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C-MET Inhibitors as New Members of the NSCLC Treatment Armamentarium—A Pooled Analysis

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Abstract

Objective: Capmatinib and tepotinib, two recently FDA-approved and highly specific small-molecule inhibitors of c-MET exon 14 skipping mutations are new and important therapeutic options for the treatment of NSCLC patients harbouring c-MET alterations. However, the precise role of these molecules as a new treatment option is still not fully defined. **Methods:** In an attempt to further evaluate the contributions of c-MET inhibitors to the armamentarium of treatment options for advanced and metastatic NSCLCs, relevant phase II and III studies were retrospectively analyzed in terms of ORR and mPFS (mOS numbers are still not available for current c-MET trials and therefore not considered for statistical purposes). **Results:** Treatment of advanced and metastatic NSCLC patients harbouring c-MET exon 14 skipping mutations with the novel and highly selective c-MET inhibitors is significantly superior ($p < 0.0001$) when compared with standard chemotherapy. However, when c-MET inhibitors are compared with immunotherapy or the combination of immunotherapy and chemotherapy, no significant differences in terms of ORR and PFS were found, but treatment with c-MET reported be much more tolerable. **Conclusion:** The novel and highly selective c-MET inhibitors capmatinib and tepotinib are promising novel treatment options for patients with c-MET-dysregulated NSCLC primarily in the first-line setting, albeit a clear mOS benefit has not yet been established. Since immunotherapy did not appear to be particularly effective in NSCLC patients harbouring c-MET alterations, the vast majority of these patients are treated with immunotherapy plus chemotherapy. C-Met inhibitors appear to be equally effective and thereby sparing patients from the toxic effects of the chemotherapy. The routine testing of c-MET exon 14 skipping mutations should be performed as the GEOMETRY

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mono-1 data clearly showed higher response rates with capmatinib in treatment-naive than in pretreated patients, indicating that c-MET exon 14 skipping mutations should preferably be molecularly assessed at baseline. C-MET exon 14 skipping mutations are, therefore, clear biomarkers of response to c-MET inhibitors.

Keywords

NSCLC, Treatment Options, c-MET Inhibitors, Statistical Analysis

1. Introduction

First-line treatment of advanced or metastatic NSCLCs (non-small cell lung cancers) has changed dramatically during the last two decades, and novel treatment options such as tyrosine kinase inhibitors (e.g., EGFR, ALK, RET, Braf, c-MET) and immunotherapies (e.g., PD-1, PD-L1, CTLA-4) have demonstrated significant benefit for several NSCLC patients sparing them from the toxic effects of chemotherapy [1]. Overall, to date five different and approved treatment options have been established for advanced or metastatic NSCLCs (outline in **Figure 1**).

Capmatinib and tepotinib, two recently FDA-approved [2] and highly specific small-molecule inhibitors of c-MET exon 14 skipping mutations are new and important therapeutic options for the treatment of NSCLC patients harbouring c-MET alterations. Both drugs showed substantial antitumour activity in patients with advanced NSCLC with a c-MET exon 14 skipping mutation, particularly in those not been treated previously [3] [4].

Several lines of evidence have demonstrated that harbouring altered c-MET in NSCLC patients is associated with lower ORRs (overall response rates) and shorter mPFS (medium progression-free survival) and mOS (medium overall survial) than in tumours without such mutations [5]. In addition, c-MET with exon 14 skipping mutations is thought to be associated with a significantly higher PD-L1 expression. However, it should be noted that the putative cross-talk between c-MET activation and PD-L1 expression is not fully understood [6] Clearly, there are multiple pathways by which c-MET can influence PD-L1 expression and key player remain to be identified (reviewed by [7]). Furthermore, c-MET alterations have been found to be positively correlated with enhanced expression of immune-inhibitory molecules (e.g., PD-L1), decreased expression of co-stimulatory markers (e.g., CD137, CD252 etc.), and c-MET obviously is also implicated in controlling the inflamed TME (tumour microenvironment) [8] [9].

