterations were included in this review, with PFS ranging from 3.3 to 5.6 months. Camidge et al. [40] carried out a randomized open-label phase II study of intravenous emibetuzumab 750 mg every 2 weeks (Q2W) plus erlotinib 150 mg OD versus intravenous emibetuzumab 750 mg Q2W monotherapy in patients with acquired resistance to erlotinib and *MET* diagnostic-positive NSCLCs ($n=111$). The combination of emibetuzumab plus erlotinib demonstrated a PFS of 3.3 months and an ORR of 3%, whereas emibetuzumab monotherapy exhibited a PFS and an ORR of 1.6 months and 4.3%, respectively. The authors further concluded that acquired resistance to erlotinib in patients with *MET*-positive disease was not reversed by emibetuzumab plus erlotinib or by emibetuzumab alone (Table 3) [40].

3.1.3 MET-Targeted Therapy in NSCLC with De Novo *MET* Amplification/Overexpression

Tumors harboring de novo *MET* amplifications (high level, i.e., *MET* to chromosome 7 centromere (CEP7) ratio ≥ 5) are primarily dependent on the MET signaling pathway for growth [41]. These amplifications are identified in < 1–5% of NSCLCs and indicate a poor prognosis [41]. Further, the literature suggested that, compared with low-level *MET* amplifications, higher-level *MET* amplifications are more likely to be indicative of oncogenic dependence on *MET*, thereby offering actionable subtypes of NSCLC. On the other hand, *MET* overexpression represents a poor predictor of benefit from *MET* TKIs in the absence of a known driver of *MET* dependence. However, *MET* overexpression or de novo *MET* amplification as oncogenic driver events remain under debate. Some trials have used MET inhibitors in *MET* amplification.

3.1.3.1 Crizotinib Monotherapy The PROFILE 1001 study by Camidge et al. [42] evaluated the efficacy of crizotinib in patients with *MET*-amplified NSCLC categorized according to *MET*/CEP7 ratios (low ≥ 1.8 to ≤ 2.2; medium > 2.2 to < 5; or high ≥ 5) and reported that patients with high *MET* amplification (*MET*/CEP7 ≥ 4) had an ORR of 40% compared with low (ORR 33.3%) and medium (ORR 14.3%) *MET*/CEP7 ratio groups, inferring that patients with high *MET* amplification could benefit from the MET-targeted therapy (Table 3) [42].

3.1.3.2 Capmatinib Monotherapy The GEOMETRY mono-1 study evaluated the efficacy and safety of capmatinib in patients with high-level *MET*-amplified advanced

NSCLC (GCN ≥ 10) compared with low-level (GCN < 4) or midlevel (GCN 4–5 or 6–9) *MET*-amplified advanced NSCLC. In this study, patients with GCN ≥ 10 and no prior line of therapy exhibited higher ORRs (40%) and PFS (4.2 months) than other cohorts, indicating a better response with higher *MET* amplification [21].

3.1.4 New *MET* Inhibitors for NSCLC

Findings from MET-targeted therapy studies have suggested the reliability of MET inhibitors for NSCLC. Further, these achievements paved the way for researchers across the globe to look for other MET-targeted therapies, which has resulted in the production of several MET inhibitors, including Sym 015 [43], JNJ-372 (JNJ-61186372) [44], ningetinib [45], bozitinib [46], ABBV-399 (telisotuzumab vedotin; teliso-v) [36], and ADC (TR1801-ADC) [47], among others, that are in various phases of development. However, no further information about these studies is included in the current review as they did not meet the search criteria.

3.2 Gastric Cancers

The heterogenous molecular nature of gastric cancers offers amenable molecular targets, and emerging evidence suggests that *MET*-aberrant signaling provides actionable therapeutic targets in gastric cancer, so these are currently the subject of intense clinical investigation [48]. This review included two phase III, four phase II, and two phase I studies evaluating clinical outcomes in advanced/metastatic gastric carcinomas (GCs). Five of these reported the clinical outcomes of MET-inhibitor monotherapy, including crizotinib, savolitinib, AMG 337, ABT-700, and foretinib, in patients with GC harboring *MET* amplification [49–53].

3.2.1 Savolitinib Monotherapy

Lee et al. [53] reported results from the phase II VIKTORY umbrella trial, demonstrating that savolitinib monotherapy in metastatic and/or recurrent gastric adenocarcinoma ($n = 20$) exhibited an ORR of 50% (10/20) in a subset of patients with gastric cancer harboring *MET* amplifications. Further genomic analysis revealed that patients with high *MET* GCN > 10 (by tissue next-generation sequencing) exhibited ORRs of 70% (7/10) to savolitinib, inferring that the *MET*-amplified subset of patients experienced the largest absolute decrease in tumor burden (Table 4) [53].

3.2.2 Crizotinib Monotherapy

Aparicio et al. [54] reported results from the AcSe-crizotinib program involving patients with chemotherapy-refractory *MET*-amplified (GCN ≥ 6) esogastric adenocarcinoma ($n = 9$) receiving crizotinib 250 mg BID. They found an ORR of 5/9 (55.6% [95% CI 21.2–86.3]), an mPFS of 3.2 months (95% CI 1.0–5.4), and an OS of 8.1 months (95% CI 1.7–24.6) (Table 4) [54].

