MET-dependent solid tumours — molecular diagnosis and targeted therapy

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Abstract | Attempts to develop MET-targeted therapies have historically focused on MET-expressing cancers, with limited success. Thus, MET expression in the absence of a genomic marker of MET dependence is a poor predictor of benefit from MET-targeted therapy. However, owing to the development of more sensitive methods of detecting genomic alterations, high-level *MET* amplification and activating *MET* mutations or fusions are all now known to be drivers of oncogenesis. *MET* mutations include those affecting the kinase or extracellular domains and those that result in exon 14 skipping. The activity of MET tyrosine kinase inhibitors varies by *MET* alteration category. The likelihood of benefit from MET-targeted therapies increases with increasing levels of *MET* amplification, although no consensus exists on the optimal diagnostic cut-off point for *MET* copy number gains identified using fluorescence in situ hybridization and, in particular, next-generation sequencing. Several agents targeting exon 14 skipping alterations are currently in clinical development, with promising data available from early-phase trials. By contrast, the therapeutic implications of *MET* fusions remain underexplored. Here we summarize and evaluate the utility of various diagnostic techniques and the roles of different classes of MET-targeted therapies in cancers with *MET* amplification, mutation and fusion, and MET overexpression.

Dysregulation of the receptor tyrosine kinase c-MET (hereafter referred to as MET) is an established driver of oncogenesis[1] (BOX 1). In comparison with many other proto-oncogenes, MET is notable in that three different types of genomic alteration can lead to clinically relevant oncogenesis: amplification, mutation and fusion. All three of these states pose distinct diagnostic challenges in the clinic. Furthermore, these alterations can be identified in two major contexts — either as primary or secondary drivers of cancer growth. Primary MET dependence is exemplified by tumours that rely solely on overactive MET signalling to fuel their growth. Secondary MET dependence is characterized by reliance on another oncogenic driver (such as mutant *EGFR*) with concurrent dependence on MET[2,3]. Secondary MET dependence can be de novo or acquired following the selective pressures of inhibitors of the primary driver oncoprotein[4–7].

Identifying tumours that are oncogenically addicted to MET is crucial, owing to the clinical availability of multiple MET-directed therapeutics. A variety of anti-MET or anti-hepatocyte growth factor (HGF) antibodies/antibody–drug conjugates (ADCs) and multikinase or selective MET tyrosine kinase inhibitors (TKIs) have been tested. For example, the multikinase MET inhibitor crizotinib demonstrated activity in patients with *MET* exon 14-altered and *MET*-amplified lung cancers[8]. Likewise, selective next-generation MET TKIs, including tepotinib, capmatinib and savolitinib, demonstrated activity in the same MET-driven cancers[9–11]. However, the identification of such tumours during cancer diagnosis has, thus far, been hindered by the lack of standardized cut-off points and testing methodology for MET-dependent states that are measured as a continuous variable (such as *MET* amplification) and by the inability of less-sophisticated assays to reliably capture both *MET* copy number gains and the wide variety of *MET* mutations and *MET* fusions that can lead to oncogenesis.

Thankfully, the field of MET-directed targeted therapy has seen incremental gains over the past few years owing to two factors: (1) the adoption of advanced diagnostic technologies that more effectively identify MET-dependent cancers, and (2) the contemporary strategy of molecular enrichment for patients with tumours of this phenotype in prospective trials investigating the efficacy of targeted therapies. In May of 2020, capmatinib received approval by the US FDA for the treatment of MET exon 14-altered lung cancers.

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Key points

- The degree of *MET* amplification is a continuous variable that can be measured using fluorescence in situ hybridization or next-generation sequencing. No consensus exists on the most appropriate diagnostic cut-off point for *MET* amplification.
- Patients with solid tumours harbouring high-level *MET* amplifications have a greater likelihood of benefit from single-agent or combination MET-targeted therapies than those with lower *MET* copy number gains.
- *MET* mutations are highly heterogeneous and can range from those that involve the *MET* kinase domain to those that result in *MET* exon 14 skipping.
- The activity of type I or type II MET tyrosine kinase inhibitors can substantially differ by *MET* mutation type.
- A wide variety of *MET* fusions have been identified, although the biology of these alterations and their implications for responses to MET-targeted therapies are not well characterized.
- MET overexpression in the absence of a known driver of MET dependence is a poor predictor of benefit from MET-targeted therapies.

This was a landmark approval of the first MET inhibitor for a genomically enriched population of MET-dependent cancers. In addition, tepotinib has been granted Breakthrough Therapy by the US FDA and fast-track designation by regulatory authorities in Japan[12–14].

As the landscape of diagnostic platforms and therapeutic repertoire for MET-dependent cancers has developed rapidly, in this review we summarize the current data on actionable *MET* alterations (such as *MET* amplification, mutations and fusions), their clinicopathological behaviour in various tumour types, contemporary diagnostic strategies and novel efforts to target MET. In addition, we discuss the pitfalls of relying on MET overexpression as the sole means of determining MET dependency.

MET amplifications

MET copy number gains can occur through polysomy or focal amplification. Polysomy occurs when chromosome 7, where *MET* is located, is inappropriately replicated by either isolated chromosomal or whole-genome duplication[15,16]. The presence of multiple chromosomes thus results in an increase in the number of *MET* copies, albeit with parallel increases in the copy number of other oncogenes located on chromosome 7 (including *EGFR*, *BRAF* and *CDK6*). With amplification, *MET* undergoes regional or focal copy number gains without chromosome 7 duplication[17] (FIG. 1). Thus, focal *MET* amplification is more likely to lead to oncogenic MET addiction than polysomy[17]. These findings parallel those from patients with breast cancer, in whom tumours harbouring *HER2* copy number gains owing to polysomy have a similar phenotype to that of *HER2*-negative tumours[18]. *MET* amplification can lead to elevations in MET expression, receptor activation and ligand-independent downstream signalling in preclinical models[19,20].

Diagnosis

Various techniques can be used to detect *MET* copy number alterations. These include fluorescence in situ hybridization (FISH), quantitative real-time PCR (qRT-PCR), and next-generation sequencing (NGS)[21]. Furthermore, NGS can be used to analyse primary tumour material or circulating tumour DNA (ctDNA) obtained from plasma, or other bodily fluids. Unfortunately, the specific cut-off points that define *MET* amplification vary with each technique and/or assay.

Fluorescence in situ hybridization. FISH is a commonly used technique leveraging fluorophore-coupled DNA fragments to tag and detect genomic regions of interest, usually in formalin-fixed paraffin-embedded (FFPE) tissue sections. One or more fluorophores can be used during testing to differentiate between specific regions. Following exposure to labelled probes, targeted gene sequences of interest will fluoresce with the respective colours. The number of signals identified indicates the number of copies of the gene (FIG. 1). Signals from a predetermined number of tumour cells are manually counted, and the mean number of signals per malignant cell is calculated. Samples analysed using FISH are examined using fluorescence microscopy to enable signal detection. The differentiation of signals arising from malignant and nonmalignant cells is critical for accurate assessment of copy number. Interpretation in some samples can be challenging; certain morphologies can cause tissue sectioning artefacts and overlapping signals. Also, a common limitation of FISH with FFPE tissue sections is that a large proportion of cells might display one (or no) signal, consistent with signal dropout owing to truncation of the cell nucleus. Signals from these cells should not be reported. Such issues might reduce the total number of evaluable cells, particularly when present in very small samples. Also, owing to signal dropout, incorporation of appropriate controls is essential.

MET copy number increases can be defined using FISH in two main ways. The first method relies on determining gene copy number (GCN). Using the Cappuzzo criteria, *MET* amplification is defined as a mean of five or more copies of *MET* per cell (*MET* GCN ≥5)[22–24]. Alternative definitions include a *MET* GCN of ≥6 (REF.[25]) and a *MET* GCN of ≥15 (REFS[26,27]). Unfortunately, simply determining GCN does not distinguish between selective *MET* amplifications and *MET* polysomy. In the second method, this limitation is overcome by calculating the ratio of *MET* to chromosome enumerating probe against chromosome 7 (CEP7); a separate fluorophore is used for the latter locus. Determination of this ratio adjusts for the number of chromosomes present and differentiates between selective *MET* amplifications and chromosomal duplication while also controlling for nuclear truncation such that cells with only a single CEP7 signal are not counted. A *MET* to CEP7 ratio ≥2.0 is typically used to define *MET* amplification[23,24,28–32]. Others have categorized the degree of amplification into three groups using *MET* to CEP7 ratios: low (≥1.8 to ≤2.2), intermediate (>2.2 to <5) and high (≥5)[17].

Next-generation sequencing. The methods used to determine *MET* copy number and the cut-off points for *MET* amplification vary across different NGS platforms[33–35]. Similar to the criteria applied for FISH, no consensus exists on a single definition of *MET* amplification. Most methods for determining copy number variants by NGS use the sequencing read depth approach. This method assumes that the read depth signal is proportional to the

Box 1 | **Pathophysiology of MET in cancer and the microenvironment**

Under physiological conditions, hepatocyte growth factor (HGF), the ligand for MET, regulates the epithelial-to-mesenchymal transition, which is involved in tissue repair and embryogenesis[223]. In cancer, increased MET activity promotes tumour growth by providing anti-apoptotic and pro-migratory signals[224]. Furthermore, the *MET* gene can be regulated by several transcription factors, including hypoxia-inducible factor 1 (HIF1)[225]. The inhibition of angiogenesis results in hypoxic stress that leads to MET-mediated local invasion and distant metastasis in preclinical models[226,227].

The MET pathway can also regulate the tumour microenvironment. During tissue repair, upregulation of HGF and increased HGF–MET autocrine signalling promotes the development of an immunosuppressive microenvironment. This occurs by conversion of immunologically active macrophages (M1 phenotype) to a tumour-growth-stimulating (M2) phenotype and by induction of a tolerogenic phenotype in dendritic cells[228,229]. MET inhibition can abrogate these effects while concurrently increasing the level of PD-L1 expression[230]. Thus, the combination of immunotherapy (for example, with an immune-checkpoint inhibitor) and a MET-targeted therapy is currently being explored in multiple ongoing trials (NCT03914300, NCT03866382, NCT03793166, NCT02819596 and NCT03742349).

number of copies of chromosomal segments in the specimen. Several bioinformatics tools have been developed for this approach[36–41]; however, these have limited sensitivity and specificity. Some algorithms focus on specific target regions and use selected control samples (such as sequence-read replicates) for read depth comparison to improve sensitivity and specificity[42]. Other algorithms use a control (blood or samples of non-malignant tissue) from the same patient to further enhance sensitivity, facilitate the systematic identification of clonal and subclonal copy number events, and provide more accurate integer copy number calls that are adjusted for purity, ploidy and tumour heterogeneity, from clinical sequencing data[34,43]. Notable advantages of NGS-based detection of copy number alterations, in addition to enabling the concurrent assessment of sequence variants across panels of hundreds of genes, include a high level of resolution and the ability to discern focal gene amplification from broad chromosomal gains.