Some clinical evidence suggests that immune checkpoint inhibitors are less effective in tumours with driver mutations including c-MET, and the efficacy of immunotherapy for NSCLC patients harbouring c-MET exon 14 skipping mutations remains very poor. The conclusion of a report based on the IMMUNOTARGET registry suggests where driver mutations are found, targeted therapies such as TKIs should be used before contemplating immunotherapy [10].

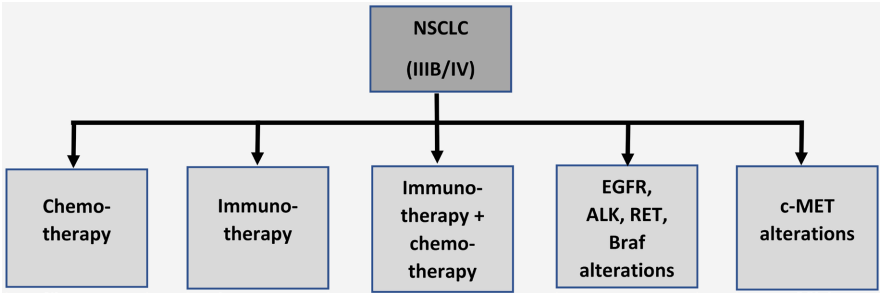

Figure 1. Approved treatment options for advanced or metastatic NSCLCs.

2. Methods

In an attempt to further evaluate the contributions of c-MET inhibitors to the armamentarium of treatment options for advanced and metastatic NSCLCs, relevant phase II and III studies were retrospectively analyzed in terms of ORR and mPFS (mOS numbers are still not available for current c-MET trials and therefore not considered for statistical purposes).

Almost all randomized immunotherapy studies with checkpoint inhibitors (e.g., anti-PD-1, anti-PD-L1) excluded NSCLC patients harbouring EGFR, ALK, or RET alterations from enrollment. Despite this observation, trials with TKIs targeting EGFR, ALK, Braf, or RET were also included in this analysis. From each data set mean ORR number (±SE) and mean PFS (±SE) were calculated. For the sake of clarity immunotherapy trials were separately analysed for PD-1 and PD-L1 monoclonal antibodies. Although only very few studies with checkpoint inhibitors as first-line treatment in NSCLC patients with a confirmed c-MET mutation status have been published, these results were also included in the analysis.

Finally, the obtained numbers were then compared with the ones for trials with c-MET inhibitors using the Student t-test (unpaired, two-tailed) with a significance threshold of $p < 0.05$.

3. Results

For chemotherapy (platinum-doublets as standard first-line chemotherapy of choice for advanced or metastatic NSCLC patients) results were extrapolated from earlier reference studies [11] [12] and shown in **Table 1**. From these results mean ORR and PFS were calculated to be 26.5% ± 2.5% and 4.5 months ± 0.34 months, respectively.

For immunotherapies (anti-PD-1 and anti-PD-1) as first-line therapy for advanced and metastatic NSCLCs [13] [14] [15] [16] [17] results are shown in **Table 2**. From these results mean ORR and PFS were calculated to be 37.0% ± 1.4% and 6.2 months ± 2.0 months for anti-PD-L1 antibodies, respectively. For anti-PD-1 antibodies the calculated values were 35.4% ± 8.4% (ORR) and 7.3 months ± 3.0 months (PFS).

For immunotherapies (anti-PD-L1 and anti-PD-1) in combination with chemotherapy (*i.e.*, platinum-doublets) as first-line therapy for advanced and me-

tastatic NSCLCs [18] [19] [20] [21] [22] results are shown in **Table 3**. From these results mean ORR and PFS were calculated to be 50.2% ± 7.6% and 6.7 months ± 0.8 months for anti-PD-L1 antibodies, respectively. For anti-PD-1 antibodies the calculated values were 52.7% ± 5.2% (ORR) and 7.6 months ± 1.2 months (PFS).

Table 1. ORRs and mPFS for advanced and metastatic NSCLCs following treatment with platinum-based chemotherapy (Numbers taken from [11] [12]).