3.2.3 Combination Therapy

Iveson et al. [55] reported the efficacy results from a double-blind randomized phase II study of rilotumumab in combination with epirubicin, cisplatin, and capecitabine in patients with advanced gastric or esophagogastric junction cancer harboring *MET* overexpression. They reported an ORR of 20 (50%) and PFS and OS of 5.7 and 10.6 months, respectively (Table 4) [55]. A phase I study of a *MET* antibody, ABT-700, conducted by Kang et al. [51] in patients with advanced gastric or esophageal cancer with *MET* amplification reported that ABT-700 was well-tolerated, with an ORR of 75% ($n = 4$). They further concluded that *MET* amplification appeared to be more common in treatment-refractory tumors than in primary untreated tumors, suggesting the need for further screening efforts focusing on this treatment-refractory patient population (Table 4) [51]. Van Cutsem et al. [50] carried out a phase II multicenter single-arm cohort study of AMG 337 in patients with *MET*-amplified (*MET*/CEP-7 ratio ≥ 2.0.) gastric/gastroesophageal junction/esophageal adenocarcinoma and other *MET*-amplified solid tumors. AMG 337 monotherapy resulted in an overall ORR of 18% in heavily pretreated patients with advanced *MET*-amplified gastric/gastroesophageal junction/esophageal adenocarcinoma and overall PFS and OS of 3.4 and 7.9 months, respectively. No activity was observed in *MET*-amplified NSCLCs (Table 4) [50]. A phase III trial of onartuzumab 10 mg/kg plus mFOLFOX6 (leucovorin, fluorouracil, and oxaliplatin; $n = 279$) versus placebo plus mFOLFOX6 ($n = 283$) in patients with metastatic human epidermal growth factor receptor 2-negative and *MET*-positive gastroesophageal adenocarcinoma demonstrated that the addition of onartuzumab to first-line mFOLFOX6 did not significantly improve clinical benefits, either in the overall population or in *MET* 2+/3+ subgroup populations (Table 4) [56].

Several *MET* inhibitors and monoclonal antibodies have been tested in gastric cancers; however, only a few of the tested agents proved to be of substantial clinical benefit. A lack of consensus and poor biomarker determination, as well as the diverse resistance mechanisms, limits the clinical efficacy of *MET* inhibitors in gastric cancer.

3.3 Papillary Renal Cell Carcinoma

We included a total of six studies analyzing the effectiveness of *MET* inhibitors (crizotinib, savolitinib, foretinib) in patients with PRCC harboring *MET* alterations. SAVOIR,

Table 3 Clinical outcomes of MET inhibitors in non-small-cell lung cancer with MET amplification/overexpression

Study	Study design	Cancer type	Study; population (*MET* +)	*MET* alteration type	*MET* alteration status	Therapy	ORR, %	mPFS, mo	OS, mo
Monotherapy									
Camidge et al. [42]	Phase I (NCT00585195)	Advanced NSCLC	40 (37 evaluable)	*MET* amp	–	Crizotinib 250 mg BID	*MET*/CEP7 category: low (≥ 1.8–≤ 2.2) 33.3%; medium (> 2.2–< 5) 14.3%; high (≥ 5) 40.0%	*MET*/CEP7 category: low 1.8 mo; medium 1.9 mo; high 6.7 mo	–
Li et al. [86]	Prospective observational	Advanced NSCLC	33 (23 evaluable)	*MET* OE	De novo	Crizotinib	–	3.2 mo (ITT population) *MET* IHC (100%+++): 7.4 mo vs. *MET* IHC (50%++w100%+++) 1.9 m mo. For FISH-positive pts, 8.2 mo and FISH negative m 1.3 mo	13.2
Landi et al. [88]	Phase II (NCT 02499614)	NSCLC (locally advanced or metastatic)	26 (MET amp [*n* = 16], MET exon 14 SM [*n* = 9], concurrent amp and mutation [*n* = 1])	*MET* exon 14 SM/*MET* amp	–	Crizotinib 250 mg BID	27%	4.4 mo; 6-mo PFS: 30.9%; 12-mo PFS: 20.6%	Mo 5.4: 6-mo OS: 43.9%; 12-mo OS: 26.3%
Wolf et al. [21]	Phase II	NSCLC	364	*MET* amp/*MET* exon 14 SM	–	Capmatinib 400-mg tablet BID	GCN ≥ 10: 29 (19–41) GCN 6–9: 12 (4–26) GCN 4 or 5: 9 (3–20) GCN < 4: 7 (1–22) *MET* exon 14 SM and any GCN: 41 (29–53) GCN ≥ 10: 40 (16–68) *MET* exon 14 SM and any GCN: 68 (48–84) GCN ≥ 10, *MET* exon 14 SM and any GCN: 48 (95% CI 30–67)	GCN ≥ 10: 4.1 (2.9–4.8) GCN 6 to 9: 2.7 (1.4–3.1) GCN 4 or 5: 2.7 (1.4–4.1) GCN < 4: 3.6 (2.2–4.2) *MET* exon 14 SM and any GCN: 5.4 (4.2–7.0) GCN ≥ 10: 4.2 (1.4–6.9) *MET* exon 14 SM and any GCN: 12.4 (8.2–NE)	–
Moro-Sibilot et al. [89]	Phase II (NCT02034981)	NSCLC (locally advanced or metastatic)	MET > 6 copies cohort (*n* = 25), MET-mutated cohort (*n* = 28) (MET exon 14; *n* = 25)	*MET* amp and mutation (exons 14 and 16–19)	–	Crizotinib 250 mg BID	MET > 6 copies cohort: at 2 cycles 16%. Best ORR 32%. MET exon 14 cohort: ORR at 2 cycles 12%, best ORR 40%	*MET* > 6 copies cohort: 3.2 mo; *MET* exon 14 cohort: 3.6 mo	*MET* > 6 copies cohort: 7.7 mo; MET exon 14 cohort: 9.5 mo
Seto et al. [90]	Phase II GEOMETRY mono-1 study (NCT02414139)	Stage IIIb or IV NSCLC	45 (Japanese)	*MET* exon 14 SM, *MET* amp	–	Capmatinib 400-mg tablets BID fasting (21-day cycles)	GCN ≥ 10: 5 (16.7–76.6); GCN ≥ 4 and < 6: 1 (0.3–44.5); GCN < 6:1 (0.4–64.1); GCN ≥ 10: 2 (15.8–100.0)	–	–
Schuler et al. [80]	Phase I (NCT01324479)	Advanced NSCLC (stage IIIB or IV)	55	*MET* amp, *MET* OE	–	Capmatinib 600 or 400 mg BID	Investigator assessment 20%; BIRC 22%	Investigator assessment 3.7 mo; BIRC assessment 3.7 mo	–
Park et al. [87]	Observational	Stage IIIB/IV NSCLC	196. SISH positive (*n* = 20), IHC positive (*n* = 87)	*MET* OE/MET amp	–	Erlotinib 150 mg PO (28 days)	IHC positive: 8 (9.2%); SISH positive 1 (5.0%)	IHC positive: 2.0 (1.8–2.2), SISH positive: 1.7 (1.2–2.2)	–

