

The role of mesenchymal-epithelial transition factor (c-MET) in cancer development and treatments

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Abstract. The mesenchymal-epithelial transition factor (c-MET) is classified into the tyrosine kinase receptor family. Its indispensable role in regulating the cell cycle through various downstream pathways has made it one of the most essential transmembrane receptors. A MET receptor monomer contains six domains, and each has its own function when activated by hepatocyte growth factor (HGF). Due to its complexity, c-MET aberrations including point mutations, amplification, protein overexpression, splicing site mutation, fusion, and HGF autocrine or paracrine upregulate cell proliferation and are common in most aggressive cancer types such as colorectal cancer, lung cancer, liver cancer, and glioblastoma. Correspondingly, cancer therapies targeting c-MET have been researched for decades. This review presented the mechanisms under c-MET activation, discussed its role in cancer development, and summarized recent advancements in clinical trials. c-MET inhibitors, especially combined with other therapeutic inhibitors, appeared to be a promising strategy when taking selectivity, resistance, and tolerability into account.

Keywords: mesenchymal-epithelial transition factor, hepatocyte growth factor, MET aberration, cancer therapy, immunotherapy.

1. Introduction

Embedded in the phospholipid bilayer, transmembrane receptor proteins include an extracellular domain that associated with ligand interactions and a cytoplasmic domain that activates downstream signaling pathways mainly through phosphorylation [1]. MET, or N-methyl-N'-nitroso-guanidine human osteosarcoma transforming gene, is a proto-oncogene that encodes the mesenchymal-epithelial transition factor (c-MET), which plays an indispensable role in regulating cell migration, angiogenesis, scattering, motility, proliferation, and embryogenesis [2]. c-MET potently binds with hepatocyte growth factor (HGF) and activates downstream signalling pathways mainly through phosphorylation. In this review, we discussed MET's mechanisms as the underlying carcinogenesis of various cancers including lung cancer, colorectal cancer, glioblastoma, and liver cancer. Dysfunctions of c-MET such as point mutations, amplification, protein overexpression, splicing site mutation, fusion, or HGF autocrine and paracrine all contribute to the carcinogenesis [3]. Current therapies targeting c-MET are in concentrated research, especially small molecular inhibitors such as Tepotinib, Crizotinib (Xalkori), and Cabozatinib. Many have displayed potent clinical activity and some of them have already been released into the market. At present, more and more inhibitory compounds are being investigated in clinical trials, especially combinations of different strategies to alleviate metastasis and drug resistance.

This review summarized the underlying mechanisms of c-MET and unveiled its role in various cancer development as well as targeted treatments.

2. Basic mechanism of MET

2.1. The HGF/c-MET Signal-Receptor Pair

HGF is a member of a group of factors that have the angiogenic ability as heparin-binding growth factors. HGF was discovered as a novel growth factor that promotes hepatocyte growth in rats in 1984, and it has since been classified as a scatter factor, tumor cytotoxic factor, and fibroblast-derived factor (secreted by fibroblast) [4]. It is translated from human chromosome 7q21.1 and produced as a single-

chain inert precursor, which later forms a disulfide-linked α/β double-chain heterodimer after extracellular cleavage by serine proteases (Figure 1A). This mature double-chain HGF composes of the 69-kDa α -chain and the 34-kDa β -chain [5]. The activation of HGF depends upon ligand interactions.

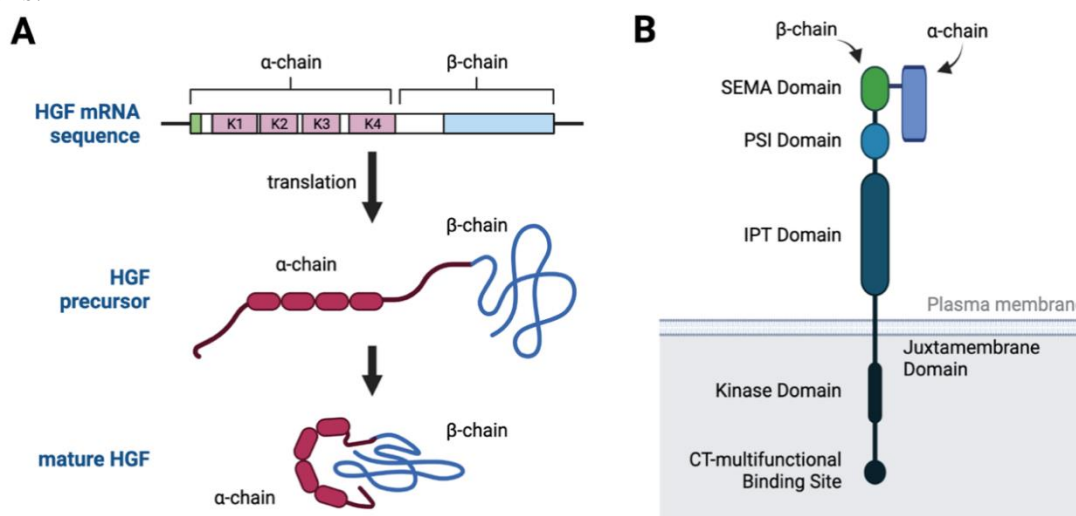


Figure 1 Molecular structure of HGF and c-MET receptor: (A) the formation process of HGF signal. (B) c-Met receptor protein. Created with Biorender.com.

The K1 loop structure at the N-terminal of the α chain is a high-affinity binding site for c-Met, but it cannot activate c-Met. Only when c-Met binds to the α chain of HGF, does the β chain of HGF binds with low affinity and induces the activation of c-Met. Ligand binding induces the phosphorylation of amino residue Tyr 1234 and 1235 on c-Met, further activating downstream pathways [6].

One of the few effective HGF receptor proteins is c-MET, a heterodimer comprised of a 50-kDa highly glycosylated-chain subunit and a 145-kDa-chain joined by a disulfide linkage [2]. c-MET contains seven functional areas and is generally expressed in the stem or progenitor cells. Those domains include semaphoring (SEMA) domain (residue 25-514), plexins-semaphorins-integrins (PSI) domain (residue 515-561), immunoglobulin-plexin-transcription (IPT) domain (residue 562-922), helical transmembrane region (residue 923-956), Juxta-membrane domain, Kinase domain, and C-terminal (CT) multifunctional binding site (Figure 1B) [7]. The extracellular SEMA region is responsible for HGF binding, and the membrane-proximal domain usually plays a negative role in regulating c-Met signaling. Besides, the catalytic domain can activate downstream signals by autophosphorylation and positively regulate the catalytic activity of tyrosine kinases. Moreover, the CT multifunctional binding region mainly recruits various protein factors and linker molecules in the cytoplasm to transmit signals [2, 6-8].