Regimen	N	ORR	mPFS
Carboplatin + Paclitaxel	201	32%	5.5 months
Carboplatin + Vinorelbine	201	30%	4.6 months
Carboplatin + Docetaxel	289	17%	3.7 months
Cisplatin + Paclitaxel	288	21%	3.3 months
Cisplatin + Gemcitabine	863	28.2%	5.1 months
Cisplatin + Pemetrexed*	862	30.6%	4.8 months

*non-squamous cell histologies only.

Table 2. ORRs and mPFS with checkpoint inhibitors as first-line monotherapy in NSCLC patients (modified after [13].

Drug	Study	ORR	mPFS	Reference
Atezolizumab	NCT024093342 (IMPower 110), N = 572 (phase III), atezolizumab vs. chemotherapy (PL-L1 ≥ 50%)	38.3% vs. 26.8%	8.1 vs. 5.0 mo.	Herbst *et al.* 2020 [14]
Pembrolizumab	NCT02142738 (KeyNote-024), N = 305 (phase III), pembrolizumab vs. chemotherapy (PD-L1 ≥ 50%)	44.8% vs. 27.8%	10.3 vs. 6.0 mo.	Reck *et al.* 2016 [15]
Nivolumab	NCT02041533 (Checkmate-026), N = 541 (phase III), nivolumab vs. chemotherapy (PD-L1 > 5%)	26% vs. 31%	4.2 vs. 5.9 mo.	Carbane *et al.* 2017 [16]
Durvalumab	NCT02453282 (MYSTIC), N = 1118 (phase III), durvalumab vs. durvalumab + tremelimumab vs. chemotherapy	35.6%* vs. 34.4% vs. 37.7%	4.2* vs. 3.0 vs. 5.4 mo.	Rizvi *et al.* 2020 [17]

*not significant.

Table 3. ORRs and mPFS with checkpoint inhibitors plus chemotherapy as first-line mono-therapy in NSCLC patients.

Drug	Study	ORR	mPFS	Reference
Atezolizumab	NCT02367794 (IMPower 131), N = 1021 (phase III), atezolizumab + chemotherapy vs. Placebo + chemotherapy	49.7% vs. 41%	6.3 vs. 5.6 mo.	Jotte *et al.* 2020 [18]
Atezolizumab	NCT02366143 (IMPower 150), N = 1202 (phase III), atezolizumab + bevacizumab + chemotherapy vs. Placebo + bevacizumab + chemotherapy	63.5% vs. 48.8%	8.3 vs. 6.8 mo.	Socinski *et al.* 2018 [19]
Pembrolizumab	NCT02775435 (Keynote-407), N = 559 (phase III), pembrolizumab + chemo-therapy vs. placebo + chemo-therapy (squamous)	57.9% vs. 38.4%	6.4 vs. 4.8 mo.	Paz-Ares *et al.* 2018 [20]
Pembrolizumab	NCT 02578680 (Keynote-189), N = 616 (phase III), pembrolizumab + chemotherapy vs. placebo + chemotherapy (adeno)	47.5% vs. 18.9%	8.8 vs. 4.9 mo.	Gandhi *et al.* 2018 [21]
Durvalumab	NCT03164616 (POSEIDON), N = 1013 (phase III), durvalumab + chemotherapy vs. chemotherapy	37.3% vs. 25.6%	5.5 vs. 4.8 mo.	Johnson *et al.* 2021 [22]

For immunotherapies (anti-PD-1 and anti-PD-1) as first-line therapy for advanced and metastatic NSCLC patients harbouring c-MET exon 14 mutations [23] [24] [25] [26] results are shown in **Table 4**. For this subgroup mean ORR was found to be 16.5% ± 0.5% and mean PFS was calculated to be 2.7 months ± 0.8 months.

In addition, the results of two c-MET inhibitors as first-line treatment for NSCLC patients harbouring c-MET exon 14 skipping mutations [3] [4] are listed in **Table 5**. Mean ORR for these two c-MET inhibitors was 56.85% ± 12%, mean PFS was found to be 10.5 months ± 2.0 months.