Table 3 (Continued)

Study	Study design	Cancer type	Study; population (*MET* +)	*MET* alteration type	*MET* alteration status	Therapy	ORR, %	mPFS, mo	OS, mo
Combination therapy									
Tepotinib plus gefitinib									
Wu et al. [30]	Phase Ib/II (NCT01982955) RCT	NSCLC advanced or metastatic	55	*MET* OE or *MET* amp	Acquired	Tepotinib 500 mg/day plus gefitinib 250 mg vs. chemotherapy (pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin; $n=24$)	Overall: 45%, MET IHC 3+: 4.33; *MET* amp: 2.67 vs. 8% (33%)	Investigator-assessed: 4.9 vs. 4.4 mo: mPFS (investigator assessment) was 8.3 mo with tepotinib plus gefitinib vs. pts with MET IHC3+ and doubled to 16.6 mo with tepotinib plus gefitinib in pts with MET amp	Overall: 17.3 mo vs. chemotherapy: 18.7 mo; MET IHC3+: OS 37.3 vs. 17.9 mo; MET amp: OS 37.3 vs. 13.1 mo
Osimertinib plus savolitinib									
Sequist et al. [32]	Phase Ib (NCT02143466)	NSCLC (locally advanced or metastatic)	Part B 138 pts. Subcohort B1 = 72 (previous EGFR TKI treatment); B2 = 54 no EGFR-TKI pretreatment and Thr790Met negative; B3: 18 no previous EFGR TKI, Thr790Met-positive pts	*MET* amp	Acquired	Osimertinib 80 mg plus savolitinib 600 mg	Overall part B 48%. B1: 30%; B2: 65%; B3: 67%	Overall part B; median 7.6 mo. B1: 5.4 mo; B2: 9.0 mo; B3: 11.0 mo	–
			Part D: 42 pts. No previous third-generation EFGR TKI, Thr790Met-negative pts	*MET* amp		Osimertinib 80 mg plus savolitinib 300 mg	64%	9.1 mo	–
Other combination therapies									
Wu et al. [33]	Phase Ib/II (NCT01610336)	NSCLC ($n=161$)	Phase Ib ($n=61$)	*MET* amp	Acquired	Gefitinib 250 mg OD + capmatinib 100–800 mg OD or 200–600 mg BID	0.23%	–	–

Table 3 (Continued)

Study	Study design	Cancer type	Study; population (*MET* +)	*MET* alteration type	*MET* alteration status	Therapy	ORR, %	mPFS, mo	OS, mo
			Phase II ($n=100$)			Capmatinib 400 mg BID plus gefitinib 250 mg OD	Overall: 29%; GCN ≥ 6 (n = 36): 47%; 4 ≤ GCN < 6 (n = 18): 22%; GCN < 4 (n = 41): 12%; IHC 3+ (n = 78): 32%; IHC 2+ ($n=16$): 19%; IHC 0 ($n=4$): 25%	All pts: 5.5–5.6 mo; GCN ≥ 6 (n = 36), 5.49–7.29 mo; GCN < 6 (n = 18) 5.39–7.46 mo; GCN < 4 (n = 41) 3.91–5.55 mo; IHC 3+ (n = 78) 5.45–7.10 mo; IHC 2+/GCN ≥ 5 (n = 8) 7.29–9.07 mo	–
Yang et al. [37]	Phase Ib (NCT02374645)	NSCLC (advanced)	44	*MET* amp	Acquired	Savolitinib 600 mg OD plus gefitinib 250 mg OD	–	–	–
McCoach et al. [39]	Phase I (NCT01911507)	Lung adenocarcinoma	18	*MET* expression	–	INC280 five dose levels (100–600 mg PO BID) + erlotinib 100 and 150 mg	–	–	–
McCoach et al. [91]	Phase I/II (NCT01911507)	Advanced/metastatic NSCLC	17	*MET* amp, MET exon 14 SM	–	INC280: 400 mg BID + erlotinib 150 mg BID	Cohort A (EGFR mutant $n=12$) 50%; cohort B (EGFR wildtype, $n=5$) 75%	–	–
Nishio et al. [38]	Phase I (JO25725; JapicCTI-111563)	NSCLC	Six: five adenocarcinoma, one SCC	*MET* OE	–	Onartuzumab 15 mg/kg plus erlotinib 150 mg/day PO	–	–	–
Camidge et al. [36]	Phase1b (NCT02099058)	NSCLC	42 (37 [36 evaluable]; EGFR M+ in 29 pts, EGFR M- in 7 pts)	*MET* amp/MET exon 14 SM	–	Telisotuzumab vedotin[a] 2.4 mg/kg (dose-escalation phase) or 2.7 mg/kg plus erlotinib 150 mg OD	EGFR M+: 34.5% EGFR M-: 28.6%	EGFR M+ group mo NR; EGFR M - group 5.9 mo	–
Felip et al. [92]	Phase Ib/II (NCT02335944)	Stage IIIB/IV NSCLC	68 (23)	–	Acquired	Capmatinib 400 mg BID + nazartinib 100 mg OD	43.5 (23.2–65.5)	7.7 (5.4–12.2)	18.8 (14.0–21.3)