2.2. The MET Signaling Pathways

The HGF/c-Met signaling pathway is involved in physiological processes such as embryonic development (essential in liver development), organ regeneration, and tissue damage repair. After the combination of HGF and c-Met, Tyr-1234 and Tyr-1235 is activated, thus promoting the recruitment of intracellular effector adaptor proteins such as signal-relay molecule PI3K, SH2 domain-containing transforming protein (SHC) adaptors SHP2, growth factor receptor-bound protein 2 (GRB2), SRC, CBL, mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases ERK1 and ERK2, Jun amino-terminal kinases (JNKs), GRB2-associated binding protein 1 (GAB1) that offers additional binding sites and pathways including RAS-MAPK and PI3K-AKT, phospholipase C γ 1 (PLC γ 1) that involves in tumor progression and metastasis, and signal transducer and activator of transcription 3 (STAT3) that can activate a series of human cancer [3, 9-12]. It is also demonstrated that c-MET can bind to surface receptors. Besides, interacting with GAB1 scaffolding protein, CD44 can also participate in the HGF/c-Met pathway. Other tyrosine kinases such as ROR1, plexin B1,

integrins, and CD151 also regulates the outputs of MET pathways for efficacy (Figure 2) [3]. Stimulating CBL by the phosphorylation of the juxta-membrane domain will activate downstream signals such as RAS-MAPK, PI3K-AKT, SRC, and STAT3, leading to the ubiquitination of c-Met protein. Consequently, the inability to hydrolyze c-Met efficiently can lead to carcinoma. Besides, the downstream APK pathway is mainly responsible for cell survival and repairment, while the SATA3 and RAS related pathways control cell proliferation and differentiation. Notably, most of those proteins control or interfere with the cell cycle, cell transformation, and thus might result in tumor proliferation and metastasis [13].

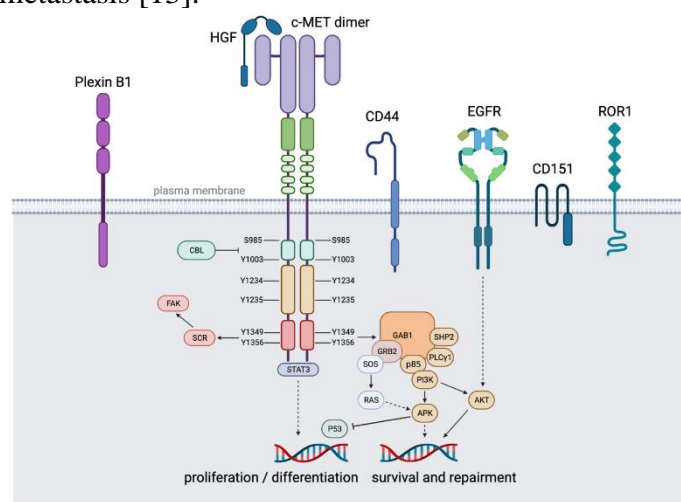


Figure 2 Signaling Pathways related to HGF/c-Met (partial). Created with Biorender.com.

Additionally, the MET pathway also interacts with epidermal growth factor receptor (EGFR) and KRAS signaling pathway, which induces the phosphorylation of downstream kinases such as PI3K, RAF, and RAL [14, 15]. The EGFR gene is located on human chromosome 7 p11.2, with a total of 21 exons. EGFR is the expression product of the proto-oncogene *cerbB1*, a member of the epidermal growth factor receptor (HER) family. *In vivo*, c-MET cooperate perfectly with EGFR: c-MET upregulation can activate downstream signaling pathways of EGFR. All the crosstalk is essential for the molecular pathogenesis of several cancers, including non-small cell lung cancer (NSCLC) and breast cancer.

2.3. Abnormalities in MET Pathways

Aberrant MET expression is testified to be prevalent in various malignant cancers. According to the AACR GENIE reports, MET is altered in 2.83% of malignant solid tumor patients [16]. Structural and genetic analysis of abnormal c-MET receptor has revealed four underlying mechanisms, including point mutations, amplification, protein overexpression, splicing site mutation, fusion, or HGF autocrine and paracrine (Figure 3) [3].

Current literatures quantitatively demonstrated that c-MET aberrations are identified mostly in cell lines that possess the potential for metastasis. This wide variety of MET mutations correlates with the clustering of metastatic tumors: more than 95% of cases in a study (n=133) contains tumors of metastatic fronds. [17] At present, fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), PCR-SSCP, immunohistochemistry (IHC) and chromosome analysis are the main experimental and clinical techniques to identify MET aberrations in tumors. Nevertheless, unveiling specific biomarkers of some tumors *in vivo* is still problematic to researchers, and actual results of the increase in MET mutation frequency sometimes are not as anticipated [3].

2.3.1. Point Mutation

Along with MET amplification, MET point mutations is the first identified MET alteration in human body [3]. It presents in 2.02% of all malignant solid tumor patients, suggesting its dominant role in MET abnormalities [16]. Among all the point mutations, most of them concentrated on

domains responsible for ligand binding or receptor signaling, including SEMA domain, Juxta-membrane domain, and Catalytic domain [3]. For example, in the statistical analysis, N375S in the extracellular SEMA domain is the most common mutation and can lead to a change in amino acid size, while T1010I, R988C, and Y1248H are also prevalent [17]. Besides, it is important to notice that point mutations in c-MET receptors are frequently associated with co-mutations in downstream pathways, which might also be accounted for cancer formation [18].

2.3.2. Amplification

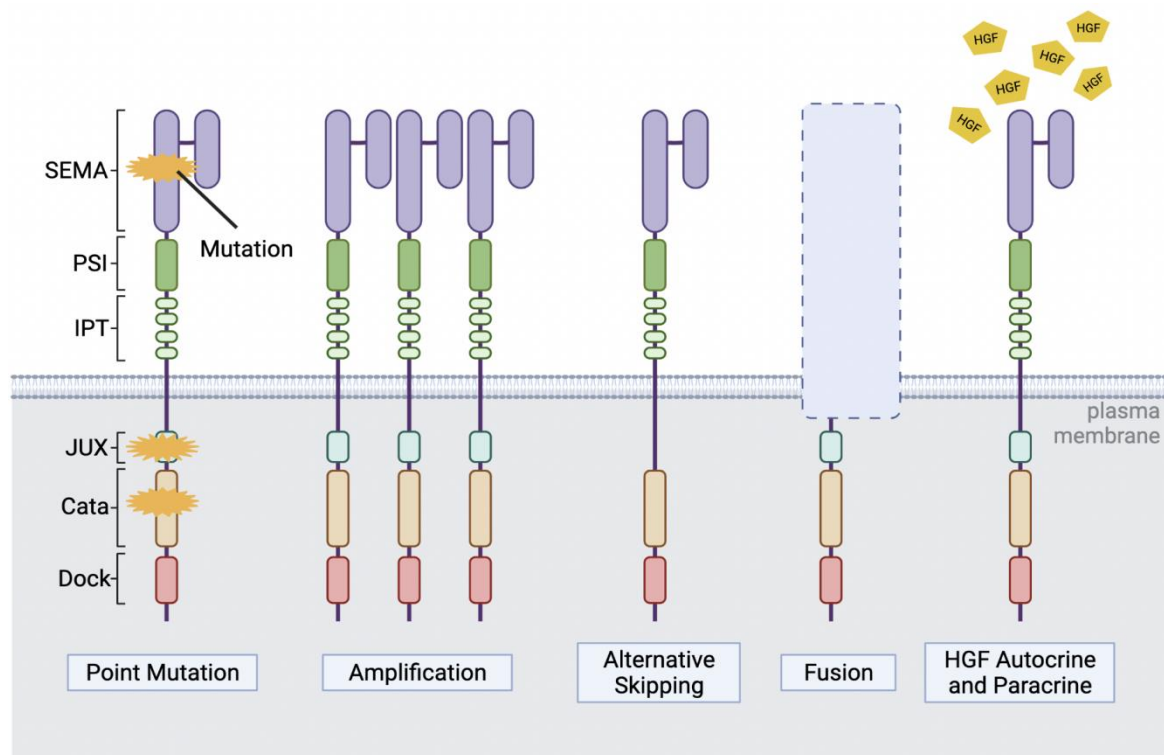


Figure 3 Summary of c-MET aberrations. Created with Biorender.com.