Two types of NGS-based assays are used in the clinic: amplicon-based NGS and hybrid capture-based NGS. These techniques differ in terms of the method of DNA enrichment[44]. Briefly, hybrid capture-based NGS enables the more accurate assessment of copy number variations in *MET* and in other genes. This strength reflects the fact that hybrid capture enables the interrogation of broader regions of the genome as well as the identification and removal of sequence replicates, thereby enabling a more accurate determination of sequence coverage depth and overall copy number changes. By contrast, with the amplicon-based approach (in which the amplified regions are limited solely to stretches of DNA flanked by established primers) the genomic territory covered is limited, significant sequence bias can be introduced and sequence replicates cannot be removed, and thus the true sequence coverage depth is affected.

Several technical issues should be considered when using NGS. Firstly, the detection of copy number gains and/or losses is dependent on tumour purity and sample selection because non-malignant cells often become admixed with malignant cells during analysis[33–35]. Secondly, the use of poor-quality DNA (from archived tumour samples) can lead to an increase in the level of noise and make the accurate analysis of copy number alterations more difficult. Thirdly, given the common use of read depth as a pivotal component for copy number assessment, the assay used must have both deep and uniform sequence coverage in order to successfully provide both sensitive and specific clinical results[45]. Finally, investigations of the level of concordance between *MET* amplification quantified using NGS and using FISH have yet to be conducted. This lack of formal comparison makes the interpretation of NGS results more difficult, considering that FISH is currently the better studied method of detecting *MET* amplifications.

Other assays. NGS of plasma ctDNA samples enables the detection of *MET* amplifications. Calling methods for this technique are similar to those applied to NGS of tumour material[46,47]. Obtaining samples of ctDNA is generally less invasive than biopsy sampling and has the potential to overcome tumour heterogeneity, which can confound the accuracy of NGS of tumour biopsy samples; however, the accuracy of plasma-based calls is dependent on the sensitivity and resolution of the analysis platform and is reliant on the tumour shedding a sufficient amount of genetic material[46–49]. As such, the findings of several studies have demonstrated that amplifications can be missed using this method[46,50,51]. qRT-PCR of tumour material has also been used to detect *MET* amplifications, although the performance of this technique is not well characterized compared to that of FISH and NGS[7,52–59]. Again, the cut-off points used to define *MET* amplifications vary and no clear standardized definition has been proposed.

Clinical features

De novo MET amplifications. De novo *MET* amplifications are found across a wide variety of solid tumours. These amplifications are typically identified in <1–5% of non-small-cell lung cancers (NSCLCs)[30,60–63], <1–10% of gastric cancers[24,26,28,64–66], 2–4% of colorectal cancers (CRCs)[67,68], 13% of type 1 papillary renal cell carcinomas (PRCCs) and 3% of type 2 PRCCs[69], and at lower frequencies in oesophageal carcinomas and hepatocellular carcinomas (HCCs)[23,29,70]. No notable associations between *MET* amplification and smoking have been observed in patients with NSCLC[60,71]. *MET* amplifications can also be found in several cancer types in which these alterations have not been widely investigated, including glioblastoma, melanoma, gynaecological cancers and lymphoma, according to The Cancer Genome Atlas and the cBioPortal databases[72–76]. In many of these cancers, *MET* amplifications confer a poor prognosis[22,24,26,28,30]. Importantly, the apparent frequency of *MET* amplifications varies between cohorts, and the true frequency of *MET* amplifications within a particular context is often challenging to determine. Variability in the frequency of *MET* amplifications found in different studies is unsurprising given the lack of consensus on the optimal assay or cut-off point to use.

The NSCLC literature provides evidence that, compared with lower-level *MET* amplifications, high-level *MET* amplifications are more likely to be indicative of oncogenic dependence on MET. In one series of patients

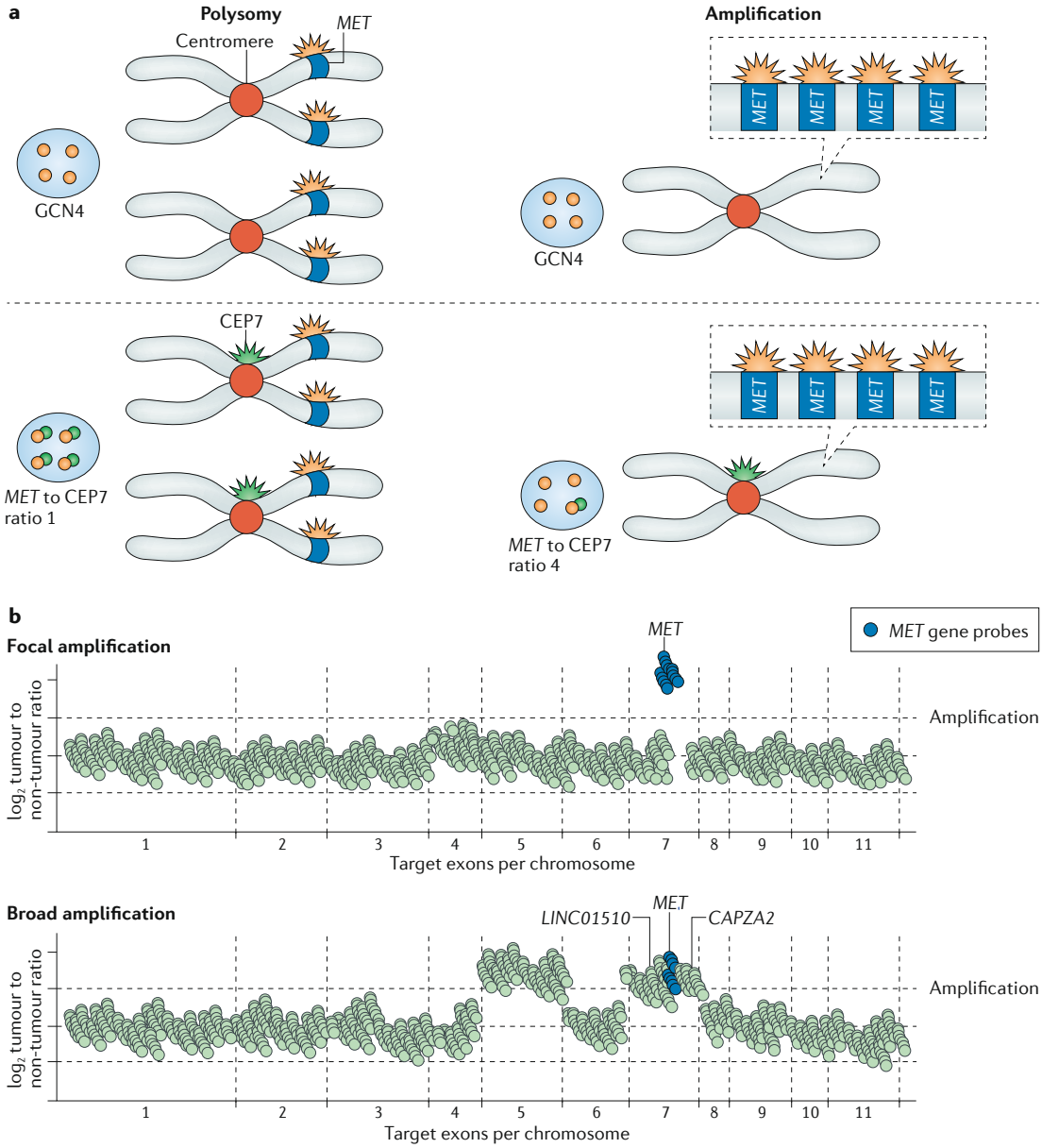

Fig. 1 | **Diagnosis of *MET*-amplified cancer. a** | The FISH-based determination of *MET* gene copy number (GCN) requires only a single probe (orange — locus specific identifier) against *MET*, which is quantified to determine GCN. This strategy does not enable differentiation between polysomy and true focal amplification because other regions of the chromosome are not interrogated and the absolute number of *MET*-containing chromosomes cannot be determined. By contrast, the addition of a probe targeting repetitive regions of the centromere (chromosome enumerating probe against chromosome 7 (CEP7), green) enables focal amplification to be confirmed. The resultant *MET* to CEP7 ratio thus enables differentiation between whole-genome duplications or polysomy, which have a low *MET* to CEP7 ratio (left, ratio of 1), and focal amplifications, which have a high *MET* to CEP7 ratio (right, ratio of 4; for simplicity, only the probes for one chromatid are depicted). **b** | Focal *MET* amplifications can be distinguished from broad chromosomal gains that include *MET* using next-generation sequencing (NGS). In the latter, adjacent genes such as *LINC01510* and *CAPZA2* are concurrently amplified. Focal *MET* amplifications are associated with a greater likelihood of dependence on MET.

with NSCLC, tumours that had high-level *MET* amplifications determined using FISH (*MET* to CEP7 ratio ≥5) did not also harbour other oncogenic drivers (such as *EGFR* mutations or *ALK* fusions), whereas those with low (*MET* to CEP7 ratio ≥1.8 to ≤2.2) or intermediate (*MET* to CEP7 ratio >2.2 to <5) levels of *MET* amplification were more likely to have concurrent alterations in other oncogenes (0% versus 52% and 50% of patients, respectively)[17]. A separate study[77] suggested that focal *MET* amplifications quantified using NGS better represent a true oncogenic driver state than broad gains on chromosome 7 that include *MET*.

Acquired MET amplifications. Tumours harbouring de novo high-level *MET* amplifications are primarily dependent on MET signalling for growth, whereas

those that are reliant on other oncogenes (such as mutant *EGFR*) can develop a secondary dependence on the MET pathway as a mechanism of resistance to targeted therapy[2]. Depending on the cut-off point and assays used, acquired *MET* amplifications can be identified in 5–20% of patients with NSCLC with sensitizing *EGFR* mutations following resistance to first-generation, second-generation or third-generation EGFR TKIs[3,6,78,79]. *EGFR*-mutant cell lines harbouring *MET* amplifications are dependent on MET-mediated bypass signalling via PI3K in the presence of the EGFR inhibitors gefitinib or erlotinib[2]. MET-mediated activation of HER3 is needed to induce PI3K signalling in these cells[2,55]. *MET* amplification has also been found to be a mechanism of resistance to ALK inhibitors in patients with *ALK* fusion-positive NSCLC[80]. In addition, acquired *MET* amplifications have been identified in unselected patients with CRC receiving anti-EGFR monoclonal antibodies[7] and in a patient with *BRAF*^{V600E}-mutant CRC who received combination therapy with EGFR and BRAF inhibitors[81].