Table 3 (Continued)

Study	Study design	Cancer type	Study; population (*MET* +)	*MET* alteration type	*MET* alteration status	Therapy	ORR, %	mPFS, mo	OS, mo
Camidge et al. [40]	Phase II (NCT01900652) (RCT)	NSCLC stage IV	111	–	Acquired	IV LY 750 mg Q2W + erlotinib 150 mg OD on a 28-day cycle	LY + E 3.0%, LY 4.3%	LY + E (3.3 mo), LY (1.6 mo)	NR

amp amplification, *BID* twice daily, *BIRC* blinded independent review committee, *EGFR* epidermal growth factor receptor, *FISH* fluorescence in situ hybridization, *GCN* gene copy number, *IHC* immunohistochemistry, *IRB* institutional review board, *IRC* independent review committee, *ITT* intent to treat, *IV* intravenous, *LY* emibetuzumab, *LY+ E* emibetuzumab + erlotinib, *M+* Mutation positive, *M-* Mutation negative, *MET* mesenchymal-epithelial transition, *mo* months, *mPFS* median progression-free survival, *NE* not evaluable, *NR* not reported, *NSCLC* non-small-cell lung cancer, *OD* once daily, *OD* once daily, *OE* overexpression, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PO* oral administration, *pts* patients, *Q2W* every 2 weeks, *SCC* squamous cell carcinoma, *SISH* silver in situ hybridization, *SM* skipping mutation, *TKI* tyrosine kinase inhibitor, – indicates not reported

[a]ABBV-399; teliso-v

a phase III randomized clinical trial, evaluated the efficacy of savolitinib 600 or 400 mg versus sunitinib 50 mg in patients with *MET*-amplified/chromosome 7 gain PRCC. Chouieri et al. [57] reported a PFS of 7.0 (95% CI 2.8–not calculated [NC]) versus 5.6 (95% CI 4.1–6.9) and OS NC (95% CI 11.9–NC) versus 13.2 (95% CI 7.6–NC) and further concluded that efficacy data favored savolitinib over sunitinib and showed superior safety (Table 4). Schöffski et al. [58] reported a phase II trial (the European Organisation for Research and Treatment of Cancer [EORTC] 90101 CREATE trial) in patients with type 1 PRCC with *MET* exon mutations (16–19)/*MET* amplification, demonstrating that crizotinib had higher 1-year PFS (75%) and 1-year OS (75%) rates with long-lasting disease control in a *MET*-positive subcohort compared with a *MET*-negative subcohort (PFS rate 27.3%, OS rate 36.9%) [58]. Choueiri et al. [59] also conducted a large single-arm biomarker-profiled phase II trial of savolitinib in patients with type I or II PRCC with dysregulated *MET* pathway (*MET*/HGF GCN gain) and reported a median PFS of 6.2 versus 1.4 months in *MET*-driven and *MET*-negative groups, respectively, and concluded that savolitinib has acceptable antitumor activity and tolerability in patients with *MET*-driven PRCC (Table 4) [59]. Besides *MET* inhibitor monotherapy, novel combination therapies have also been tested in PRCC. Suarez Rodriguez et al. [60] reported the OS results for durvalumab and savolitinib from a phase I/II study involving patients with metastatic PRCC ($n=42$), demonstrating an overall ORR of 27% with PFS and OS of 4.9 and 12.3 months, respectively. A higher ORR of 40% was observed in the *MET*-positive subgroup [60] (Table 4). However, further trials involving patient stratification based on *MET* alteration status are required to authenticate the effectiveness of these novel combination therapies