Amplification of the MET gene is characterized as an increase in the number of copies of the gene (GCN). At present, there are two mechanisms behind the increase: (1) MET gene increased in comparison to centromere 7 or other healthy structures. (2) both MET gene and centromere 7 duplicate in numbers [19]. Cells with high c-MET receptor expression levels were found to have a higher potential of proliferation, migration, and angiogenesis, ultimately leading to cancer. In mouse models, silencing the overexpressed MET gene resulted in the decrease in tumor growth and metastasis both *in vivo* and *in vitro* [20]. Among several cancers caused by MET amplification, lung adenocarcinoma displayed a high correlation, with 123 cases more than the second top disease with MET amplification [16]. Specifically, in NSCLC patients, roughly 1-3% of cases embed an increase in MET gene copies under the next-generation sequencing (NGS) [19]. Besides, although the possibility of MET amplification is not high considering all kinds of alterations, it is often accompanied by strong c-MET protein expression, and thus is one of the factors of poor prognosis. Nonetheless, data has shown that c-MET inhibitors have a significant benefit in patients with high MET amplification [21].

2.3.3. Protein Overexpression

To adapt to adverse conditions, one way cancer cells choose is to develop cancer expedient through the upregulation of MET transcription. Usually, this activation can be caused by additional oncogenes, abnormal environment, and substances produced in the stroma [22]. However, the overexpression of c-MET protein as one of the activation forms is still controversial. Although the incidence of c-MET protein overexpression in lung adenocarcinomas can be as high as 65%, it does not act as a primary

oncogenic driver. Instead, it is more often a secondary event after the activation of other driver genes, thereby promoting tumor growth [22].

2.3.4. Splicing Site Mutation

An important therapeutically relevant MET mutation is caused by the deletion of exon 14 in the mRNA during transcription, or METex14 skipping, which will lead to the elimination of the juxta-membrane domain (Δ aa 936-1,009). The juxta-membrane of the MET14 exon contains the Y1003 and c-CblE3 ubiquitin ligase binding sites. When a MET14 exon-skipping mutation occurs, the binding site for Y1003 and c-CBL is lost, resulting in ubiquitination declination and persistent c-MET activation. That is, the cell lost the ability to degrade or inhibit the function of MET pathways [23]. The exon 14 mutation frequency is approximately 3-4% of lung adenocarcinomas and 20-30% of pulmonary sarcomatoid carcinomas [2]. In addition, other cancer types such as gastric cancer (7.1% mutation rate), colorectal cancer (9.3% mutation rate), and glioma (0.4% mutation rate) were found to have mutations that cause skipping in exon 14 of the MET gene [16, 24]. Furthermore, METex14 mutation has been perceived as important biomarker for therapeutical analysis.

2.3.5. Fusion

MET fusion genes are usually lacking proper juxta-membrane regulatory sequences or N-terminal partners [25]. The mutation in MET exon 14 also results in oncogenic fusion. Ordinarily, fusion will produce a "chimeric protein" on the cell surface, which can promote tumor growth. The frequency at which the MET gene fuses with other genes is approximately 1%, relatively lower than other aberrant c-MET expressions. Gene associated with c-MET fusions currently found in cancers include TPR, TRIM4, EPS15, DCTN1, PTPRZ1, NTRK1, HLA-DRB1, KIF5B, STARD3NL, ZKSCAN1, CLIP2, TFG, LRRFIP1, UBE2H, PPFIB1, ATXN7L, etc. [25, 26].

2.3.6. HGF Autocrine and Paracrine

Cancer cells can secrete large amounts of HGF into the tumor microenvironment (TME) to transform to a more aggressive phenotype. During this process, HGF activates HGF/c-Met signaling in cancer cells in an autocrine manner, as well as stimulates HGF-activated c-Met receptors in surrounding stromal cells through paracrine, further increasing HGF expression in the TME. According to Xie *et al.*, both HGF autocrine and HGF paracrine displayed a high positive correlation with the phosphor-MET levels *in vivo*, such as in the glioblastomas, demonstrating their carcinogenicity. Similar to METex14 skipping, the sensitivity test of c-MET inhibitors in mice indicates that HGF autocrine status may serve as a predictive biomarker [27].

2.4. c-MET Pathway and EGFR Resistance

Tolerance to EGFR-TKI therapy is thought to be caused by the c-MET pathway. The epidermal growth factor receptor, or EGFR, belongs to the epidermal growth factor receptors family (HER). It causes receptor dimerization and tyrosine autophosphorylation, which leads to cell proliferation and is linked to the progression of NSCLC. As a result, EGFR tyrosine kinase inhibitors (TKIs) that reversibly or irreversibly block EGFR tyrosine kinase activity have been widely employed as first-line therapy in the treatment of NSCLC in recent years. [28, 29]. However, because it is a tyrosine kinase receptor, c-MET can use the ERBB3-PI3K-AKT and MAPK-ERK1/2T pathways to bypass the blocked EGFR phosphorylation kinase pathway [6]. In this way, amplified or overexpressed c-MET promotes downstream signal transduction without the inference of EGFR-TKIs, thus leading to cancer cell proliferation and resistance to EGFR-TKIs. Originally identified in Gefitinib resistance model, this mechanism gives rise to approximately 20% of acquired resistance to Gefitinib and Erlotinib, thus further emphasizing the importance of c-MET inhibitors in therapeutic researches [30].

3. MET inhibitors

Recent studies have suggested that c-MET plays an inalienable role in various cancer formations. Therefore, a wide range of c-MET inhibitors are in the process of preclinical or clinical research, and some have already been released into the market. Directing at the c-MET signaling pathway, c-MET targeting drugs can be divided into HGF-targeted therapy, c-MET-targeted therapy, and immunotherapy.

3.1. HGF Inhibitors/Antibodies

HGF inhibitors can bind and neutralize HGF, preventing the combination of HGF and c-Met receptors, thereby inhibiting the activation of downstream signaling pathways. NK4 serves as a competitive inhibitor of HGF and behaves as a specific antagonist for HGF/c-Met pathways, and the N-terminal hairpin domain is essential to the HGF-antagonist activity. After treatment with NK4 for four weeks, the growth of pancreatic cancer was suppressed for 61% [31]. Rilotumumab (AMG-102) progressed into phase III clinical trials, which was cut off due to lack of efficacy. Ficlatusumab (AV-299) is a humanized antibody whose clinical trials were mostly negative. Nonetheless, a recent trial with Ficlatusumab plus chemotherapy agent cytarabine proved their effectiveness [32, 33].

3.2. c-MET Antibodies

Activation of the c-Met signaling pathway requires c-Met dimerization after HGF binding, which in turn triggers phosphorylation by downstream kinases. Competition of c-Met antibody with HGF and binding of c-Met leads to degradation and inactivation of c-Met. Current studies include Onartuzumab (MetMAb), Emibetuzumab (LY2875358) (ongoing), LY3164530 (ongoing), JNJ-61186372 (ongoing), SAIT301 (ongoing), ABT-700 (h224G11) (ongoing), ARGX-111 (ongoing), DN30, MCLA-129 (ongoing) [33].