When *MET* amplification occurs as a secondary driver after initial therapy, it can occur in a subclonal population of tumour cells. Investigators using an NGS assay that interrogates nucleic acid sequences derived from a mixed population of tumour cells containing *MET*-amplified and non-amplified clones to identify acquired MET dependency need to bear in mind that the assay could underestimate the extent of *MET* amplification[82]. NGS-based assays might also fail to detect changes in *MET* copy number in this context. The use of complementary assays, such as FISH or single-cell sequencing, could be considered in situations in which NGS-based testing fails to reveal subclonal alterations in *MET* copy number.

Targeted therapy

De novo amplifications. PROFILE 1001 was one of the earliest studies to examine the activity of MET-targeted therapy in tumours stratified by the degree of *MET* amplification[83]. This phase I trial included an expansion cohort of patients with *MET*-amplified NSCLC in which the activity of crizotinib was examined in relation to the level of amplification: low (*MET* to CEP7 ratio ≥1.8 to <2.2), intermediate (*MET* to CEP7 ratio ≥2.2 to <5) and high (*MET* to CEP7 ratio ≥5) amplification groups. The objective response rate (ORR) was highest (67%) in the high amplification group, compared with ORRs of 0% and 17% in the low and intermediate groups, respectively. The cut-off points of the intermediate and high amplification groups were subsequently modified to *MET* to CEP7 ratios of >2.2 to <4 and ≥4, respectively[84]. In an update of PROFILE 1001 in which these cut-off points were used, the best overall outcomes consistently remained in the high amplification group (*MET* to CEP7 ratio ≥4; ORR 40%, median progression-free survival (PFS) 6.7 months), compared with an ORR of 33% (median PFS 1.8 months) and ORR of 14% (median PFS 1.9 months) in the low (*MET* to CEP7 ratio ≥1.8 to ≤2.2) and intermediate (*MET* to CEP7 ratio >2.2 to <4) amplification groups, respectively (FIG. 2).

Data on the activity of selective MET TKIs in lung cancers with varying degrees of *MET* copy number increase have emerged, with a focus on selection based on GCN (TABLE 1; see TABLE 2 for adverse events of the various agents as monotherapies). Capmatinib was investigated in a trial that classified NSCLCs according to *MET* GCN: GCN <4, GCN >4 to <6 and GCN ≥6 (REF.[85]). The ORR was highest (47%) in the group with a *MET* GCN ≥6, compared with ORRs of 0% and 17% in the groups with GCN <4 and GCN ≥4 to <6, respectively. The activity of savolitinib has been investigated in patients with *MET*-amplified PRCC[86]. As opposed to the two prior studies, in which FISH was used[84,85], NGS was used in this study, with *MET* amplification defined as *MET* GCN ≥6 (REF.[86]). Patients with *MET*-amplified PRCC were more likely to respond (ORR 43%) than those with a GCN <6 (ORR 0%) (TABLE 1).

Finally, data from the AcSé study, in which patients received crizotinib, support the use of the *MET* to CEP7 ratio over *MET* GCN in evaluating MET dependency[87]. The study demonstrated enrichment for responders in the group with high-level (*MET* to CEP7 ratio ≥5) or intermediate-level (*MET* to CEP7 ratio >2.2 to <5) *MET*-amplified NSCLCs compared with the groups with low-level *MET* amplifications (*MET* to CEP7 ratio ≥1.8 to ≤2.2) or polysomy (*MET* GCN >6 and *MET* to CEP7 ratio <1.8).

Acquired resistance. In tumours with primary dependence on another oncogene and secondary dependence on MET, combination therapy targeting both the primary driver and MET can be effective. For example, the combination of an EGFR TKI with a MET TKI is clinically active in patients with *EGFR*-mutant NSCLC who acquire *MET* amplifications after disease progression on a prior EGFR TKI. In a cohort of patients with *EGFR*-mutant NSCLC with acquired *MET* copy number increases/amplifications (GCN ≥5 or *MET* to CEP7 ratio ≥2 by FISH or NGS) who received osimertinib and savolitinib, after progression on osimertinib[88], the ORR was 30%. In a trial in which patients with *EGFR*-mutant NSCLC who acquired *MET* copy number increases or amplifications (GCN ≥5 or *MET* to CEP7 ratio ≥2 on FISH) after progression on a first-generation or second-generation EGFR TKI received gefitinib plus tepotinib, the ORR was 67%[89]. Other agents, such as the EGFR–MET bispecific antibody JNJ-372, have shown promising activity in patients with *EGFR*-mutant cancers that have become resistant to EGFR TKIs[90], and the activity of these drugs should be characterized further in tumours with acquired *MET* amplifications.

Interestingly, the activity of combination therapy also increases with increasing *MET* copy number (FIG. 2). A phase Ib/II study evaluated the activity of gefitinib and capmatinib in patients with *EGFR*-mutant NSCLC harbouring *MET* copy number increases who were stratified by *MET* GCN (GCN <4, GCN ≥4 to <6 and GCN ≥6)[91]. The ORR was highest (47%) in the GCN ≥6 group compared with ORRs of 12% and 22% in the GCN <4 and GCN ≥4 to <6 groups, respectively.

Taken together, higher levels of *MET* amplification predict an increased likelihood of benefit from MET-directed targeted therapies. This prognostic implication applies to both single-agent MET inhibitors

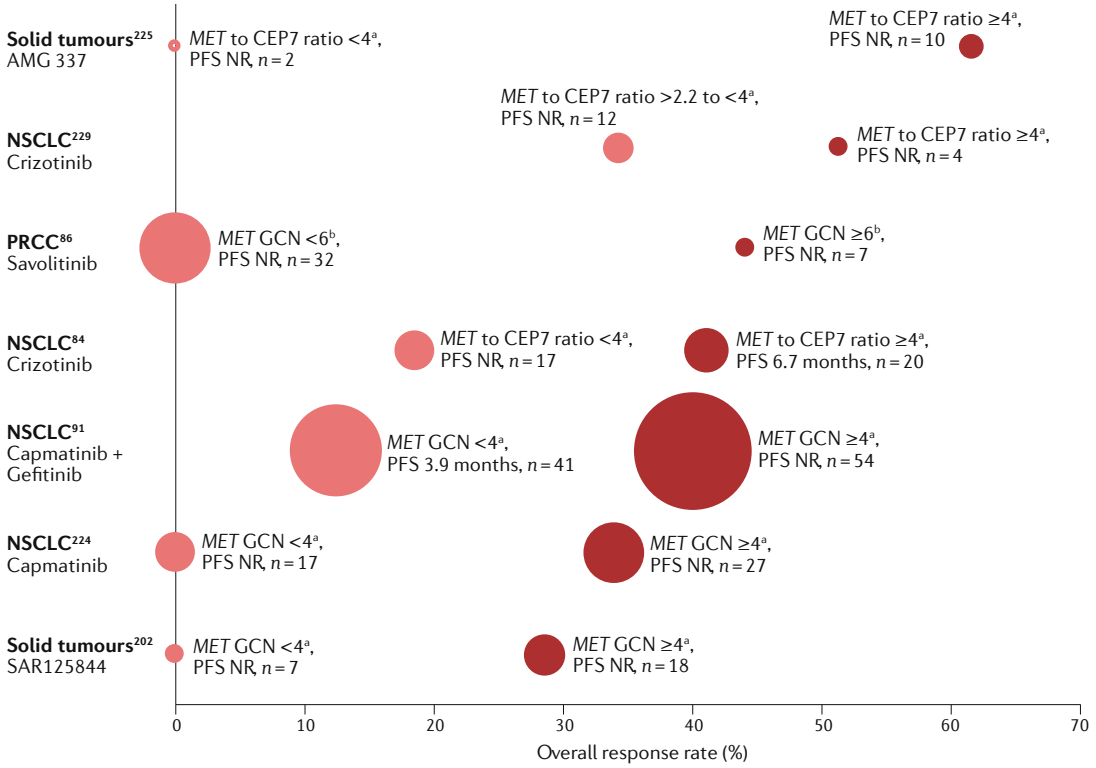

Fig. 2 | **Targeted therapies and response rates in patients with *MET*-amplified cancers.** Patients with cancers harbouring *MET* amplifications or increases in *MET* gene copy number (GCN) derive increased levels of benefit from MET-directed targeted therapies. Trials included patients with non-small-cell lung cancer (NSCLC) or papillary renal cell cancer (PRCC) and those with other solid tumours. Exact cut-off points for *MET* amplification or GCN varied between trials, although a cut-off *MET* to chromosome enumerating probe against chromosome 7 (CEP7) ratio ≥4 or *MET* GCN of ≥4 was chosen for consistency of data comparisons between trials that used fluorescence in situ hybridization (FISH) for diagnosis; patient-level data were reviewed to calculate response rates. A *MET* GCN cut-off of ≥6 was applied to data from the only trial that utilized next-generation sequencing (NGS) for quantification of *MET* copy number. Objective response rates are shown for cancers that fall below these cut-off points (light red circles) and cancers that met or exceeded these cut-off points (dark red circles). The size of each circle represents the size of the subpopulation within each trial (with the smallest circle representing a trial including two patients), and each row represents a single trial. NR, not reported; PFS, progression-free survival. [a]*MET* amplification determined using FISH; [b]*MET* amplification determined using NGS.

in patients with de novo *MET*-amplified cancers and combination therapies that include a MET inhibitor in patients with cancers that develop *MET* amplifications as a mechanism of resistance to therapies targeting a non-*MET* primary oncogenic driver. Thus, the need for standardized definitions of *MET* amplification has substantial implications not only for diagnosis, but also for the identification of patients with cancers who are oncogenically addicted to MET and more likely to benefit from MET-directed targeted therapies.

MET mutations

Genomic diversity

Activating mutations can occur at a diverse range of positions within *MET* and include alterations involving the kinase domain, intronic splice sites that flank exon 14 and the extracellular domain.