3.4 Other Cancers

A total of 13 studies demonstrating the clinical outcomes of *MET*-targeted therapies in metastatic colorectal cancer [61], glioblastoma [62], advanced hepatocellular carcinoma (HCC) [63], clear-cell sarcoma [64], solid tumors [65–69], and other cancers [70–72] were included in this review (Table 5). In studies with solid tumors, capmatinib (INC280) 100–600 mg BID was used in a dose-escalation cohort [65, 67] and 600 mg BID was used in a dose-expansion cohort [67], whereas the dose of SAR125844 was 570 mg/m^2. Only one study reported the clinical evidence for an antibody–drug conjugate in solid tumors: telisotuzumab (ADT 700) 15 mg/kg [66]. Among these studies, the best ORR was 14.3% with SAR125844 in gastric cancers, followed by telisotuzumab (ORR 8.9%) in advanced solid tumors (lung, gastric, esophageal, ovarian, and colorectal cancer) (Table 5). Other studies reported clinical evidence for monotherapy, including INC280 [62], tepotinib [63], and emibetuzumab [71] in glioblastomas and HCC. Decaens et al. [63] reported the efficacy and safety of tepotinib 500 mg OD in a single-arm phase II trial involving patients with *MET*-amplified HCC who had previously received sorafenib. The authors reported that, irrespective of IHC 2 versus 3+ or in situ hybridization (ISH)-positive versus -negative status, tepotinib resulted in antitumor activity with a median OS of 5.6 months and mPFS in the overall population of 3.4 months (IHC 2+ vs. 3+ mPFS 4.0 vs. 3.2 months: ISH positive vs. negative: PFS 4.2 vs. 3.2 months, respectively) [63].

Table 4 Clinical outcomes of MET inhibitors in papillary renal cell carcinoma and gastric cancers

Study	Study design	Cancer type	Study population (*MET* +)	*MET* alteration type	Therapy	ORR, %	PFS
PRCC							
Schöffski et al. [58]	Phase II (NCT01524926)	PRCC type 1	41 (23 eligible with PRCC) (4)	*MET* mutation exons (16–19)/ MET amp	Crizotinib 250 mg BID	50.0	1-year PFS 75.0%; 2-year PFS 75.0%
Choueiri et al. [59]	Phase II (NCT02127710)	PRCC (type I and II)	109 (44 [MET-driven group])	*MET*/HGF gene copy number gain	Savolitinib (HMPL504/volitinib, AZD6094) 600 mg OD	–	6.2 mo
Gan et al. [94]	Phase I (NCT01773018)	PRCC	4	*MET* copy number increase	AZD6094 (HMPL504/volitinib)	–	–
Choueiri et al. [95]	Phase II (NCT00726323)	PRCC (advanced)	74 (36)	Germline *MET* mutation ($n=11$); somatic mutation ($n=5$); gain of chromosome 7= ($n=18$); MET amp ($n=2$)	Foretinib 240 mg OD (intermittent arm); cohort B, foretinib 80 mg daily (daily dosing arm)	–	–
Choueiri et al. [57]	Phase III NCT03091192	Metastatic PRCC	60	*MET* amp, chromosome 7 gain	Savolitinib 600 mg PO (or 400 mg if < 50 kg) OD continuously, or sunitinib 50 mg PO OD in 6-wk cycles of 4 wks tx followed by 2 wks without tx	–	Savolitinib 7.0 (2.8–NC); sunitinib 5.6 (4.1–6.9)
Suarez Rodriguez et al. [60]	Phase I/II (NCT02819596)	Metastatic PRCC	42 (41)	*MET* expression	Durvalumab 1500 mg Q4W and savolitinib 600 mg OD	Overall: 27%; previously untreated cohort (n=27) 33%	4.9 mo (95% CI 2.5–12.0)
Gastric cancers							
Aparicio et al. [54]	Phase II (NCT02034981)	Esogastric adenocarcinoma	570	*MET* amp	Crizotinib 250 mg BID	55.6%	3.2 mo
Van Cutsem et al. [50]	Phase II (NCT02016534)	GC/GEJ/esophageal and other solid tumors	60	*MET* amp	AMG 337 × 300 mg PO OD)	Overall 16%	3.4 mo
Kang et al. [51]	Phase I (NCT01472016)	Advanced GEC	6 (4)	*MET* amp	ABT-700 × 15 mg/kg IV	75%	27, 18, and 24 wks, for three pts with PR
Shah et al. [52]	Phase II (NCT00725712)	Metastatic GC	74 (3 [intermittent cohort])	*MET* amp	Foretinib 240 mg/day	–	1.7 mo

Table 4 (Continued)

Study	Study design	Cancer type	Study population (*MET* +)	*MET* alteration type	Therapy	ORR, %	PFS
Shah et al. [56]	Phase III (NCT01662869) RCT	Advanced gastroesophageal adenocarcinoma	562 (onartuzumab plus mFOLFOX6 [*n*=279] vs. PL plus mFOLFOX6 [*n*=283]) (*MET* 2+/3+ GEC in the PL plus mFOLFOX6 109 [38.5%]; *MET* 2+/3+ GEC in onartuzumab plus mFOLFOX6 groups, 105 [37.6%])	*MET* OE	Onartuzumab 10 mg/kg plus mFOLFOX6 vs. PL + mFOLFOX6	44.6 vs. 53.8%	6.7 vs. 6.8 mo
Lee et al. [53]	Phase II NCT#02299648: savolitinib monotherapy (biomarker D, #02449551); savolitinib + docetaxel (biomarker D, NCT#02447406), savolitinib + docetaxel (biomarker E, NCT#02447380);	Metastatic and/or recurrent gastric adenocarcinoma	715; *MET* amp (25/715, 3.5%); *MET* OE by IHC 3+ (42/479, 8.8%)	*MET* amp/*MET* OE	Savolitinib	50% (10/20; 95% CI 28.0–71.9)	–
Iveson et al. [55]	Phase Ib (NCT00719550)	Advanced or metastatic gastric or esophagogastric junction adenocarcinoma	121 included (91)	*MET* OE	Rilotumumab 15 mg/kg + ECX (epirubicin 50 mg/m^2 IV on D1, cisplatin 60 mg/m^2 IV on D1, and capecitabine 625 mg/m^2 BID PO on D1–21) Q3W for maximum of 10 cycles	20 (50%)	5.7 mo (4.5–7.0)
Catenacci et al. [93]	Phase III study (NCT01697072)	Locally advanced or metastatic gastric or GEJ adenocarcinoma	1477 (1291 evaluable) (1043 c-MET +)	–	Rilotumumab 15 mg/kg IV, epirubicin 50 mg/m^2 IV, and cisplatin 60 mg/m^2 IV per 21-day cycle. Capecitabine 625 mg/m^2 PO BID vs. PL	29.8% (24.3–35.7)	Rilotumumab plus ECX: 5.6 (5.3–5.9); PL plus ECX 6.0 (5.7–7.2)