3.3. c-MET Tyrosine Kinase Inhibitors

ATP competitive and ATP non-competitive inhibitors are the two types of c-Met inhibitors. On the basis of distinct forms of binding, ATP competitive inhibitors are further split into two classes: class I and class II. [34] Till 2021, five small-molecule c-MET inhibitors, Crizotinib (Xalkori), Cabozatinib, Capmatinib, Savolitinib and Tepotinib, have been approved by FDA for the treatment of specific cancers. Crizotinib receptors include c-MET, ALK, and ROS1. From 2011 to 2016, Crizotinib was given permission to different ALK-positive or ROS1 positive NSCLC. Similar to Crizotinib, Cabozatinib is also a multi-target tyrosine kinase inhibitor, targeting c-MET, VEGFR1/2/3, RET, AXL, KIT, TRKB, FLT-3, and TIE-2 [35]. Recently, Tepotinib (TepMetko) from Merck gained permission in the Japanese market for the treatment of advanced NSCLC patients with METex14 skipping mutation.

3.4. Immunotherapy and Combined Therapy

Immunotherapy is a novel cancer treatment that stimulates human immune defence against abnormal cells. Immune checkpoint inhibitors may improve the outcomes of c-MET derived cancer, and currently, anti-PD-1/PD-L1 agents are the most common treatment for various cancer. Although anti-PD-1/PD-L1 agents themselves did not do well in clinical trials, combining them with c-MET inhibitors exhibit an excellent response rate and would have a promising future [36]. Besides, combining c-MET inhibitors with immunotherapy is only a tip of the iceberg. Scientists are presently combining c-MET inhibitors with themselves and other signaling pathway inhibitors and have achieved desired outcomes as we can see in the latter part of this study.

4. c-MET as a target in cancer therapy

At present, c-MET is illustrated in carcinomas, mesotheliomas, and sarcomas with its potential prognostic importance [37]. The role of c-MET in cancer development and treatment for four representative cancer types, including lung cancer, liver cancer, glioblastoma, and colorectal cancer are summarized and discussed. In table 1, clinical trials related to c-MET in 2020-2022 are summarized.

4.1. c-MET and Lung Cancer

As lung cancer scores top at the common cause of cancer-related death, c-MET proto-oncogenic activity has been detected in both NSCLC (75%-78% of lung cancer) and small cell lung cancer (12%-15% of lung cancer). Nearly thirty years ago, scientists first detected the presence of c-MET in 88% of SCLC cells, although compared with NSCLC, activating mutations on c-MET are relatively rare [38]. Subsequent findings suggested that missense or insertion mutations such as R988C, T1010I, exon 10, and intron 13 in the Juxtapose membrane domain greatly promoted carcinogenesis. Aberrations in other parts of c-MET have also been recorded [39]. Several strategies are proposed to alleviate the role of c-MET in SCLC. Even though preclinical studies of monotherapy and combination therapy such as PHA665752, Crizotinib, and Golvatinib demonstrated feasibility, clinical trials are not optimistic [40]. In phase Ib/II study of Ganitumab or Rilotumumab in combination with platinum-based chemotherapy (NCT00791154), the objective response rate (ORR) of the placebo, Rilotumumab, ganitumab was 59%, 68%, 63% each, and overall survival (OS) was 10.8, 12.2, 10.7 months respectively, suggesting a low response rate [41]. At present, Pembrolizumab, Vibostolimab or Atezolizumab in combination with chemotherapy is in phase III clinical trials (NCT05224141), and Berzosertib plus Topotecan is in phase II (NCT04768296).

In NSCLC patients, METex14 skipping, c-MET amplification, c-MET fusion and overexpression are all recognized. METex 14 skipping exists in 2%-4% of NSCLC and proved to happen most in sarcomatoid carcinoma (4.9%-31%), which is a subtype of NSCLC [42]. The occurrence rate for amplification and overexpression then is 2%-5% and 15%-70% each. Notably, NSCLC patients may experience different c-MET aberrations at the same time [25]. Although combined treatment with Crizotinib has driven severe adverse effects, it has the median overall survival (mOS) of metastatic NSCLC patients of 24.6 months [43]. Similarly, Cabozantinib has the mOS for 9.2 months and has demonstrated therapeutic potential when combined with Erlotinib or EGFR-TKIs to treat EGFR wild-type NSCLC [44]. More recently, Tepotinib designed by Merck went into the market in Japan, serving as an ATP-competitive c-MET inhibitor with selectivity 1000-fold higher than others. As an anti-MET antibody, Onartuzumab plus Erlotinib's efficacy is in debate, as large clinical trials failed to confirm its effectiveness represented in previous studies [45]. Several anti-HGF antibodies are also put into clinical trials with NSCLC patients, including Rilotumumab and Ficlaturzumab. Rilotumumab combined with Gefitinib lifted mOS for 18.1 months, while the Ficlaturzumab improved median progress-free survival rate (PFS) for 5.5 months [46, 47]. Furthermore, immunotherapy is starting to emerge after targeted therapy and chemotherapy. Various combination recipes are currently under investigation, but the cytotoxicity related to immunotherapy remains a problem.

4.2. c-MET and Liver Cancer

Chronic liver diseases including cirrhosis and hepatitis B or C are the prominent cause of Hepatocellular carcinoma (HCC), and they are proved to have effects on c-MET activation [48]. Liver cells that suffer from diseases are gradually removed from the body, triggering the upregulation of HGF/c-MET and cell regeneration [49]. Around half of HCC, the third most common cause of cancer-related death worldwide, features MET abnormalities: 50% mRNA overexpression, 28% c-MET protein overexpression, 24% gene amplification, and 4% gene mutation [50]. In detail, three missense mutations (K1262R, M12681, T11911) and the mutations in the Juxta-membrane domain were observed in HCC patients. The hepatic satellite cells also secrete a large amount of HGF into

peritumoral areas [49]. Besides, several studies have discovered that certain miRNAs are deregulated in HCC cells and inference with downstream signaling pathways, including HGF/c-MET. In some HCCs, miR-34a is downregulated due to p53 loss of function. miR-34a deficiency will then promote the expression of MET receptors [51].

Table 1. 2020-2022 clinical trials on HGF/c-MET inhibitors

| Compound | Cancer Type | Phase | Outcomes | Identifier |
|--------------------------------|---|-------|---|-------------|
| Volitinib | Advanced Gastric Adenocarcinoma | II | Result pending | NCT02449551 |
| Cabozantinib, Pamiparib | Advanced/ Refractory Malignant Solid Neoplasm | I | Result pending: recruiting | NCT05038839 |
| TPX-0022 | Advanced Solid Tumor, Metastatic Solid Tumors, MET Gene Alterations | I | Result pending: recruiting | NCT03993873 |
| Glumetinib | C-Met Exon 14 Mutation | I/II | Result pending: recruiting | NCT04270591 |
| INC280 (capmatinib) | Carcinoma, Non-Small-Cell Lung | II | Result pending: active but not recruiting | NCT02414139 |
| INC280, bevacizumab | Glioblastoma Multiforme, Gliosarcoma, Colorectal Cancer, Renal Cell Carcinoma | I | Result pending: active but not recruiting | NCT02386826 |
| PLB1001 | Glioma | I | Final result not posted. At least two advanced sGBM patients have had a partial response, with just minor side effects. It also proved to have blood brain barrier permeability | NCT02978261 |
| Tivantinib | Hepatocellular Carcinoma | III | Phase III displayed negative result of tivantinib on c-MET-high patients with advanced hepatocellular carcinoma | NCT01755767 |
| Cabozantinib, Nivolumab | Hepatocellular Carcinoma, Liver Cancer | II | Result pending: active but not recruiting | NCT05039736 |
| APL-501, APL-101, Nivolumab | Hepatocellular Carcinoma, Renal Cell Carcinoma | I/II | Result pending: active but not recruiting | NCT03655613 |
| Cabozantinib, Nivolumab | Hepatocellular Carcinoma, Liver Cancer | II | Result pending: active but not recruiting | NCT05039736 |
| Cabozantinib | Multiple Myeloma, Refractory Multiple Myeloma, Relapsed/Refractory Multiple Myeloma | I/II | Terminated (Phase I treatment response was not as planned, and the myeloma therapy field has altered since the trial began.) | NCT03201250 |
| Tivantinib, Erlotinib | Non-Squamous, Non-small cell lung cancer | III | Terminated (Because the protocol-defined stopping barrier for futility was met, the sponsor made a choice based on intermediate OS data.) Present data: Tivantinib and Erlotinib exhibit insignificant improvement in overall survival compared to placebo and Erlotinib. | NCT01244191 |
| Capmatinib, Nazartinib | Non-small cell lung cancer | I/II | Result pending: recruiting | NCT02335944 |
| INC280 single agent, erlotinib | Non-small cell lung cancer | I | Terminated (Failure in the enrollment of participants) | NCT02468661 |