Kinase domain mutations. *MET* mutations were first described in 1997 in patients with hereditary PRCC[92]. These germline mutations include V1092I, H1094R/Y, M1131T, V1188L, V1220I, M1250T and D1228H/N/V. *MET* kinase domain mutations increase kinase activity and lead to phenotypic transformation or the formation of tumour foci in vitro when transfected into NIH 3T3 cells[93]. These alterations also induce tumour formation in mouse models in vivo[93,94]. Studies published 20 years later demonstrated that somatic *MET* mutations occur in sporadic PRCCs. These alterations are found in up to 15% of patients[69,95,96], predominantly in those with type 1 (17%) and less commonly in those with type 2 PRCC (2%)[69,97]. The spectrum of *MET* mutations in sporadic PRCCs includes V1092I, H1094L/R/Y, N1100Y, H1106D, M1131T, V1188L, L1195V, V1220I, D1228H/N/V, Y1230A/C/D/H, Y1235D and M1250I/T and overlaps with the spectrum of germline *MET* mutations[92,98,99] (FIG. 3). Interestingly, some of these mutations are less active than others, and concomitant *MET* amplification might be necessary to drive oncogenesis[94,95,100]. Activating *MET* kinase domain mutations have also been found in patients with other cancers, including those with HCC and head and neck cancer[101,102]. The MET^{Y1235D} mutation can be found in up to 14% of patients with head and neck cancer[103].

In addition to occurring de novo, *MET* kinase domain mutations can also emerge as a mechanism of acquired

Table 1 | **Targeted therapy outcomes by *MET* copy number status**

Drug	Trial phase (*n*)	Amplification criteria	Assay used	MET subgroup	Outcomes
Solid tumours					
SAR125844[202]	Phase I (72)[a]	*MET* to CEP7 ratio ≥2.0[f] and *MET* GCN >4	FISH	All patients	ORR 17% (5/29)
Capmatinib[212]	Phase I (38)[b]	*MET* to CEP7 ratio ≥2.0 or *MET* GCN ≥5[g]	FISH	*MET* GCN <4	ORR 0% (0/22)
				MET GCN ≥4 to <6	ORR 0% (0/6)
				MET GCN ≥6	ORR 0% (0/3)
AMG 337[213]	Phase I (111)[a]	*MET* to CEP7 ratio ≥2.0	FISH	All patients	ORR 10% (11/111); mDOR 202 days
				MET to CEP7 ratio <4	ORR 0% (0/2)
				MET to CEP7 ratio ≥4	ORR 60% (6/10)
Gastroesophageal cancers					
AMG 337[214]	Phase II (60)[c]	*MET* to CEP7 ratio ≥2.0	FISH	All patients	ORR 18% (8/45); mDOR 6.0 months
Foretinib[215]	Phase II (74)	*MET* to CEP7 ratio ≥2.0	FISH	All patients	ORR 0% (0/71); mDOR 1.7 months
				MET-amplified	ORR 0% (0/3)
Hepatocellular carcinoma					
Capmatinib[216]	Phase II (30)	*MET* H-score ≥50 or *MET* to CEP7 ratio >2.0 or *MET* GCN ≥5	FISH	All patients	ORR 10% (3/30)
				MET IHC score 3+ or 2+ in ≥50% of tumour cells and *MET* GCN ≥5	ORR 30% (3/10)
NSCLCs					
Crizotinib	Phase I (37)[84]	*MET* to CEP7 ratio ≥1.8	FISH	*MET* to CEP7 ratio ≥1.8 to ≤2.2	ORR 33% (1/3); mPFS 1.8 months
				MET to CEP7 ratio >2.2 to <4.0	ORR 14% (2/14); mPFS 1.9 months
				MET to CEP7 ratio ≥4.0	ORR 40% (8/20); mPFS 6.7 months
	Phase II[217] (17)[a,e]	*MET* GCN ≥6 and IHC 2+ or 3+	FISH	All patients	ORR 31% (5/16); mPFS 5.0 months
				MET to CEP7 ratio >2.2 to <5.0	ORR 36% (5/14); mPFS 4.4 months
				MET to CEP7 ratio ≥5.0	ORR 0% (0/2)
	Phase II[87] (25)[a]	*MET* GCN ≥6 and IHC 2+/3+	FISH	All patients	ORR 32% (8/25); mPFS 3.2 months
Capmatinib[85]	Phase I (44)	*MET* to CEP7 ratio ≥2.0 or MET GCN ≥5[h,i]	FISH	All patients	ORR 20% (11/55)
				MET GCN <4	ORR 0% (0/17)
				MET GCN ≥4 to <6	ORR 17% (2/12)
				MET GCN ≥6	ORR 47% (7/15)
NSCLCs (EGFR-mutant)					
Savolitinib (300 mg daily) plus osimertinib[88]	Phase I (36)	Previously treated with first-generation/second-generation EGFR TKI and T790M-negative; *MET* to CEP7 ratio ≥2 or *MET* GCN ≥5 by FISH or NGS[i]	FISH or NGS	All patients	ORR 64% (23/36); mPFS 9.1 months
Savolitinib (300 or 600 mg daily) plus osimertinib[88]	Phase I (51)	Previously treated with first-generation/second-generation EGFR TKI and T790M negative; *MET* to CEP7 ratio ≥2 or *MET* GCN ≥5 by FISH or NGS[i]	FISH or NGS	All patients	ORR 65% (33/51); mPFS 9.0 months
Savolitinib (300 or 600 mg daily) plus osimertinib[88]	Phase I (18)	Previously treated with first-generation/second-generation EGFR TKI and T790M-positive; *MET* to CEP7 ratio ≥2 or *MET* GCN ≥5 by FISH or NGS[i]	FISH or NGS	All patients	ORR 67% (12/18); mPFS 11.0 months
Savolitinib (300 or 600 mg daily) plus osimertinib[88]	Phase I (69)	Previously treated with third-generation EGFR TKI; *MET* to CEP7 ratio ≥2 or *MET* GCN ≥5 by FISH or NGS[i]	FISH or NGS	All patients	ORR 30% (21/69); mPFS 5.4 months

Table 1 (cont.) | **Targeted therapy outcomes by *MET* copy number status**

Drug	Trial phase (*n*)	Amplification criteria	Assay used	MET subgroup	Outcomes
NSCLCs (EGFR-mutant) (cont.)					
Tepotinib plus gefitinib[89]	Phase II (12)	Previously treated with first-generation/second-generation EGFR TKI and T790M-negative; *MET* to CEP7 ratio ≥2 and/or *MET* GCN ≥5	FISH	All patients	ORR 67% (8/12); mPFS 16.6 months
Savolitinib plus gefitinib[218]	Phase I (44)	Previously treated with EGFR TKI; *MET* to CEP7 ratio ≥2 or *MET* GCN ≥5	FISH	All patients	ORR 25% (11/44)
Gefitinib plus capmatinib[91]	Phase II (100)	GCN ≥5 or IHC 2+/3+ in >50%; then GCN ≥5 plus IHC 2+/3+; then GCN ≥4 or IHC 3+; *MET* to CEP7 ratio ≥1.8	FISH	All patients	ORR 29% (29/100); mPFS 5.5 months
				MET GCN <4	ORR 12% (5/41); mPFS 3.9 months
				MET GCN ≥4 to <6	ORR 22% (4/18); mPFS 5.4 months
				MET GCN ≥6	ORR 47% (17/36); mPFS 5.5months
PRCC					
Savolitinib[86]	Phase II (79)[a]	Focal *MET* GCN ≥6	NGS	All patients	10% (8/79)
				MET GCN <6 or not MET-driven	0% (0/32)
				MET GCN ≥6	43% (3/7)

FISH, fluorescence in situ hybridization; GCN, gene copy number; IHC, immunohistochemistry; mDOR, median duration of response; mPFS, median progression-free survival; NGS, next-generation sequencing; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PRCC, papillary renal cell carcinoma. [a]Available patient-level data with *MET* gene copy numbers or *MET* to CEP7 ratio and response results used to produce these results. [b]Only data from patients receiving a stable dose in the dose expansion cohort used. [c]Only patients from cohort 1 used. [d]Not MET-driven defined as no MET focal amplification, no MET kinase domain mutation, no HGF amplification and no chromosome 7 gain. [e]One patient not RECIST evaluable. [f]MET positivity also defined as IHC ≥50% of tumour cells with 2+/3+. [g]MET positivity also defined as H-score ≥150 or IHC ≥50% with 2+/3+ or H-score ≥50 for hepatocellular carcinoma and glioblastoma. [h]MET positivity also defined as H-score ≥150 or IHC ≥50% with 2+/3+. [i]MET positivity also defined as IHC ≥50% 3+.

resistance to MET TKIs. In patients with NSCLC harbouring *MET* exon 14 mutations, MET^{Y1230C}, MET^{Y1230H}, MET^{D1228H} and MET^{D1228N} have all been found to mediate resistance to crizotinib by disrupting drug binding[104–108]. *MET* kinase domain mutations also emerge as a mechanism of resistance to the combination of an EGFR TKI and a MET TKI in patients with *EGFR*-mutant NSCLC with *MET* amplification-mediated resistance to prior single-agent EGFR TKI therapy[109].

MET exon 14 alterations. MET activation results in transphosphorylation of the Y1003 residue of the juxtamembrane domain encoded by exon 14 within the MET kinase activation loop[110]. Phosphorylation of this residue mediates MET binding to c-Cbl E3 ligase, resulting in ubiquitylation and ultimately degradation of MET as part of an autoregulatory negative feedback loop[111]. *MET* exon 14 alterations comprise a heterogeneous group of mutations that are all able to interfere with this process and result in increased and sustained MET signalling. The most common of these mutations are either base substitutions or indels, each occurring in around half of all patients[112,113].

MET exon 14 alterations were originally identified in small-cell lung cancers (SCLCs)[114], although later studies revealed that these mutations are more commonly found in patients with NSCLC, with a prevalence of 3–4%[112,113,115,116]. These alterations are further enriched in sarcomatoid carcinoma (occurring in 9–22% of patients), which is an aggressive subtype of NSCLC that can be highly resistant to chemotherapy[117]. *MET* exon 14 alterations occur at lower frequencies in other cancers, including gastric cancers and neuroblastomas[112,118,119]. As well as being found de novo in various malignancies, *MET* exon 14 alterations have also been shown to mediate resistance to EGFR TKIs in patients with *EGFR*-mutant NSCLC[5,120]. Among patients with NSCLC, a higher proportion of those with *MET* exon 14 skipping have a history of smoking compared with those harbouring other drivers, such as *ALK*, *ROS1* or *RET* fusions, although never-smokers still make up a substantial proportion of patients with *MET* exon 14 skipping alterations[9,121,122].

Most *MET* exon 14 alterations interfere with RNA splicing. In the wild-type state, the intronic regions of *MET* pre-mRNAs are removed by splicing before the transcript is translated into a protein. Mutations that occur in regions that flank *MET* exon 14 (such as the polypyrimidine tract or splice donor–acceptor regions) effectively disrupt the splicing process and result in exon 14 being skipped[21]. The loss of the encoded juxtamembrane domain leads to the loss of the Y1003 ubiquitin-binding site on MET. Consequently, MET degradation is decreased and MET expression increases, driving oncogenesis[123–125]. Most of these splice site mutations take the form of indels, with a wide range of sizes. Missense mutations that result in D1010 substitutions, such as D1010H/N/Y, are also able to disrupt splicing[126].