Finally, ORR and mPFS in the first-line setting for the currently approved TKIs targeting EGFR, ALK, and RET were analysed (**Table 6**). Mean ORRs for these inhibitors were 70% ± 4.3% (EGFRmut), 69.2% ± 6.8% (ALK), and 66.9% ± 3.1% (RET). Mean PFS values was calculated to be 12.9 months ± 1.8 months (EGFRmut), 16.5 months ± 3.8 months (ALK), and 13.3 months ± 4.3 months (RET). The results of the chemotherapy group and the c-MET group were then compared with the results obtained from the other groups, and results are summarized in **Table 7**.

Table 4. Outcome of NSCLC patients harbouring c-MET exon 14 skipping mutations following first-line immune therapies with checkpoint inhibitors.

Reference	c-MET Status	PD-L1 Status	Outcome (Pembrolizumab)
Mazieres *et al.* 2021 [23]	c-MET exon 14 skipping mutations (N = 36/551)	PD-L1 > 1% in 66.8% of patients	ORR: 16% mPFS: 3.4 mo. mOS: 18 mo.
Sabari *et al.* 2018 [24]	c-MET exon 14 skipping mutations (N = 147)	PD-L1 > 1% in 63% of patients	ORR: 17% mPFS: 1.9 mo. mOS: 18.2 mo.
Baba *et al.* 2019 [25]*	c-MET exon 14 skipping mutations (N = 1, case report)	PD-L1: 95%	refractory to IOs, responsive to chemotherapy
Reis *et al.* 2018 [26]*	c-MET exon 14 skipping mutations (N = 2, case report)	PD-L1: >50% in both patients	refractory to pembrolizumab

*not included in the analysis.

Table 5. Outcome of NSCLC patients harbouring c-MET exon 14 skipping mutations following first-line therapies with highly selective c-MET inhibitors.

Inhibitor	Study Design	ORR	mPFS	References
Capmatinib	NCT02414139 (GEOMETRY mono-1), N = 364 (phase II), Capmatinib monotherapy	68.8%	12.5 mo.	Wolf *et al.* 2020 [3]
Tepotinib	NCT02864992 (VISION), N = 152 (phase II), Tepotinib monotherapy	44.9%	8.5 mo.	Paik *et al.* 2020 [4]

Table 6. Comparison of approved TKIs for first- and second-line treatment of advanced or metastatic NSCLCs (FDA and EMA).

Drug	Target	Treatment Line	ORR	mPFS
1G: Gefitinib (Iressa®)	EGFRmut	1st line	71.6%	9.2 months[1]
1G: Erlotinib (Tarceva®)	EGFRmut	1st line	54.5%	10.4 months[2]
2G: Afatinib (Giotrif®)	EGFRmut	1st line	67.8%	11.0 months[3]
2G: Dacomitinib (Vizimpro®)	EGFRmut	1st line	74.9%	14.7 months[1]
3G: Osimertinib (Tagrisso®)	EGFRmut	1st line 2nd line	80% 71%	18.9 months[4] 10.1 months[5]
1G: Crizotinib (Xalkori®)	ALK	1st line 2nd line	74% 65%	10.9 months[6] 7.7 months[7]
2G: Ceritinib (Zykladia®)	ALK	1st line 2nd line	72.5% 39.1%	16.6 months[8] 5.4 months[9]
3G: Alectinib (Alecensa®)	ALK	1st line 2nd line	82.9% 51%	25.7 months[10] 8.3 months[11]
3G: Brigatinib (Alunbrig®)	ALK	1st line 2nd line	73.7% 56%	24 months[12] 16.7 months[13]
4G: Lorlatinib (Lorviqua®)	ALK	2nd line	42.9%	5.5 months[14]
1G: Selpercatinib (Retsevmo®)	RET	1st line	63.8%	17.5 months[15]
1G: Pralsetinib (Gavreto®)	RET	1st line	70%	9.0 months[16]

G: Generation; ORR: overall response rate; mPFS: medium progression-free survival; [1]ARCHER Study; [2]EURTAC Study; [3]LUX-Lung 6-Study; [4]FLAURA Study; [5]AURA3 Study; [6]1014 Study; [7]1007 Study; [8]ASCEND-4 Study; [9]ASCEND-5 Study; [10]ALEX Study; [11]NP28673 & NP28761 Study; [12]ALTA IL Study; [13]ALTA Study; [14]NCT01970865; [15]LIBRETTO-001 Study; [16]ARROW Study; [17]VISION Study; [18]GEOMETRY-mono 1 Study.