| | | | | |
|------------|----------------------------|----|----------------------------|-------------|
| Capmatinib | Non-small cell lung cancer | II | Result pending: recruiting | NCT04677595 |
|------------|----------------------------|----|----------------------------|-------------|

Table 2. 2020-2022 clinical trials on HGF/c-MET inhibitors

| Compound | Cancer Type | Phase | Outcomes | Identifier |
|--|--|-------|---|-------------|
| INC280, Gefitinib | Non-small cell lung cancer | II | Positive results indicate that the combination of capmatinib with gefitinib is promising for patients with both EGFR and MET mutation. | NCT01610336 |
| MSC2156119J | Solid Tumors | I | Tepotinib can reduce or stabilize tumor burden and is well tolerated | NCT01014936 |
| Adavosertib, Savolitinib, Darolutamide, CFI-400945, Ipatasertib, Durvalumab, Tremelimumab, Carboplatin | Prostate Cancer | II | Result pending: recruiting | NCT03385655 |
| Pazopanib, ARQ 197 | Sarcoma, Stomach Neoplasms, Neoplasms | I | Result pending | NCT01468922 |
| SPH 3348 | Solid Tumor | I | Result pending: recruiting | NCT05088070 |
| PF-02341066, PD-0325901, Binimetinib | Solid Tumor, Colorectal Cancer | I | 7 out of 30 that received Binimetinib combined with PF-02341066 stayed stable | NCT02510001 |
| GST-HG161 | Solid Tumor, C-Met Mutation-Related Tumors | I | Result pending | NCT04228406 |
| MSC2156119J | Solid Tumors | I | Twelve Japanese patients were treated. They were well tolerated with no observed toxicity. Adverse events were at low grades. | NCT01832506 |
| PF-02341066, Rifampin, Itraconazole | Systemic Anaplastic Large-Cell Lymphoma, Advanced Malignancies Except Leukemia, Non-small cell lung cancer | I | Patients with high-level MET-amplified NSCLC responded to crizotinib with high ORR while there's little response in patients with concurrent KRAS, BRAF, or EGFR mutations. | NCT00585195 |
| Cabozantinib S-malate, Dacarbazine, Temozolomide | Uveal Melanoma AJCC v7 | II | Recruiting. Present data showed that about thirty percent of patients in each combination didn't have progression free survival event at 4 months (PFS4) | NCT01835145 |

At present, Tepotinib in preclinical and clinical trials exhibits a high response rate and tumor suppression efficacy. In METamp HCC pt-derived xenografts (PDXs) mice models, approximately 96.5% of tumor volume is reduced [52]. In more recent phase Ib/II trials that compared the efficacy and safety of Tepotinib and Sorafenib, Tepotinib achieved an OS of 9.3 months (median FPS was 3.2 months) and Sorafenib achieved an OS of 8.6 months with the median FPS of 2.8 months. Nonetheless, Tepotinib performs better antitumor activities in terms of TTP, PFS, and ORR [53]. Importantly, some other c-MET inhibitors displayed neutral or even negative results in clinical trials, such as Tivantinib (NCT01755767), Axitinib (NCT01210495). Notably, autophagy may account for the resistance of c-MET inhibitors in liver cancers since the pathway is essential to the ordinary metabolism in cancer cells [54]. Upon inhibition, cancer cells would create alternative metabolic

pathways to resist drugs, resulting in low efficacy in clinical trials. Besides, an emerging therapy other than inhibitors utilizing small non-coding RNAs (miRNA) can also suppress tumor formation. Especially, miRNA -101-3p successfully reduced tumor volume or migration, suggesting a promising and novel future for the clinical treatments of HCC [55].

4.3. c-MET and Glioblastoma

Glioblastoma (GBM) is the most common type of brain tumor, with an average survival of less than one year and a five-year survival rate of less than 5%. There is currently no cure due to the complex structure of the human brain and the tumor's early metastasis [56]. Genetic aberrations frequently happen in GBMs and their subtypes. One of them is the dysregulation of growth factors signaling pathways, including the HGF/c-MET pathway which induces proliferation and invasion. According to Xie *et al.*, approximately 30% of GBM patients harbour overexpressed c-MET [27]. Genetic alterations, mutations (such as missense mutation on Arg132 of *IDH1*), and fusion (such as PTPRZ1-MET) also plays an indispensable role in the progression of glioblastoma from low grade to high grade [57]. Furthermore, MET also contributes to the drug resistance of target therapies for vascular endothelial growth factor (VEGF) and EGFR.

In previous data from clinical trials, the overall OS is not optimistic. First, many inhibitors cannot pass through the blood-brain barrier (BBB). Even though some small molecule inhibitors succeed in reaching the tumor, patients with poor outcomes frequently experience drug tolerance or tumor recrudescence. For instance, both Rilotumumab and Onartuzumab succeeded in preclinical testing but exhibited no clinical benefits in phase II studies [58, 59]. Likewise, Cabozatinib only presented faint drug efficacy in a phase II trial (NCT00704288). In fact, most antibodies or inhibitors targeting HGF/c-MET signaling pathways have not proceeded into clinical trials. The only underway clinical trial targeting c-MET is recruiting GBM patients with METex14 skipping to receive APL-101 (NCT03175224). Furthermore, in the field of GBM treatment, there are still huge research gaps. Combination treatments, more infiltrative drugs, or further clinical trials may be required in the future.