MET mutations that do not directly affect splicing can recapitulate a similar phenotype. For example, mutations that lead to Y1003 substitution (such as Y1003F/N/S) are able to interfere with c-Cbl E3 ligase binding[124].

Similar to *MET* exon 14 RNA splice site mutations, Y1003 substitutions transform non-malignant cells, lead to increased levels of proliferation and promote tumour growth[123,124]. Large deletions that encompass exon 14 result in loss of the juxtamembrane domain that carries Y1003 (REFS[56,123,124]).

Other mutations. The semaphorin domain of the MET protein interacts with HGF (the ligand for MET) and is involved in dimerization leading to receptor activation[127]. Mutations in this domain include E34K, H150Y, E168D, L269V, L299F, S323G, M362T, N375S and C385Y[115,128–131] (FIG. 3). N375S is the most common of these alterations and occurs in 3–14% of NSCLCs[132]. Whether semaphorin domain mutations (particularly N375S) are activating or not remains a point of contention. N375S has been shown to participate in carcinogenesis through activation of downstream SRC and/or ERK1/2 signalling[133], although data have also shown that some semaphorin domain mutations decrease the HGF binding affinity of MET and are found in individuals without cancer[132,134].

Diagnosis

DNA sequencing. *MET* exon 14 alterations are highly heterogeneous; therefore, an effective NGS assay must be able to capture this wide variety of mutations[112]. As mentioned previously, amplicon-based NGS and hybrid-based NGS are the two main types of assays used in the clinic. In amplicon-based NGS, genes of interest are sequenced using primers that flank defined genomic regions[135]. This approach can enable a shorter turnaround time and improved capture of targeted and difficult-to-sequence regions compared to hybrid-based approaches, although it is also more prone to sequencing errors in repetitive regions, bias and allelic dropout. Many *MET* exon 14 alterations, particularly indels that result in splicing defects, are located outside these amplified regions and might be missed[136,137]. Furthermore, mutations such as large indels might involve a primer binding site and thus interfere with binding; this possibility likewise prevents the detection of these alterations using amplicon-based assays[135]. Several studies have demonstrated that a substantial fraction of *MET* exon 14 alterations (>50% of alterations in certain scenarios) can be missed using amplicon-based NGS[136,137].

By contrast, the use of hybrid capture-based NGS avoids some of the issues associated with amplicon-based NGS[137]. In hybrid-capture NGS, tumour DNA is sheared, captured using long oligonucleotide baits and then amplified. Sequence reads for a target have several different start and stop coordinates; therefore, duplicates can be identified and removed from the dataset, enabling the true extent of sequencing coverage to be determined. The challenges associated with sequencing repetitive sequences can be adjusted for through careful bait design and balancing. By tiling over appropriate intronic regions, hybrid capture-based NGS forestalls these primer binding issues and can enable the detection of mutations located further into the introns. The use of a capture-based approach enables corrections for some of the sequencing bias and allele dropout issues associated with amplicon-based NGS[135]. Hybrid capture-based NGS also outperforms amplicon-based NGS in calling missense mutations. Both platforms usually have a high depth of coverage of genes of interest, which ensures accuracy, although amplicon-based platforms are more commonly associated with false-positive or false-negative results, consequently affecting the threshold of sensitivity that the assay can provide.

RNA sequencing. DNA sequencing enables the detection of mutations located within exons that are predicted to result in *MET* exon 14 skipping, although DNA sequencing cannot confirm the absence of the exon itself, because modifications such as splicing occur post-translationally. As such, RNA sequencing platforms have the potential to complement DNA-based techniques such as NGS[137]. Given the diversity of *MET* exon 14 splice site alterations, interpreting whether or not certain mutations identified using NGS truly result in exon 14 skipping can be challenging. Such interpretations can be made based on the proximity to splice donor and/or acceptor regions, although this becomes more challenging with alterations located deeper into the introns. By contrast, RNA sequencing enables the direct identification of the loss of exon 14 transcription. Furthermore, the challenges associated with the need to sequence large introns are avoided with RNA-based sequencing, owing to the absence of introns in mRNA. However, RNA is less stable than DNA, which limits its shelf-life especially in preserved tissue[138]. Furthermore,

Table 2 | **Common adverse effects of MET-targeted therapies as monotherapies**

Drug	Common treatment-related and/or emergent adverse events (% of patients)	Grade 3 or 4 adverse events (% of patients)
AMG 337[213]	Headache (63), nausea (31), vomiting (19), fatigue (18), peripheral oedema (17)	Abdominal pain (5), headache (5), fatigue (5), hyponatraemia (5), vomiting (4), back pain (4), nausea (4)
Capmatinib[9]	Peripheral oedema (42), nausea (33), increased serum creatinine (20), vomiting (19)	Peripheral oedema (8), fatigue (3), nausea (2), vomiting (2), decreased appetite (1), diarrhoea (0.3)
Crizotinib[8]	Oedema (51)[a], vision disorder (45)[a], nausea (41), diarrhoea (39), vomiting (29)	Elevated serum transaminases (4), oedema (1), constipation (1), bradycardia (1)
Foretinib[215]	Fatigue (44), hypertension (35), nausea (27), diarrhoea (27), serum AST increased (23)	Serum AST increased (10), fatigue (6), serum GGT increased (6), serum ALT increased (4), hypertension (4), serum AP increased (2), rash (2)
SAR125844[202]	Asthenia/fatigue (58), nausea (32), abdominal pains (28), constipation (28), dyspnoea (28),	Serum ALT increased (7), anaemia (6), dyspnoea (6), asthenia/fatigue (4), abdominal pains (3), non-cardiac chest pain (3)
Savolitinib[219]	Nausea (39), fatigue (21), vomiting (17), peripheral oedema (17), serum AST increased (11), blood creatinine increased (11)	Serum AST increased (3), fatigue (2), anaemia (<1), decreased appetite (<1), hyperkalaemia (<1), peripheral oedema (<1), proteinuria (<1), rash (<1), vomiting (<1)
Tepotinib[10]	Peripheral oedema (48), nausea (23), diarrhoea (21), serum creatinine increased (13), asthenia (9)	Peripheral oedema (8), serum ALT increased (2), serum amylase increased (2), asthenia (1), serum AST increased (1), diarrhoea (1)

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase. [a]Clustered term.

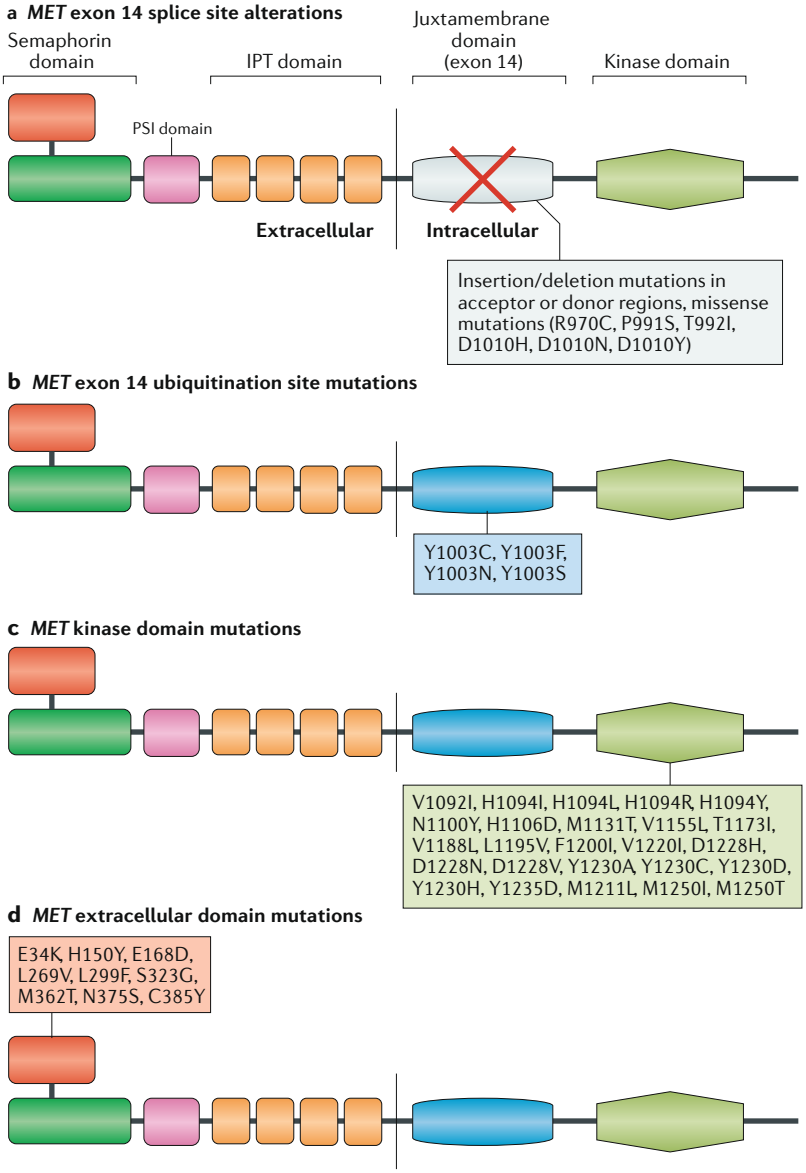

Fig. 3 | ***MET* mutations.** The MET protein consists of the extracellular semaphorin domain in red and green, a plexin–semaphorin–integrin (PSI) domain in pink, four immunoglobulin-like regions in plexins and transcription factor (IPT) repeats in orange, a juxtamembrane domain (encoded by exon 14) in blue, and a kinase domain in green. **a** | *MET* exon 14 splice site alterations result in exon 14 exclusion. These splice variants lack a ubiquitin-binding site in the juxtamembrane domain, resulting in impaired MET degradation and increased MET signalling. **b** | Missense mutations located in the juxtamembrane domain-encoding region of *MET* prevent spliceosome binding in the *MET* pre-mRNA or modify the Y1003 ubiquitylation site in the MET protein. These ultimately recapitulate the biology of *MET* exon 14 splice site alterations. **c** | Mutations in the kinase domain lead to increased activation of the MET kinase and can be associated with conformational changes that favour the xDFG-out state. **d** | Other mutations can occur in the semaphorin domain, which contains the hepatocyte growth factor-binding site. The implications of semaphorin domain mutations for MET function are currently unclear.

given the high level of variability of mRNA expression in non-malignant and tumour tissues and the challenges involved in interpreting these results, RNA sequencing is currently used as an adjunct to traditional sequencing methodologies, such as for confirming *MET* exon 14 skipping[139]. In summary, whereas the effects of newly detected mutations on *MET* exon 14 expression can be difficult to interpret using DNA-based platforms, RNA sequencing enables the direct determination of whether or not exon 14 has been transcribed.