Table 7. Statistical calculations for the different treatment opportunities for advanced and metastatic NSCLC patients in comparison with the c-MET and chemotherapy subpopulation (Student t test, two-tailed unpaired). ORR: overall response rate; PFS: progression-free survival; PD-1: immunetherapy with anti-PD-1 monoclonal antibodies; PD-L1: immunotherapy with anti-PD-L1 monoclonal antibodies. N.A.: not applicable.

Treatment	Immunotherapy	Immunotherapy + Chemotherapy	Immunotherapy (c-MET mutation-positive)	c-MET mutations	EFGR mutations	ALK rearrangement	RET mutations
Chemotherapy (ORR)	PD-1: p = 0.04 PD-L1: p = 0.016	PD-1: p = 0.0001 PD-L1: p = 0.0002	PD-1: p = 0.0018 PD-L1: N.A.	p = 0.0005	p < 0.0001	p = 0.0001	p = 0.0001
Chemotherapy (PFS)	PD-1: p = 0.02 PD-L1: p = 0.03	PD-1: p = 0.0012 PD-L1: p = 0.0008	PD-1: p = 1.15 PD-L1: N.A.	p = 0.0002	p = 0.0007	p = 0.0056	p = 0.04
c-MET mutations (ORR)	PD-1: p = 0.12 PD-L1: p = 0.28	PD-1: p = 0.25 PD-L1: p = 0.47	N.A	N.A.	N.A.	N.A.	N.A.
c-MET mutations (PFS)	PD-1: p = 0.66 PD-L1: p = 0.79	PD-1: p = 0.13 PD-L1: p = 0.34	N.A	N.A.	N.A	N.A.	N.A.
Immunotherapy (c-MET mutation-positive) (ORR)	PD-1: p = 0.15	PD-1: p = 0.01	N.A.	PD-1: p = 0.07	N.A.	N.A.	N.A
Immunotherapy (c-MET mutation-positive) (PFS)	PD-1: p = 0.27	PD-1: p = 0.07	N.A.	PD-1: p = 0.07	N.A.	N.A.	N.A.

4. Discussion

The results presented here clearly demonstrate that treatment of advanced and metastatic NSCLC patients harbouring c-MET exon 14 skipping mutations with the novel and highly selective c-MET inhibitors is significantly superior ($p < 0.0001$) when compared with standard chemotherapy. This finding adds weight to the proposal that these drugs represent the new first-line standard-of-care therapy for advanced and metastatic NSCLCs harbouring c-MET exon 14 skipping mutations sparing patients from the toxic effects of chemotherapy.

However, when c-MET inhibitors are compared with immunotherapy or the combination of immunotherapy and chemotherapy, no significant differences in terms of ORR and PFS were found. This can be explained, at least in part, by the fact that only two c-MET inhibitor phase II studies with a low number of patients enrolled were available for this analysis. Moreover, the c-MET status of almost all immunotherapy studies has not been confirmed suggesting that the "true" effect of immunotherapies in this patient population is somewhat impaired by the unknown c-MET status.

Of note, NSCLC patients harbouring c-MET alterations exert several clinicopathological features such as advanced age (frail patients), adeno histology, non-smoker, females, higher propensity for extrathoracic metastases, and finally worse prognosis [5] [27]. Futhermore, treatment with immunotherapy did not appear to be particularly effective in NSCLC patients harbouring c-MET alterations—as a result the vast majority of these patients are, therefore, treated with immunotherapy plus chemotherapy [7] [28].