4.4. c-MET and Colorectal Cancer

Cell stemness is vital in the progression of colorectal cancer (CRC), and c-MET overexpression critically contributes to CRC proliferation or metastasis. Recent study found that the lipolytic factor *ABHD5* is proved to play a role in c-MET dysregulation: the knockdown of *ABHD5* activates c-MET signaling pathways to sustain CRC cell stemness, which ultimately leads to tumorigenesis and malignancy [60]. Similarly, 15.3% of CRC patients (n=255) harbour c-MET over-expressions, and the mOS is significantly shorter in c-MET overexpression patients [61]. Notably, c-MET amplification and mutation are rare events in CRC [62]. Besides, MET promotes resistance to antiangiogenic therapies or TKIs. Indeed, fibroblast-derived HGF stimulates proliferation under EGFR inhibition [63, 64]. Therefore, in preclinical trials, c-MET inhibitors are usually dosed with other pathway inhibitors. JNJ-38877605 (c-MET inhibitor) combined with cetuximab (EGFR inhibitor) induced up to 90% regression 6 weeks after injecting into mice [63]. In clinical trials, SAIT301, an anti-MET antibody is proved to have potent anti-tumor activity upon sixteen patients with a high response rate [65]. In a more recent trial combining PF-02341066 and Binimetinib, 7 out of 30 diseases remained stable, 22 were progressive, and 1 died of malignancy (NCT02510001). On the other hand, the Rilotumumab plus panitumumab achieved benefit for wild-type *KRAS* mCRC patients with an ORR of 31% [66]. Therefore, in CRC, the combined treatments can not only control immediate cancer progression but also prevent drug resistance, which could be considered an important aspect for future research.

5. Conclusion

The mechanism of the HGF/c-Met signaling pathway has displayed essential roles in both normal and abnormal cell functioning. The upregulation of c-MET especially through overexpression,

amplification, and mutation has been detected in a wide range of cancers. These discoveries suggest a promising future for anticancer c-MET inhibitors both alone and in combination with other target therapies. Recent studies in lung cancer, CRC, glioblastoma, and liver cancer expanded our knowledge in the specific role of HGF/c-Met pathways in cancer and present limits as well. The cytoplasmic domain of c-MET stimulates essential cell-cycle regulating kinases such as GAB1, STAT3, P53, and APK after binding appropriate ligand. In lung cancer, METex14 skipping is a prevalent cause of NSCLC, and several single or combined inhibitory agents lead to efficient response rates. In liver cancer, chronic diseases and mRNA dysregulation contribute to c-MET overexpression. Importantly, in all the four types of cancer discussed, inhibiting c-MET helps fight against drug resistance in EGFR inhibitory treatments. To commercialize c-MET treatments, further clinical trials are required to prove the efficacy of combining c-MET pathway inhibitors with chemotherapy and immunotherapy in preventing resistance, metastasis, and relapse.

REFERENCES

- [1] M.L. Casem, Chapter 9 - endocytosis, in Case studies in cell biology, M.L. Casem, Editor. 2016, Academic Press: Boston. p. 217-240.
- [2] H.N. Mo and P. Liu, Targeting met in cancer therapy. *Chronic Dis Transl Med*, 2017, pp. 148-153. DOI: <https://dx.doi.org/10.1016/j.cdtm.2017.06.002>
- [3] P.M. Comoglio, L. Trusolino, and C. Boccaccio, Known and novel roles of the met oncogene in cancer: A coherent approach to targeted therapy. *Nat Rev Cancer*, 2018, pp. 341-358. DOI: <https://dx.doi.org/10.1038/s41568-018-0002-y>
- [4] K. Matsumoto and T. Nakamura, Hepatocyte growth factor, in *Encyclopedia of endocrine diseases*, L. Martini, Editor. 2004, Elsevier: New York. p. 436-442.
- [5] S. Raj, K.K. Kesari, A. Kumar, et al., Molecular mechanism(s) of regulation(s) of c-met/hgf signaling in head and neck cancer. *Mol Cancer*, 2022, pp. 31. DOI: <https://dx.doi.org/10.1186/s12943-022-01503-1>
- [6] X. Huang, E. Li, H. Shen, et al., Targeting the hgf/met axis in cancer therapy: Challenges in resistance and opportunities for improvement. *Front Cell Dev Biol*, 2020, pp. 152. DOI: <https://dx.doi.org/10.3389/fcell.2020.00152>
- [7] Q. Wang, S. Yang, K. Wang, et al., Met inhibitors for targeted therapy of egfr tki-resistant lung cancer. *J Hematol Oncol*, 2019, pp. 63. DOI: <https://dx.doi.org/10.1186/s13045-019-0759-9>
- [8] S. Gallo, V. Sala, S. Gatti, et al., Cellular and molecular mechanisms of hgf/met in the cardiovascular system. *Clin Sci (Lond)*, 2015, pp. 1173-1193. DOI: <https://dx.doi.org/10.1042/CS20150502>
- [9] U. Schaeper, N.H. Gehring, K.P. Fuchs, et al., Coupling of gab1 to c-met, grb2, and shp2 mediates biological responses. *J Cell Biol*, 2000, pp. 1419-1432. DOI: <https://dx.doi.org/10.1083/jcb.149.7.1419>
- [10] G. Sala, F. Dituri, C. Raimondi, et al., Phospholipase cgamma1 is required for metastasis development and progression. *Cancer Res*, 2008, pp. 10187-10196. DOI: <https://dx.doi.org/10.1158/0008-5472.CAN-08-1181>
- [11] A. Gelain, M. Mori, F. Meneghetti, et al., Signal transducer and activator of transcription protein 3 (stat3): An update on its direct inhibitors as promising anticancer agents. *Curr Med Chem*, 2019, pp. 5165-5206. DOI: <https://dx.doi.org/10.2174/0929867325666180719122729>
- [12] P.J. Roberts and C.J. Der, Targeting the raf-mek-erk mitogen-activated protein kinase cascade for the treatment of cancer. *Oncogene*, 2007, pp. 3291-3310. DOI: <https://dx.doi.org/10.1038/sj.onc.1210422>
- [13] Y. Zhang, M. Xia, K. Jin, et al., Function of the c-met receptor tyrosine kinase in carcinogenesis and associated therapeutic opportunities. *Mol Cancer*, 2018, pp. 45. DOI: <https://dx.doi.org/10.1186/s12943-018-0796-y>
- [14] G.V. Scagliotti, S. Novello, and J. von Pawel, The emerging role of met/hgf inhibitors in oncology. *Cancer Treat Rev*, 2013, pp. 793-801. DOI: <https://dx.doi.org/10.1016/j.ctrv.2013.02.001>
- [15] S. Eser, A. Schnieke, G. Schneider, et al., Oncogenic kras signalling in pancreatic cancer. *Br J Cancer*, 2014, pp. 817-822. DOI: <https://dx.doi.org/10.1038/bjc.2014.215>