Anchored multiplex PCR (AMP sequencing) is an RNA-based technique that can identify *MET* exon 14 alterations. Using this method, RNA is used as a template to generate complementary DNA (cDNA) from tumour material[140]. Multiplex PCR enables the incorporation of molecular barcodes that enable the quantification of sequences and the correction of sequencing errors as the cDNA is sequenced and amplified. The loss of exon 14 is then identified in cDNA. In one study[141], the utility of AMP RNA sequencing in identifying MET exon 14 alterations was examined in a total of 232 patients with NSCLC that were deemed 'driver-negative' by DNA-based hybrid-capture NGS. A total of 33 targetable alterations, including six *MET* exon 14 skipping alterations, were identified using AMP RNA sequencing that were not detected using DNA-based NGS. An analysis of the genomic sequences of the six alterations identified using RNA sequencing was then conducted, and novel *MET* exon 14 splice site alterations were detected after further manual review of data from five of the six patients[136]. No *MET* mutation was detected in the remaining patient, suggesting that *MET* exon 14 skipping occurred by another mechanism.

Molecular counting, using the nCounter system, has also been used to identify *MET* exon 14 loss at the RNA level. This system uses probes to detect *MET* transcripts of interest, including a fluorescently tagged 5′ reporter probe and a biotinylated 3′ capture probe[142]. By contrast to AMP sequencing, molecular counting does not require the reverse transcription of RNA to cDNA and does not require amplification of the source material. Instead, target-specific colour-coded probes are used to highlight the sequences of interest and the colour intensities are quantified and tabulated using a digital analyser for image acquisition[142]. Further studies of this method are needed, particularly because the performance of molecular counting for the detection of *MET* exon 14 skipping has not been compared directly with that of AMP[143,144].

Targeted therapy

Kinase domain mutations. MET-directed targeted therapies are active against certain *MET* kinase domain mutations. However, the activity of the various MET TKIs against specific alterations is variable. Specifically, while type II MET inhibitors, such as cabozantinib and foretinib, have preclinical activity against several kinase domain mutations (such as D1228N, M1250T and H1094Y/L[145]), type I MET inhibitors, such as crizotinib, lack any substantial activity against tumours harbouring these alterations. As such, *MET* kinase domain mutations have emerged as mechanisms of resistance to crizotinib in patients with *MET*-amplified and *MET* exon 14-altered cancers. The ability of these mutations to switch the conformation of the MET kinase from an active (xDFG-in) to an inactive (xDFG-out) conformation is likely to contribute to crizotinib resistance because type I MET inhibitors preferentially bind to the active confirmation of MET kinase, while type II MET inhibitors bind to the inactive confirmation[146] (BOX 2).

Data from patients with tumours harbouring de novo *MET* kinase domain mutations are largely limited to those with PRCC. In a study involving patients with hereditary PRCCs harbouring germline *MET* mutations who received foretinib, the ORR was 50%[147]. Data on patients who acquired *MET* kinase domain mutations as mechanisms of resistance to prior MET TKIs are currently limited to those with NSCLC[104–106,108]. Patients were identified as having cancers that developed *MET* kinase domain mutations as mechanisms of resistance to the combination of an EGFR TKI and crizotinib (administered to patients with *EGFR*-mutant cancers with *MET* amplification-mediated resistance to a prior EGFR TKI)[148]. In a case study, switching from crizotinib to the type II MET inhibitor cabozantinib (both in combination with osimertinib) on the emergence of a putative resistance mutation in *MET* (D1228N) resulted in the re-establishment of disease control.

MET exon 14 alterations. As opposed to kinase domain mutations that can alter the conformation of the MET kinase, MET exon 14 variants theoretically have a kinase domain that is similar to that of the wild-type form of MET[111]. Thus, both type I and type II MET TKIs are able to inhibit such variants, and both types have shown preclinical activity in models of *MET* exon 14-altered cancers[126]. The clinical activity of MET inhibition in *MET* exon 14-altered NSCLCs was originally established prospectively with crizotinib, a type Ia multikinase MET inhibitor[8].

Investigators enrolled 69 patients with advanced-stage *MET* exon 14-altered NSCLC into an expansion cohort of the phase I PROFILE 1001 study, which explored the efficacy of crizotinib. The median PFS duration was 7.3 months and, of the 65 patients with evaluable responses, the ORR was 32% (TABLE 3). These results supported the inclusion of crizotinib in the NCCN guidelines for this indication[149]. These data also supported the FDA's decision to designate crizotinib as a Breakthrough Therapy for the treatment of patients with *MET* exon 14-altered NSCLC, following disease progression on platinum-containing chemotherapy, in 2018 (REFS[150,151]).

Box 2 | **Type 1 and type 2 MET inhibitors**

Type I MET tyrosine kinase inhibitors (TKIs) target the ATP-binding pocket of the active form of MET[231]. Type Ia agents, such as the multikinase ALK, ROS1 and the MET inhibitor crizotinib, interact with MET moieties such as the Y1230 residue, the hinge region and the solvent-front G1163 residue. Type Ib inhibitors tend to be more MET-selective agents that, in contrast to type Ia agents, do not interact with G1163 (REF.[126]). Type Ib inhibitors include capmatinib, tepotinib, savolitinib and APL-101. Unsurprisingly, these have been demonstrated to overcome solvent-front substitutions in vitro (such as G1163E/R) that confer resistance to crizotinib.

Type II MET TKIs (cabozantinib, merestinib and glesatinib) are likewise ATP-competitive, but bind the ATP pocket in the inactive state by extending to a hydrophobic back pocket[126,232,233]. Binding to this configuration enables these agents to act against MET kinase domain mutations that confer resistance to type Ia and type Ib inibitors[126,234], including D1228E/G/H/N and Y1230C/D/S/H/N. Conversely, the MET L1195V and MET F1200I/L mutations are associated with resistance to type II MET inhibitors[126,232,233]. Thus, switching between type I and type II MET inhibitors might be an effective strategy in patients with MET-dependent cancers, depending on the specific resistance mutation that emerges.

Since the designation of crizotinib as a Breakthrough Therapy, newer agents, including the selective type Ib MET inhibitors capmatinib, tepotinib and savolitinib, have been tested in patients with *MET* exon 14-altered NSCLC[9–11] (TABLE 3). Notably, these selective agents are more potent inhibitors of MET than crizotinib[126]. In the GEOMETRY trial[9], the ORRs to capmatinib monotherapy in patients with treatment-naive or chemotherapy-treated *MET* exon 14-altered NSCLC were 68% and 41%, respectively. Capmatinib received line-agnostic approval by the US FDA for the treatment of MET exon 14-altered lung cancers based on this data set. Similarly, in the VISION trial, the ORR to tepotinib monotherapy in a cohort of 85 patients with advanced-stage *MET* exon 14-altered NSCLC was 44%[10]. In a phase II trial, the ORR to savolitinib in patients with pulmonary sarcomatoid carcinoma or other NSCLC subtypes harbouring *MET* exon 14 alterations was 55%[11]. The durability of disease control and toxicities of these agents relative to those of crizotinib have not yet been well characterized.

Response rates to MET TKIs vary widely between cohorts; therefore, several investigators have attempted to identify subgroups of patients with *MET* exon 14-altered NSCLC who are either more or less likely to respond to therapy[8,11]. Data from the PROFILE 1001 study indicate that response rates to crizotinib do not vary substantially by the location (splice acceptor versus donor site involvement) or type (InDel versus base substitution) of *MET* exon 14 alteration, or by the presence or absence of concurrent *MET* amplifications[8] (TABLE 3). These observations were subsequently confirmed by data from studies involving selective MET inhibitors such as savolitinib[11].

On-target mechanisms of acquired resistance, such as *MET* amplifications and *MET* kinase domain mutations, have been identified in patients who initially derive benefit from MET-targeted therapies. The role of HGF in acquired resistance largely remains to be determined, although *HGF* amplifications have been detected in the setting of acquired resistance[107,152]. Preclinical data supporting the role of these amplifications in *MET* exon 14-altered NSCLCs are currently not available, although HGF reduced the sensitivity to MET TKIs in a panel of *MET*-amplified human cancer cell lines and mouse xenografts[153].

MET fusions

Clinicopathological features

MET was originally identified as an oncogene after chemically transformed osteosarcoma cell lines were found to harbour the *TPR–MET* fusion[154]. *MET* fusions were thereafter identified in patients with gastric cancer, thyroid carcinoma, PRCC, lung adenocarcinoma, HCC, glioma and sarcoma. The exact frequency of *MET* fusions is poorly defined, although they are enriched in gliomas, occurring in ~12% of patients[155,156]. Beyond *TPR–MET*, multiple other *MET* fusions have since been identified[72,73,116,155,157–168] (FIG. 4). These fusions can occur through intrachromosomal fusions (such as *PTPRZ1–MET*, *CLIP2–MET*, *CAPZA2–MET* and *ST7–MET*) or interchromosomal fusions (such as *KIF5B–MET*,

Table 3 | **Targeted therapy in *MET* exon 14-altered lung cancers**

Drug	Outcomes by patient characteristics	Outcomes by alteration type	Outcomes by amplification status
Type Ia tyrosine-kinase inhibitors			
Crizotinib[8]	Overall: ORR 32% (21/65), mPFS 7.3 months	Indels: ORR 0% (0/4). Point mutations: ORR 36% (12/33). Splice acceptor site mutations: ORR 31% (5/16). Splice donor site mutations: ORR 32% (12/37)	Concurrent *MET* amplification: ORR 50% (1/2). Non-*MET* amplified: ORR NR
Type Ib tyrosine-kinase inhibitors			
Capmatinib[9]	Treatment naive: ORR 68% (19/28), mPFS 9.7 months. Pretreated: ORR 41% (28/69), mPFS 5.4 months	NR	NR
Tepotinib[10]	Overall: ORR NR, mPFS 10.8 months. Treatment-naive: ORR 44% (8/18), mPFS NR. Pretreated: ORR 45% (15/33), mPFS NR	NR	NR
Savolitinib[11]	Overall: ORR 55% (17/31)	Indels: ORR 43% (6/14). Point mutations: ORR 59% (10/17). Splice acceptor site mutation: ORR 42% (5/12). Splice donor site alteration: ORR 58% (11/19)	Concurrent *MET* amplification: ORR 100% (5/5). Non-*MET*-amplified ORR 35% (8/23)

Indel, insertion or deletion; mPFS, median progression-free survival; NR, not reported; ORR, objective response rate.