amp amplification, *BID* twice daily, *CI* confidence interval, *D* day, *ECX* Epirubicin cisplatin and capecitabine, *EGFR* epidermal growth factor receptor, *GC* gastric cancer, *GEC* gastric or esophageal cancer, *GEJ* gastroesophageal junction, *HGF* hepatocyte growth factor, *IHC* immunohistochemistry, *IV* intravenous, *MET* mesenchymal-epithelial transition, *mFOLFOX6* leucovorin, fluorouracil, and oxaliplatin, *mo* month(s), *NC* not calculated, *OD* once daily, *OE* overexpression, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PL* placebo, *PO* oral administration, *PR* partial remission, *PRCC* papillary renal cell carcinoma, *pt(s)* patient(s), *QxW* every x weeks, *RCC* renal cell carcinoma, *RCT* randomized controlled trial, *tx* treatment, *wk(s)* week(s), – indicates not reported

Table 5 Clinical outcomes of MET inhibitors in solid tumors and other cancers

Study	Study design	Cancer type	Study population (*MET* +)	*MET* alteration type	Therapy	ORR, %	PFS
Solid tumors							
Bang et al. [65]	Phase I (NCT01324479)	Advanced solid tumors	33	–	INC280 (six dose cohorts of 100–600 mg BID)	–	–
Strickler et al. [66]	Phase I (NCT01472016)	Advanced solid tumors (lung, GC, esophageal, ovarian, and CRC)	45 (10)	*MET* amp	Telisotuzumab (ADT 700) 15 mg/kg	8.9%	17.9 wks
Bang et al. [67]	Phase I (NCT01324479)	Solid tumors	76 Dose-escalation cohort: $n = 38$ (with HCC [$n = 15$], colon [$n = 8$], GC [$n = 2$], lung [$n = 1$], and other advanced solid tumors [$n = 12$]) (23 evaluable pts) Dose expansion cohort: $n = 38$ (with HCC [$n = 11$], GC [$n = 9$], and other advanced solid tumors [non-NSCLC; $n = 18$]) (31 evaluable pts)	*MET* OE	Capmatinib dose escalation: BID doses: 100 mg, 200 mg, 250 mg, 350 mg, 450 mg, and 600 mg. Dose expansion: 600 mg BID	Dose-escalation cohort: 0 (0.0–9.3) Dose expansion: 0 (0.0–9.3)	–
Angevin et al. [68]	Phase I (NCT01391533)	Solid tumors (including NSCLC)	72 (68 involved in efficacy); (29 pts with MET amp)	*MET* amp	SAR125844 (570 mg/m^2)	–	–
Shitara et al. [69]	Phase I (NCT01657214)	Solid tumors (GC, CRC, lung, kidney)	38 (19) Dose-expansion cohort: 14 (73.7%) had GC, one (5.3%) had CRC, two (10.5%) had lung cancer) Dose-escalation cohort: 3 (two with GC, one with lung cancer)	*MET* amp	SAR125844 (570 mg/m^2)	GC subpopulation 14.3%	–
Other cancers							
Hu et al. [96]	Phase I (NCT02978261)	Gliomas (high grade)	18	ZM fusion and/or *MET* exon 14	PLB-1001: 50–300 mg BID	–	80 days
Jia et al. [61]	Phase I/II (NCT02008383)	CRC (metastatic)	65 (8) (7 evaluable)	*MET* amp	Cohort: cabozantinib + panitumumab = 4; cohort: cabozantinib = 4	–	–
van den Bent et al. [62]	Phase Ib/II study (NCT01870726)	Glioblastoma	10 (phase II)	*MET* amp	INC280 monotherapy 400 mg BID	–	–

Table 5 (Continued)