- [16] A.P.G. Consortium, Aacr project genie: Powering precision medicine through an international consortium. *Cancer Discov*, 2017, pp. 818-831. DOI: <https://dx.doi.org/10.1158/2159-8290.CD-17-0151>
- [17] M. Zenali, J. deKay, Z. Liu, et al., Retrospective review of met gene mutations. *Oncoscience*, 2015, pp. 533-541. DOI: <https://dx.doi.org/10.18632/oncoscience.161>
- [18] S. Krishnaswamy, R. Kanteti, J.S. Duke-Cohan, et al., Ethnic differences and functional analysis of met mutations in lung cancer. *Clin Cancer Res*, 2009, pp. 5714-5723. DOI: <https://dx.doi.org/10.1158/1078-0432.CCR-09-0070>
- [19] C. Schubart, R. Stohr, L. Togel, et al., Met amplification in non-small cell lung cancer (nsclc)-a consecutive evaluation using next-generation sequencing (ngs) in a real-world setting. *Cancers (Basel)*, 2021. DOI: <https://dx.doi.org/10.3390/cancers13195023>
- [20] S. Corso, C. Migliore, E. Ghiso, et al., Silencing the met oncogene leads to regression of experimental tumors and metastases. *Oncogene*, 2008, pp. 684-693. DOI: <https://dx.doi.org/10.1038/sj.onc.1210697>
- [21] P. Shi, Y.T. Oh, G. Zhang, et al., Met gene amplification and protein hyperactivation is a mechanism of resistance to both first and third generation egfr inhibitors in lung cancer treatment. *Cancer Lett*, 2016, pp. 494-504. DOI: <https://dx.doi.org/10.1016/j.canlet.2016.07.021>
- [22] [22] P.M. Comoglio, S. Giordano, and L. Trusolino, Drug development of met inhibitors: Targeting oncogene addiction and expedience. *Nat Rev Drug Discov*, 2008, pp. 504-516. DOI: <https://dx.doi.org/10.1038/nrd2530>
- [23] J.B. Williamson, X. Li, G. Liu, et al., Relationship of met exon 14 splicing variants and met exon 14 skipping expression in nsclc ffpe samples. *Journal of Clinical Oncology*, 2019, pp. e14603-e14603. DOI: https://dx.doi.org/10.1200/JCO.2019.37.15_suppl.e14603
- [24] G.M. Frampton, S.M. Ali, M. Rosenzweig, et al., Activation of met via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to met inhibitors. *Cancer Discov*, 2015, pp. 850-859. DOI: <https://dx.doi.org/10.1158/2159-8290.CD-15-0285>
- [25] H. Liang and M. Wang, Met oncogene in non-small cell lung cancer: Mechanism of met dysregulation and agents targeting the hgf/c-met axis. *Onco Targets Ther*, 2020, pp. 2491-2510. DOI: <https://dx.doi.org/10.2147/OTT.S231257>
- [26] F. Blanc-Durand, R. Alameddine, A.J. Iafrate, et al., Tepotinib efficacy in a patient with non-small cell lung cancer with brain metastasis harboring an hla-drbl-met gene fusion. *Oncologist*, 2020, pp. 916-920. DOI: <https://dx.doi.org/10.1634/theoncologist.2020-0502>
- [27] Q. Xie, R. Bradley, L. Kang, et al., Hepatocyte growth factor (hgf) autocrine activation predicts sensitivity to met inhibition in glioblastoma. *Proc Natl Acad Sci U S A*, 2012, pp. 570-575. DOI: <https://dx.doi.org/10.1073/pnas.1119059109>
- [28] J. He, Z. Huang, L. Han, et al., Mechanisms and management of 3rd generation egfrtki resistance in advanced nonsmall cell lung cancer (review). *Int J Oncol*, 2021. DOI: <https://dx.doi.org/10.3892/ijo.2021.5270>
- [29] N. Karachaliou, M. Fernandez-Bruno, J.W.P. Bracht, et al., Egfr first- and second-generation tkis-there is still place for them in egfr-mutant nsclc patients. *Transl Cancer Res*, 2019, pp. S23-S47. DOI: <https://dx.doi.org/10.21037/tcr.2018.10.06>
- [30] A. Ahsan, Mechanisms of resistance to egfr tyrosine kinase inhibitors and therapeutic approaches: An update. *Adv Exp Med Biol*, 2016, pp. 137-153. DOI: https://dx.doi.org/10.1007/978-3-319-24223-1_7
- [31] K. Matsumoto and T. Nakamura, Nk4 (hgf-antagonist/angiogenesis inhibitor) in cancer biology and therapeutics. *Cancer Sci*, 2003, pp. 321-327. DOI: <https://dx.doi.org/10.1111/j.1349-7006.2003.tb01440.x>
- [32] V.E. Wang, B.W. Blaser, R.K. Patel, et al., Inhibition of met signaling with ficlatuzumab in combination with chemotherapy in refractory aml: Clinical outcomes and high-dimensional analysis. *Blood Cancer Discov*, 2021, pp. 434-449. DOI: <https://dx.doi.org/10.1158/2643-3230.BCD-21-0055>
- [33] K.H. Kim and H. Kim, Progress of antibody-based inhibitors of the hgf-cmet axis in cancer therapy. *Exp Mol Med*, 2017, pp. e307. DOI: <https://dx.doi.org/10.1038/emm.2017.17>
- [34] A. Mughal, H.M. Aslam, A. Sheikh, et al., C-met inhibitors. *Infect Agent Cancer*, 2013, pp. 13. DOI: <https://dx.doi.org/10.1186/1750-9378-8-13>

- [35] A. Puccini, N.I. Marin-Ramos, F. Bergamo, et al., Safety and tolerability of c-met inhibitors in cancer. *Drug Saf*, 2019, pp. 211-233. DOI: <https://dx.doi.org/10.1007/s40264-018-0780-x>
- [36] F. Papaccio, C.M. Della Corte, G. Viscardi, et al., Hgf/met and the immune system: Relevance for cancer immunotherapy. *Int J Mol Sci*, 2018. DOI: <https://dx.doi.org/10.3390/ijms19113595>
- [37] M. Chivukula and D.J. Dabbs, Chapter 21 - immunocytology, in *Diagnostic immunohistochemistry* (third edition), D.J. Dabbs, Editor. 2011, W.B. Saunders: Philadelphia. p. 890-918.
- [38] K. Rygaard, T. Nakamura, and M. Spang-Thomsen, Expression of the proto-oncogenes c-met and c-kit and their ligands, hepatocyte growth factor/scatter factor and stem cell factor, in sclc cell lines and xenografts. *Br J Cancer*, 1993, pp. 37-46. DOI: <https://dx.doi.org/10.1038/bjc.1993.7>
- [39] P. Bordi, M. Tiseo, F. Barbieri, et al., Gene mutations in small-cell lung cancer (sclc): Results of a panel of 6 genes in a cohort of italian patients. *Lung Cancer*, 2014, pp. 324-328. DOI: <https://dx.doi.org/10.1016/j.lungcan.2014.10.002>
- [40] M. Hardy-Werbin, R. Del Rey-Vergara, M.A. Galindo-Campos, et al., Met inhibitors in small cell lung cancer: From the bench to the bedside. *Cancers (Basel)*, 2019. DOI: <https://dx.doi.org/10.3390/cancers11101404>
- [41] B. Glisson, B. Besse, M.C. Dols, et al., A randomized, placebo-controlled, phase 1b/2 study of rilotumumab or ganitumab in combination with platinum-based chemotherapy as first-line treatment for extensive-stage small-cell lung cancer. *Clin Lung Cancer*, 2017, pp. 615-625 e618. DOI: <https://dx.doi.org/10.1016/j.clcc.2017.05.007>
- [42] M.M. Awad, G.R. Oxnard, D.M. Jackman, et al., Met exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent met genomic amplification and c-met overexpression. *J Clin Oncol*, 2016, pp. 721-730. DOI: <https://dx.doi.org/10.1200/JCO.2015.63.4600>
- [43] M.M. Awad, G.C. Leonardi, S. Kravets, et al., Impact of met inhibitors on survival among patients with non-small cell lung cancer harboring met exon 14 mutations: A retrospective analysis. *Lung Cancer*, 2019, pp. 96-102. DOI: <https://dx.doi.org/10.1016/j.lungcan.2019.05.011>
- [44] J.W. Neal, S.E. Dahlberg, H.A. Wakelee, et al., Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with egfr wild-type advanced non-small-cell lung cancer (ecog-acrin 1512): A randomised, controlled, open-label, multicentre, phase 2 trial. *Lancet Oncol*, 2016, pp. 1661-1671. DOI: [https://dx.doi.org/10.1016/S1470-2045\(16\)30561-7](https://dx.doi.org/10.1016/S1470-2045(16)30561-7)
- [45] D.R. Spigel, M.J. Edelman, K. O'Byrne, et al., Results from the phase iii randomized trial of onartuzumab plus erlotinib versus erlotinib in previously treated stage iiib or iv non-small-cell lung cancer: Metlung. *J Clin Oncol*, 2017, pp. 412-420. DOI: <https://dx.doi.org/10.1200/JCO.2016.69.2160>
- [46] T.S. Mok, S.L. Geater, W.C. Su, et al., A randomized phase 2 study comparing the combination of ficlatuzumab and gefitinib with gefitinib alone in asian patients with advanced stage pulmonary adenocarcinoma. *J Thorac Oncol*, 2016, pp. 1736-1744. DOI: <https://dx.doi.org/10.1016/j.jtho.2016.05.038>
- [47] A.A. Tarhini, I. Rafique, T. Floros, et al., Phase 1/2 study of rilotumumab (amg 102), a hepatocyte growth factor inhibitor, and erlotinib in patients with advanced non-small cell lung cancer. *Cancer*, 2017, pp. 2936-2944. DOI: <https://dx.doi.org/10.1002/cncr.30717>
- [48] D. Janevska, V. Chaloska-Ivanova, and V. Janevski, Hepatocellular carcinoma: Risk factors, diagnosis and treatment. *Open Access Maced J Med Sci*, 2015, pp. 732-736. DOI: <https://dx.doi.org/10.3889/oamjms.2015.111>
- [49] H. Wang, B. Rao, J. Lou, et al., The function of the hgf/c-met axis in hepatocellular carcinoma. *Front Cell Dev Biol*, 2020, pp. 55. DOI: <https://dx.doi.org/10.3389/fcell.2020.00055>
- [50] T. Decaens, C. Barone, E. Assenat, et al., Phase 1b/2 trial of tepotinib in sorafenib pretreated advanced hepatocellular carcinoma with met overexpression. *Br J Cancer*, 2021, pp. 190-199. DOI: <https://dx.doi.org/10.1038/s41416-021-01334-9>
- [51] E. Callegari, L. Gramantieri, M. Domenicali, et al., Micrnas in liver cancer: A model for investigating pathogenesis and novel therapeutic approaches. *Cell Death Differ*, 2015, pp. 46-57. DOI: <https://dx.doi.org/10.1038/cdd.2014.136>