TPR–MET, *GPRC5C–MET* and *CD47–MET*)[162], each type accounting for approximately half of all *MET* fusions. In paediatric patients with glioblastoma, intrachromosomal fusions seem to be more common and most frequently involve *PTPRZ1* (REF.[155]). *MET* fusions can arise from either paracentric (not including the centromere) or pericentric (including the centromere) inversions, although the latter seems to be more frequent.

MET fusions often include exon 15 of this gene, which encodes the kinase domain[155,157,158,160,161,167,169,170], and many of the upstream partner genes encode dimerization domains, resulting in ligand-independent constitutive MET activation. Furthermore, some fusion events (such as *TPR–MET*) have been found to exclude exon 14, thus enabling a mechanism of MET activation similar to that of *MET* exon 14 skipping[169]. Interestingly, fusions that include exon 14 (such as *KIF5B–MET* and *PTPRZ–MET*) seem to be less oncogenic than fusions that exclude exon 14 (REF.[155]). In *PTPRZ–MET* fusions, the *PTPRZ* promoter is typically fused to the full-length *MET* gene, including the MET dimerization domain on exon 2; this fusion results in both MET overexpression and increased activation of downstream signalling[155,171].

Diagnosis and targeted therapy

A number of analytical techniques can enable the detection of *MET* fusions, including FISH, RT-PCR and NGS[155,157,172,173]. However, none of these platforms has been well studied in this application, and complex and/or novel *MET* fusions and rearrangements can be particularly difficult to detect using FISH[174]. In this section, we therefore focus primarily on NGS, which is the increasingly preferred clinical diagnostic approach to identifying genetic alterations. DNA-based NGS enables the reliable detection of a wide variety of *MET* fusions, although several general features of these fusions make it difficult for even DNA-based hybrid capture NGS to capture all events[175]. Firstly, repetitive intronic DNA sequences can occur at fusion breakpoints. These repeats can also occur in other areas of the genome and, because hybrid capture produces short reads, using such sequences as baits can result in reads that are not mappable to the reference genome[35]. As a result, these baits are excluded from contemporary assays, thus increasing the chance of missing genomic fusion breakpoints. Secondly, the introns of select fusion partners can be prohibitively long, which makes tiling of these sequences both challenging and impractical[141]. Thirdly, DNA-based NGS is limited in its ability to detect novel gene fusion partners[174,176]. As discussed earlier, these issues can be avoided using RNA-based AMP NGS or whole-transcriptome profiling[141,176,177]. In an analysis of samples from patients with apparently driver-negative NSCLCs by DNA-based NGS, RNA-based AMP NGS revealed actionable gene fusions in 12% (27) of 232 patients[141]. This observation suggests that AMP can complement DNA-based NGS in the detection of *MET* fusions, especially in settings in which no driver alteration is found.

The utility of MET-directed targeted therapies in patients with *MET* fusion-positive cancers has, thus far, been almost ignored. MET TKIs induce apoptosis in *TPR–MET*-transformed cell lines[178], and isolated responses to crizotinib have been described in case reports relating to patients with *MET* fusion-positive lung adenocarcinoma or glioma[155,162,179]. One patient was included in the *MET* exon 14 cohort of PROFILE 1001 because the patient's NSCLC harboured a *MET* fusion that resulted in exon 14 skipping[8]; a confirmed objective response was achieved with crizotinib in this patient. Multiple clinical trials designed to evaluate the efficacy of MET TKIs, including trials in patients with tumours harbouring *MET* fusions, are currently ongoing

(NCT02978261, NCT03993873 and NCT01639508). However, the activity of a MET TKI in a large homogeneous cohort of patients with *MET* fusion-positive cancers has yet to be reported.

MET overexpression

The role of MET expression in oncogenesis should be considered in a number of contexts. Firstly, MET can be transcriptionally induced in cancer cells in the setting of hypoxia and/or inflammation, which can activate proliferation, decrease apoptosis and promote migration. Tumours can thus potentially be reliant on MET signalling even in the absence of a genomic driver such as *MET* amplification, mutation or fusion. Such states could theoretically be addressed using MET-directed targeted therapies, although the clinical experience with monoclonal antibodies in this setting has been disappointing to date[180,181], and MET TKIs have shown little activity in patients with MET-overexpressing tumours[85] (TABLE 4). Thankfully, newer MET-targeting strategies such as biparatopic antibodies (which target two distinct epitopes on the same target protein), combinations of antibodies and ADCs are being explored. Secondly, MET can be overexpressed in cancers that harbour an activating genomic signature, including those with primary and/or secondary *MET* amplifications or *MET* exon 14 alterations.

Diagnosis

Immunohistochemistry. A number of anti-MET antibodies have been used for the immunohistochemical (IHC) detection of this protein. These include monoclonal antibodies (such as SP44, cMET and MET4), polyclonal antibodies (such as polyclonal MET AF276) and antibodies to phosphorylated MET (such as pMET Y1349)[182–186]. Of these antibodies, SP44, a rabbit monoclonal anti-total MET antibody clone, is commonly used. The comparative performance of these antibodies is currently unknown. The extent and intensity of IHC staining as assessed by a pathologist provides a semiquantitative indication of MET protein expression. Various scoring systems have been used to define both MET expression and overexpression by IHC[60,184,187]. The degree of expression is typically quantified as a staining score on a scale of 0 to 3+, corresponding to negative (0), weak (1+), moderate (2+) or strong (3+) staining[184]. A staining score of 1+ indicates MET expression. A staining score of 2+ (MET overexpression) in at least 50% of the cells is a commonly used cut-off point for MET positivity in clinical trials[184]. Another scoring system, the H-score, involves multiplying the percentages of cells with a staining score of 1+, 2+ or 3+ by their staining intensity score[188]. H-scores range from 0 to 300; a score of ≥200 usually denotes overexpression, although specific cut-off scores vary between studies[60,189]. Investigators

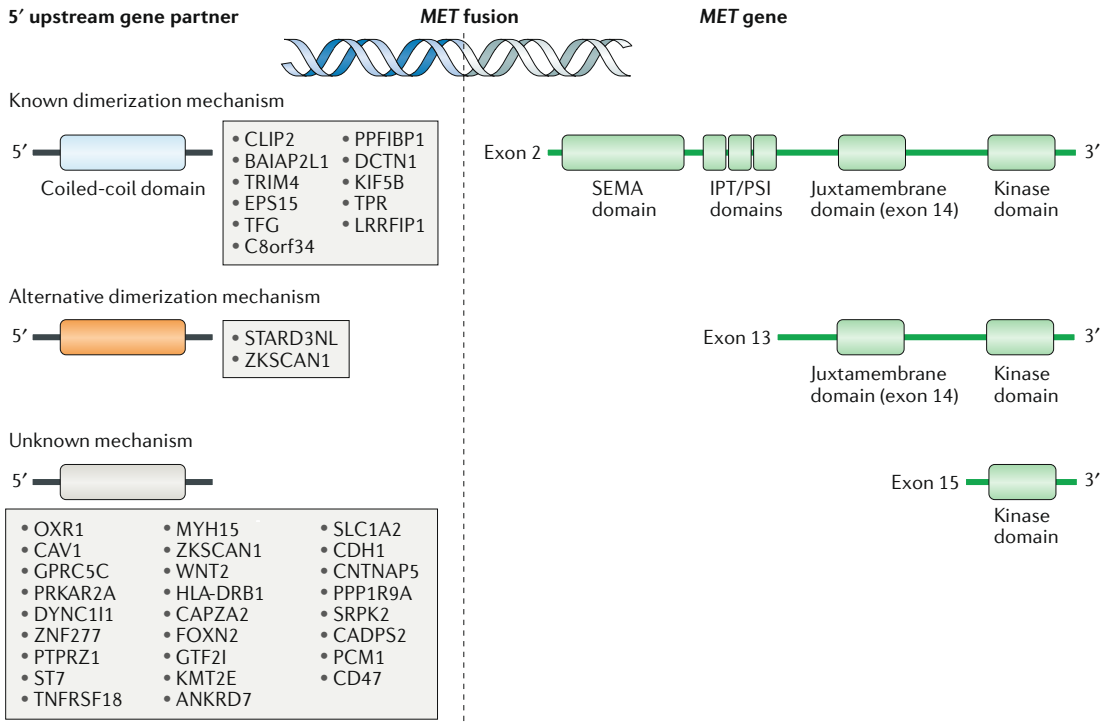

Fig. 4 | ***MET* fusions.** A wide variety of *MET* fusions have been identified. These fusions can result in constitutive MET activation in a variety of ways. **a** | The 5′ upstream partners CLIP2, TFG, KIF5B, BAIAP2L1, C8orf34 and TPR and others all have coiled-coil domains that promote chimeric oncoprotein dimerization. **b** | Other domains (such as the MLN64 N-terminal domain of STARD3NL) can mediate alternative methods of homodimerization. **c** | The 3′ *MET*-derived region typically includes the kinase domain; however, fusions that include the juxtamembrane domain or larger regions of *MET* have also been identified. Interestingly, certain fusions, such as *TPR–MET*, result in the exclusion of exon 14 of *MET*; the biology of tumours harbouring such fusions is thus thought to be similar to that of *MET* exon 14-altered cancers. The genomic locations of *MET* breakpoints are noted in the figure. IPT, immunoglobulin-like regions in plexins and transcription factor; PSI, plexin–semaphorin–integrin; SEMA, semaphorin.