Study	Study design	Cancer type	Study population (*MET* +)	*MET* alteration type	Therapy	ORR, %	PFS
Kim et al. [70]	Phase I (NCT# 02447406)	Seven GC, five melanoma, three sarcoma, two rectal cancer	17 (10)	*MET* OE/ MET amp	Savolitinib 200 mg OD, 400 mg OD, 600 mg OD, savolitinib 800 mg + docetaxel IV 60 mg/ m^2)	–	–
Decaens et al. [63]	Phase II NCT02115373	HCC (advanced)	49	*MET* amp	Tepotinib 500 mg OD	8.2%	Overall population ($n=49$) 3.4 mo; IHC 2+ ($n=41$) PFS 4.0 mo; IHC 3+ ($n=8$) 3.2 mo; ISH status positive ($n=6$) 4.2 mo, negative ($n=43$) 3.2 mo
Banck et al. [71]	Phase I (NCT0128756)	RCC HCC NSCLC	19 9 19	*MET* OE	Emibetuzumab 2000 mg Q2W IV	–	–
Schöffski et al. [64]	Phase II (NCT01524926)	Advanced or metastatic clear-cell sarcoma	43 (36 eligible); 31 (26 evaluable)	–	Crizotinib 200 mg BID, 250 mg BID	3.8%; 95% CI 0.1–19.6	131 days (49–235); 3-, 6-, 12- and 24-mo PFR 53.8% (34.6–73.0), 26.9% (9.8–43.9), 7.7% (1.3–21.7), and 7.7% (1.3–21.7)
Harding et al. [72]	Phase Ib/II (NCT02082210)	GC ($n=16$), HCC ($n=45$), RCC ($n=15$), NSCLC ($n=15$)	97 (73 evaluable)	*MET* OE	Emibetuzumab 750 mg and ramucirumab 8 mg/kg IV Q2W	–	MET expression of $\geq$2+ staining intensity in $\geq$50% of tumor cells: 7.4 mo, MET expression of $\leq$2+ staining intensity in $<$50% of tumor cells: 2.8 mo

amp amplification, *BID* twice daily, *CI* confidence interval , *CRC* colorectal cancer, *GC* gastric cancer, *HCC* hepatocellular carcinoma, *IHC* immunohistochemistry, *ISH* in situ hybridization, *IV* intravenous, *MET* mesenchymal-epithelial transition, *mo* months, *NSCLC* non-small-cell lung cancer, *OD* once daily, *OE* overexpression, *ORR* objective response rate, *OS* overall survival, PFR, *PFS* progression-free survival, *pts* patients, *Q2W* every 2 weeks, *RCC* renal cell carcinoma, *wk(s)* week(s), – indicates not reported

3.5 Ongoing Trials

A robust pipeline of *MET* inhibitors across multiple tumor types targeting different aspects of the *MET* signaling pathway is currently being explored and at various phases of clinical development. Table 6 summarizes the various ongoing trials.

4 Discussion

The *MET* pathway plays a remarkable role in the origin of cancer. Therefore, it is logical to consider *MET* as an actionable target for the treatment of invasive tumors with metastatic potential in different cancer types [3]. Current strategies for MET-targeted therapies include inhibiting

Table 6 Summary of ongoing clinical trials in different cancer types

Cancer type	Phase	*MET* alteration type	Study population (*n*)	MET inhibitor	Clinical trial ID
NSCLC	II	*MET* amp/*MET* exon 14 SM	6/25	Cabozantinib	NCT03911193
	II	*MET* amp	172[a]	Osimertinib + savolitinib	NCT03778229
	Ib	*MET* amp	23[b]/135[a]	Capmatinib ± erlotinib	NCT02468661
	II	*MET* exon 14 alterations	20	Capmatinib	NCT02750215
	II	*MET* gene mutation/amp	68[b]/200[a]	MGCD265	NCT02544633
	II	*MET* exon 14 SM	12[b]/25[a]	Merestinib	NCT02920996
	II	*MET* amp	1[b]/168[a]	SAR125844	NCT02435121
	I	*MET* exon 14 SM/amp	37[b]/60[a]	Bozitinib (PLB1001)	NCT02896231
	I/II	*MET* exon 14 SM	68[c]	Glumetinib	NCT04270591
	II	*MET* mutation/amp	68[b]/200[a]	MGCD265	NCT02544633
	I/II	*MET* amp/mutation	5770[a]	Sym015	NCT02648724
	II	*MET* expression	310[c]	Telisotuzumab vedotin (ABBV-399)	NCT03539536
	I/II	*MET*-exon14 gene mutation and/or MET gene amp, and/or MET OE	111[c]	REGN5093	NCT04077099
	I	*MET* amp/mutation	460[c]	Amivantamab	NCT02609776
Solid tumors (advanced/metastatic)	I	*MET* exon k SM/*MET* amp/*MET* fusion	120[c]	TPX-0022	NCT03993873
Solid tumors	I	*MET* amp	40[b]/80[a]	OMO-1	NCT03138083
Solid tumors (advanced/metastatic)	II	*MET* exon k SM/*MET* amp/OE	89[a]	AMG337	NCT03147976
Solid tumors, lymphomas, or multiple myeloma, including lung cancer	II	*MET* amp	–	Crizotinib	NCT02465060
Hepatocellular carcinoma	I/II	*MET* +	117[b]/158[a]	MSC2156119J	NCT01988493
Metastatic colorectal cancer	II	*MET* amp	15[a]	Savolitinib	NCT03592641
Advanced tumors (NSCLC, head and neck cancer)	I	*MET* gene mutation/amp	–	Sitravatinib	NCT02219711

amp amplification, *ID* identification, *MET* mesenchymal-epithelial transition, *NCT* national clinical trials, *NSCLC* non-small-cell lung cancer, *OE* overexpression, *SM* skipping mutation