- [52] S.J. Faivre, J.-f. Blanc, H. Pan, et al., Activity of tepotinib in hepatocellular carcinoma (hcc) with high-level met amplification (metamp): Preclinical and clinical evidence. *Journal of Clinical Oncology*, 2021, pp. 329-329. DOI: https://dx.doi.org/10.1200/JCO.2021.39.3_suppl.329
- [53] B.Y. Ryoo, A.L. Cheng, Z. Ren, et al., Randomised phase 1b/2 trial of tepotinib vs sorafenib in asian patients with advanced hepatocellular carcinoma with met overexpression. *Br J Cancer*, 2021, pp. 200-208. DOI: <https://dx.doi.org/10.1038/s41416-021-01380-3>
- [54] X. Huang, G. Zhang, X. Bai, et al., Reviving the role of met in liver cancer therapy and vaccination: An autophagic perspective. *Oncoimmunology*, 2020, pp. 1818438. DOI: <https://dx.doi.org/10.1080/2162402X.2020.1818438>
- [55] Y. Liu, J. Tan, S. Ou, et al., MicroRNA-101-3p suppresses proliferation and migration in hepatocellular carcinoma by targeting the hgf/c-met pathway. *Invest New Drugs*, 2020, pp. 60-69. DOI: <https://dx.doi.org/10.1007/s10637-019-00766-8>
- [56] F. Cheng and D. Guo, Met in glioma: Signaling pathways and targeted therapies. *J Exp Clin Cancer Res*, 2019, pp. 270. DOI: <https://dx.doi.org/10.1186/s13046-019-1269-x>
- [57] H. Hu, Q. Mu, Z. Bao, et al., Mutational landscape of secondary glioblastoma guides met-targeted trial in brain tumor. *Cell*, 2018, pp. 1665-1678 e1618. DOI: <https://dx.doi.org/10.1016/j.cell.2018.09.038>
- [58] P.Y. Wen, D. Schiff, T.F. Cloughesy, et al., A phase ii study evaluating the efficacy and safety of amg 102 (rilotumumab) in patients with recurrent glioblastoma. *Neuro Oncol*, 2011, pp. 437-446. DOI: <https://dx.doi.org/10.1093/neuonc/noq198>
- [59] T. Cloughesy, G. Finocchiaro, C. Belda-Iniesta, et al., Randomized, double-blind, placebo-controlled, multicenter phase ii study of onartuzumab plus bevacizumab versus placebo plus bevacizumab in patients with recurrent glioblastoma: Efficacy, safety, and hepatocyte growth factor and o(6)-methylguanine-DNA methyltransferase biomarker analyses. *J Clin Oncol*, 2017, pp. 343-351. DOI: <https://dx.doi.org/10.1200/JCO.2015.64.7685>
- [60] Y. Gu, Y. Chen, L. Wei, et al., Abhd5 inhibits yap-induced c-met overexpression and colon cancer cell stemness via suppressing yap methylation. *Nat Commun*, 2021, pp. 6711. DOI: <https://dx.doi.org/10.1038/s41467-021-26967-5>
- [61] S.J. Lee, J. Lee, S.H. Park, et al., C-met overexpression in colorectal cancer: A poor prognostic factor for survival. *Clin Colorectal Cancer*, 2018, pp. 165-169. DOI: <https://dx.doi.org/10.1016/j.clcc.2018.02.013>
- [62] K. Raghav, V. Morris, C. Tang, et al., Met amplification in metastatic colorectal cancer: An acquired response to egfr inhibition, not a de novo phenomenon. *Oncotarget*, 2016, pp. 54627-54631. DOI: <https://dx.doi.org/10.18632/oncotarget.10559>
- [63] P. Luraghi, G. Reato, E. Cipriano, et al., Met signaling in colon cancer stem-like cells blunts the therapeutic response to egfr inhibitors. *Cancer Res*, 2014, pp. 1857-1869. DOI: <https://dx.doi.org/10.1158/0008-5472.CAN-13-2340-T>
- [64] A.J. Scott, J.J. Arcaroli, S.M. Bagby, et al., Cabozantinib exhibits potent antitumor activity in colorectal cancer patient-derived tumor xenograft models via autophagy and signaling mechanisms. *Mol Cancer Ther*, 2018, pp. 2112-2122. DOI: <https://dx.doi.org/10.1158/1535-7163.MCT-17-0131>
- [65] J. Lee, S.T. Kim, S. Park, et al., Phase i trial of anti-met monoclonal antibody in met-overexpressed refractory cancer. *Clin Colorectal Cancer*, 2018, pp. 140-146. DOI: <https://dx.doi.org/10.1016/j.clcc.2018.01.005>
- [66] E. Van Cutsem, C. Eng, E. Nowara, et al., Randomized phase ib/ii trial of rilotumumab or ganitumab with panitumumab versus panitumumab alone in patients with wild-type kras metastatic colorectal cancer. *Clin Cancer Res*, 2014, pp. 4240-4250. DOI: <https://dx.doi.org/10.1158/1078-0432.CCR-13-2752>