Table 4 | **Targeted therapy outcomes by MET expression status**

Intervention (randomization)	Setting	Phase (*n*)	MET IHC status	Outcomes by MET status	Ref.
AF276 polyclonal antibody					
Rilotumumab (15 mg/kg) vs rilotumumab (7.5 mg/kg) vs placebo (1:1:1)[a]	CRPC	II (144)	73 patients had tumours evaluable for MET expression; 53% were classified as MET^{high} and 47% MET^{low}	mPFS 3.6 months vs 2.9 months in patients with MET^{low} vs MET^{high} tumours receiving rilotumumab (HR 2.27, 95% CI 1.10–4.71; $P=0.027$)	182
MET4 monoclonal antibody					
Rilotumumab (15 mg/kg) vs rilotumab (7.5 mg/kg) vs placebo (1:1:1)[b]	Advanced-stage gastric/GEJ cancer	II (121)	91 patients had tumours evaluable for MET expression; 68% were classified as MET^{+} and 36% MET^{-}	mPFS 4.4 months vs 6.8 months; mOS 10.6 vs 11.1 months; ORR 50% vs 32% in patients with MET^{+} vs MET^{-} tumours receiving rilotumumab	183
SP44 monoclonal antibody					
Tivantinib (360 mg or 240 mg) vs placebo (2:1)	Advanced-stage HCC	II (107)	77 patients had tumours evaluable for MET expression; 48% were classified as MET^{high}	mTTP 2.7 months vs 1.5 months; mOS 7.2 months vs 5.0 months in patients with MET^{high} vs MET^{low} tumours receiving tivantinib	203
Tivantinib vs placebo (1:1)[c]	Metastatic CRC	II (117)	67 patients had tumours evaluable for MET expression; 57% were classified as MET^{high}	ORR 44% vs 31%; mPFS 7.9 months vs 11.0 months; OS 22.3 months vs NR in patients with MET^{high} vs MET^{low} tumours receiving tivantinib	220
Onartuzumab + paclitaxel vs onartuzumab + bevacizumab vs bevacizumab + paclitaxel[d] (1:1:1)	Metastatic TNBC	II (185)	179 patients had tumours evaluable for MET expression; 12% were classified as MET IHC 2+ or 3+	mPFS 10.3 months vs 5.7 months in patients with MET^{high} vs MET^{low} tumours	221
Onartuzumab + erlotinib (single arm)	Advanced-stage *EGFR*-mutant NSCLC	II (61)	61 patients had a MET IHC score of either 2+ (53) or 3+ (8)	IHC 2+: ORR 66% mPFS 8.5 months. IHC3+: ORR 88%, mPFS 4.4 months	222
Onartuzumab + erlotinib vs placebo + erlotinib (1:1)	Recurrent NSCLC	II (137)	128 patients had tumours evaluable for MET expression; 52% were classified as either MET IHC 2+ or 3+	IHC 2+: mPFS 4.1 months vs 1.6 months, mOS NR vs 6.5 months in patients receiving onartuzumab + erlotinib vs placebo + erlotinib. IHC 3+: mPFS 2.7 months vs 1.4 months, mOS 11.1 vs 2.9 months in patients receiving onartuzumab + erlotinib vs placebo + erlotinib	184
Unknown antibody					
Capmatinib	NSCLC	I (52)	52 patients had tumours evaluable for MET expression; 94% were classified as either MET IHC 2+ or 3+	IHC 2+: ORR 17%. IHC 3+: ORR 24%	85

CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; NR, not reported; mOS, median overall survival; mPFS, median progression-free survival; mTTP, median time to progression; ORR, objective response rate; OS, overall survival; TNBC, triple-negative breast cancer. [a]All patients received mitoxantrone and prednisone. [b]All patients received epirubicin, cisplatin and capecitabine. [c]All patients received cetuximab plus irinotecan. [d]All patients received paclitaxel.

have also used the median H-score (comprising the range of H-scores obtained from samples exclusively analysed within a given study) as the cut-off point for overexpression; this approach makes standardization and generalization across studies difficult.

Mass spectrometry. Selected reaction monitoring mass spectrometry (SRM–MS) involves the serial ionization and fragmentation of tumour proteins in order to quantify the molecular mass of the MET protein per sample (in attomoles per microgram). SRM–MS enables the quantification of MET in formalin-fixed, paraffin-embedded tissue slices with robust reproducibility reported, even in samples that have been fixed for ≥1 year[190]. In comparison with IHC, SRM–MS is less vulnerable to interobserver bias and might enable the detection of lower levels of protein expression. However, SRM–MS cannot differentiate between proteins expressed in tumour and non-malignant tissues, and therefore MET quantification might be influenced by admixed stroma and/or inflammatory infiltrates. Furthermore, SRM–MS is more technically demanding and more expensive than IHC, meaning that this approach is currently less widely adopted. IHC is currently routinely used in diagnostic pathology laboratories, while the use of SRM–MS has remained largely investigational.

Screening

The presence of MET overexpression has been investigated as a method of screening for patients with activating alterations in *MET*. Unfortunately, MET overexpression is not a reliable indicator of *MET* amplifications or *MET* exon 14 alterations, and limited data are currently available on the detection of *MET* fusions[71]. This lack of a predictable association contrasts with the situation in patients with *ALK*-rearranged NSCLC, in

which ALK overexpression on IHC is strongly correlated with the presence of an *ALK* rearrangement detected by FISH[191].

MET amplification. As mentioned, MET overexpression determined using IHC does not strongly correlate with *MET* amplification[192–194]. This lack of a correlation might reflect the inclusion of samples featuring lower levels of *MET* amplification that do not result in substantial protein expression, or the possibility that expression is variably modulated by post-transcriptional and/or post-translational factors. In a series from the Lung Cancer Mutation Consortium (LCMC), *MET* amplification (defined as a *MET* to CEP7 ratio of >2.2) was only detected in one of 74 patients (1%) with MET overexpression (defined as an H-score of ≥200)[195]. In a small study of samples from patients with gastric cancer ($n = 31$), a MET IHC H-score of 150 had a 75% sensitivity and 78% specificity for the detection of *MET* amplification (defined as a *MET* to CEP7 ratio of >2.0 and a GCN of >4.0)[190]. All of the above studies used FISH to quantify *MET* amplification; limited data are available from NGS in this context.

MET mutation. Interestingly, although *MET* exon 14-altered NSCLCs are expected to overexpress MET, not all of these tumours are MET-positive on IHC or SRM–MS[107,122,196]. In a cohort of 25 patients with *MET* exon 14-altered NSCLC, only 16 (64%) were MET-positive on IHC (2+ and 3+), and about one third were found not to express MET on SRM–MS[196]. Similar to the scenario with *MET*-amplified cancers, the expression of *MET* exon 14 variants might be modulated by post-transcriptional and/or post-translational factors. In the previously discussed LCMC series, *MET* exon 14 alterations were only detected in two of 74 patients (3%) with MET overexpression (H-score ≥200)[195]. Other reports indicate that the sensitivity and specificity of MET overexpression determined using IHC as an indicator of *MET* exon 14 alterations is variable. For example, a 90% sensitivity and 47% specificity for IHC in predicting *MET* exon 14 alterations was found in one cohort of patients with NSCLC[197], and a 20% sensitivity and 83% specificity in patients with sarcomatoid lung carcinoma[189]. IHC has not routinely been explored as a screening tool for other *MET* mutations (such as kinase domain mutations) that do not result in exon 14 alterations.

Targeted therapy

Viewed in isolation, MET overexpression is not consistently predictive of benefit from MET-directed therapies. Reasons for this lack of benefit include the challenge of defining expression versus overexpression for a continuous variable and the possibility that overexpression is not equivalent to a MET-dependent state. Many cancers overexpress MET when analysed using IHC, although the frequency of overexpression is variable and dependent on the cut-off point used. For example, 24–66% of NSCLCs[193,197] and 28–63% of gastric cancers[28,64,198] have been described as *MET*-positive in various studies. Multiple therapeutic anti-MET antibodies (such as onartuzumab and emibetuzumab)[199,200], anti-HGF antibodies (ficlatuzumab and rilotumumab)[187,201] and TKIs (crizotinib, cabozantinib, tivantinib, SAR125844 and tepotinib)[202–205] have been tested in clinical trials. The overall activity of these drugs as monotherapies for patients with MET-overexpressing cancers is low (TABLE 4). For example, in a phase III trial involving patients with MET-overexpressing HCC, no significant difference was observed in the median overall survival (OS) durations between patients who received tivantinib and those who received placebo (8.4 months and 9.1 months, respectively; $P = 0.81$)[206]. Tepotinib resulted in a short median PFS duration of 2.8 months in the same setting, and the extent of MET IHC positivity did not select for improved activity[207]. Owing to the limited therapeutic successes achieved with antibody-based therapies, many drug development programmes sought to combine these therapies with chemotherapy, or EGFR-directed targeted therapies. The latter strategy was chosen given the preclinical synergy of this combination and the identification of secondary MET dependence following EGFR TKI resistance[2]. Unfortunately, although certain phase II trials seemed promising (with improvements in PFS and OS)[208], subsequent confirmatory phase III trials failed to reveal any benefit in patients with MET-overexpressing cancers (TABLE 4; see Supplementary Table 1), and the level of MET expression did not correlate with increased clinical benefit[181]. Additionally, patients with MET-overexpressing cancers on IHC were equally responsive to MET-directed therapies and placebo (Supplementary Table 1).

New anti-MET antibody-based strategies have thus been explored. These include mixtures of antibodies directed against different epitopes of the MET protein (such as Sym015) that have shown preclinical activity against MET-overexpressing and *MET* exon 14-altered cell lines[180]. MET-targeted ADCs have also been explored. These drugs have the advantage of binding to and targeting MET-expressing cancer cells regardless of the level of MET dependence, and lower levels of MET expression might be sufficient for payload delivery. As an example, a study investigating the mechanism of action of the ADC telisotuzumab vedotin did not find a correlation between the level of MET expression and the degree of therapeutic benefit in a variety of solid tumours[209,210]. Importantly, MET can also be expressed on non-malignant lung tissues[211]; therefore, pulmonary toxicities might be an issue with this type of therapy.

MET expression is a poor predictor of benefit from MET-targeted therapies in the absence of evidence of a genomic correlate of MET dependence and, therefore, the predictive nature of MET expression is being recontextualized in order to better identify cancers that are oncogenically addicted to MET. In one study involving patients with *MET* exon 14-altered NSCLC, MET expression was surprisingly heterogeneous in that 31% of cancers (5/16) did not have MET protein detectable by SRM–MS[107]. In addition, the ORR to crizotinib was higher among tumours with detectable MET expression by SRM–MS (55% of tumours, 6/11) than among tumours that did not express MET (0%, 0/5). These observations suggest that, in the correct context, prospectively identifying MET expression could maximize

the level of benefit derived with MET-directed targeted therapies. The relationship between MET expression and *MET* amplification is currently not well defined; this should be explored prospectively in ongoing trials involving MET-directed therapies (TABLE 4).

Conclusions

The process of identifying patients with MET-dependent cancers is complex. From a diagnostic perspective, clinically meaningful cut-off points need to be standardized for continuous variables including the level of *MET* amplification or MET expression before these features can be used to guide treatment-related decision making. The migration of diagnostics towards the use of more comprehensive and technically sophisticated assays is likely to be required to maximize the likelihood of detecting *MET* amplifications, mutations and/or fusions. Assays such as NGS should be considered for the detection of these alterations in both tumour biopsy and plasma samples and ideally in both DNA and RNA. The effective detection of MET-dependent cancers is crucial given that MET-directed targeted therapy is active in many of these cancers. Importantly, the level of activity of these therapies can be modulated by the type of alteration identified and the degree of oncogenic addiction to MET signalling.

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