[a]Original estimated enrollment

[b]Actual enrollment

[c]Estimated enrollment

kinase activity by preventing the *MET*-HGF extracellular association with biological antagonists or neutralizing antibodies, preventing the phosphorylation of the kinase domain with the aid of small-molecule inhibitors, and blocking *MET* signaling through relevant signal transducers [4, 5, 7, 9, 73]. Several trials evaluated the benefits of MET-targeted therapies involving various agents, including anti-*MET* antibodies (onartuzumab, emibetuzumab) [38, 74], anti-HGF antibodies (ficlatuzumab, rilotumumab) [75], and TKIs (crizotinib, tivantinib, cabozantinib). However, the overall activity of these therapies was low, possibly because of the lack of molecular stratification based on *MET* genetic status or the use of low *MET* status thresholds in those trials, diluting individual responses in patients with genetically susceptible tumors [5, 76–78]. Moreover, despite the failure of some clinical trials, investigators have observed certain benefits with MET inhibitors in a selected *MET*-altered population, which paved the way for investigators to carefully choose biomarkers and thresholds in subsequent trials of MET inhibitors, partially contributing to the success of *MET* TKIs, such as crizotinib, tepotinib, capmatinib, and savolitinib.

On the path to finding the right biomarkers for MET inhibitors, the first breakthrough was in *MET* exon 14 skipping mutations. The advent of *MET* TKIs, specifically crizotinib (PEOFILE 1001) [17], capmatinib (GEOMETRY mono-1) [21], tepotinib (VISION) [19], and savolitinib [79] has changed the therapeutic landscape of NSCLC harboring *MET* alterations (*MET* exon 14 skipping mutation), with these agents emerging as a new standard of care with

acceptable clinical benefits. Further, in the development of MET-directed EGFR-TKI resistance, the combination of *MET* TKIs and EGFR TKIs might be beneficial, with existing literature suggesting the same. Trials such as INSIGHT [30] and TATTON [32] evidenced the clinical benefits of tepotinib plus gefitinib and osimertinib plus savolitinib, respectively, in patients with NSCLC. In addition, studies evaluating the clinical benefits in tumors harboring de novo *MET* amplifications demonstrated acceptable clinical benefits with crizotinib (PROFILE 1001) [42] and capmatinib (GEOMETRY mono-1) [21] in NSCLC and further confirmed that clinical responses were higher in patients with high *MET* amplification (*MET*/CEP7 ratios ≥ 5 or GCN ≥ 10), indicating the therapeutic benefits in particular subsets of patients.

In gastric cancers, noteworthy clinical benefits were reported with savolitinib (VIKTORY) [53] and crizotinib (AcSe) [49] specifically in high *MET*-amplified subsets of patients. On the other hand, multiple studies tested chemotherapy combined with MET inhibitors but had disappointing results [56]. In PRCC, notable clinical benefits were reported with savolitinib (SAVOIR trial) [57] and crizotinib (the EORTC 90101 CREATE trial) [58] in MET-driven disease. Other novel combination therapies are currently being trialed [60].

Most trials across different cancer types have been restricted to either *MET* amplification or *MET* overexpression. Accurate patient identification and stratification is critical for the success of *MET*-targeted therapy in clinical practice [6]. However, the selection of patients with a high likelihood of clinical benefit from *MET*-targeted therapies has become more ambiguous because of disparities in the criteria for selection of biomarkers [80]. Moreover, the predictive value of *MET* aberration biomarkers in tumor tissue has not always been consistent. The root for this inconsistency may lie in the diagnostic methods selected for assessment of alterations in tumor tissue [81]. On the other hand, discordance between *MET* GCN and protein expression requires careful consideration and highlights the challenges of defining molecular inclusion criteria for clinical trials [62].

The use of next-generation sequencing to detect *MET* alteration has been widely implemented in molecular laboratories, enabling the detection of a wide array of genetic abnormalities (insertions, substitutions, copy number changes, deletions, duplications, chromosome inversions, and chromosome translocations), facilitating the accurate detection of the *MET* exon 14 splice variant with good sensitivity and specificity [82]. Furthermore, although fluorescence ISH (FISH) was considered the gold standard for the detection of *MET* amplification, the prevalence of *MET* amplification detection with FISH is variable across the literature because of a lack of consensus in definitions of *MET* positivity [83]. IHC offers similar advantages to FISH in the detection of *MET* amplification, but several studies have reported that IHC was a poor screen for the detection of actionable *MET* alterations [84].

The current review identified disparities in patient stratification, with studies adopting different cutoff ranges for *MET* positivity through the use of a range of diagnostic platforms, which may be the reason for non-consensus in the clinical outcomes among studies. To the best of our knowledge, this is the first systematic literature review summarizing the published evidence on the clinical outcomes of MET inhibitors in different cancers. However, our review has certain limitations. First, despite a careful electronic search of literature databases, some publications may have been missed. Second, comparatively few RCTs were included in this review.

5 Conclusion

This review provides an overview of the literature on various MET inhibitors in a range of clinical development phases. *MET*-selective TKIs (capmatinib, tepotinib, and savolitinib) have become the new standard of care in NSCLC, specifically with *MET* exon 14 skipping mutations. The combination of *MET* TKI and EGFR TKI (osimertinib plus savolitinib, tepotinib plus gefitinib) may be a potential solution for *MET*-driven EGFR TKI resistance. Further, *MET* alterations may be an actionable target in GC and PRCC. However, most of this evidence is based on phase I and II studies, so phase III studies are warranted to confirm the efficacy and safety of MET inhibitors in various cancers. Furthermore, to avoid disparities in evaluating clinical outcomes, unique biomarkers with accurate diagnostic platforms are much needed in MET-targeted therapeutic strategies.

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