In this regard two studies attempted to analyse the efficacy of checkpoint inhibitor (CPI) treatment of NSCLC patients harbouring c-MET exon 14 skipping mutations [24] [29]. Sabari and co-workers [24] analysed 24 NSCLC patients with c-MET exon 14 skipping mutations who received immunotherapy (22 patients with anti-PD-1 or anti-PD-L1 monotherapy, two patients received combination therapy of anti-PD-1 and anti-CTLA-4). First-line treatment was given in 11 patients, and 6 and 7 patients were treated with second and third-line protocols, respectively. Amongst these patients ORR was found to be only 17%; mPFS was 1.9 months, and OS was 18.9 months. Interestingly, the observed efficacy was neither associated with high PD-L1 levels (2/11 patients) nor with higher TMB (tumour mutational burden) (0/8 patients). In an additional study the same group of researchers [10] retrospectively analysed 551 NSCLC patients with oncogenic driver mutations in terms of their response to CPIs. The vast majority of patients had received PD-1 inhibitors [e.g., nivolumab (N = 466) and pembroizumab (N = 48)]) whereas the remaining 6% of patients were treated with atezolizumab (N = 19) or durvalumab (N = 11). Amongst all patients analysed, 36 patients had c-MET exon 14 skipping mutations (6.5%) and 11/36 of these patients revealed a higher PD-L1 expression level when compared with the overall population (30% *vs.* 10%). For all c-MET patients mPFS was 3.4 months, however, long-term responders were more frequently seen in the c-MET group

(23.4%) when compared with other subgroups (e.g., 6.4% for EGFRmut) (56). OS was found to be 18.4 months and was not correlated with PD-L1 expression or number of prior therapies. Of note, mPFS in the c-MET subgroup was also not associated with c-MET exon 14 skipping mutations or other c-MET alterations [10].

As for both modalities (c-MET inhibitors versus immunotherapy plus chemotherapy) no differences in terms of ORR and mPFS were found in our study presented here, this clearly highlights the need to treat these patients with more tolerable c-MET inhibitors sparing them from the toxic effects of chemotherapy.

It appears that demonstrating a mOS benefit with c-MET inhibitors in NSCLC patients harbouring c-MET alterations through a prospective, randomized clinical trial may be difficult for several reasons. Most clinical trials comparing targeted therapy to standard chemotherapy have failed to show an OS benefit, largely due to patient crossover from one treatment arm to the other or because of availability of other approved or investigational agents administered after disease progression [28]. Moreover, randomized trials comparing a c-MET inhibitor with chemotherapy may also be hampered due to slow patient accrual.

Some lines of evidence provided by a retrospective analysis suggest that c-MET inhibitors may prolong mOS. Awad *et al.* [28] conducted a multicenter retrospective analysis of NSCLC patients (N = 148) harbouring c-MET exon 14 skipping mutations to determine if treatment with c-MET inhibitors impacts mOS. Of the 34 metastatic patients who never received a c-MET inhibitor, mOS was found to be 8.1 months; those in this group with concurrent c-MET amplification had a trend toward worse survival compared to cancers without c-MET amplification (5.2 months vs. 10.5 months, P = 0.06). Of the 27 metastatic patients who received at least one c-MET inhibitor mOS was reported to be 24.6 months [28] which is in line with the mOS reported in some cohorts of the GEOMETRY-1 trial. From this study the authors concluded that in NSCLC patients harbouring c-MET exon 14 skipping mutations treatment with a c-MET inhibitors is associated with an improvement of mOS.

It is currently unknown whether this holds true in a prospective setting, and answering this question prospectively through randomized phase III clinical trials is clearly needed, but will be challenging (e.g., cross-over, slow recruitment etc.).

Very few studies investigated the efficacy of immunotherapies (mainly anti-PD-1) in advanced or metastatic NSCLC patients with a confirmed c-MET status (exon 14 skipping mutations). Although these patients are generally considered to have a poorer outcome following immunotherapy treatment, the difference did not reach the level of statistical significance in our analysis. However, the results should be interpreted with caution as the sample size was low and the studies were retrospectively designed.

Furthermore, the results also suggest that c-MET alterations (*i.e.*, c-MET exon 14 skipping mutations) may be an optimal predictive biomarker (besides PD-L1 expression and TMB) and should be explored further for immunotherapy re-

sponse for NSCLCs with c-MET exon 14 mutations.

Of note, this analysis has some limitations. First, trials with c-MET inhibitors were non-randomized phase II trials with no control arm, and a limited number of patients which might influence the results reported here. Second, the vast majority of all trials in this setting excluded specific alteration such as EGFR- and RET-mutations as well as ALK fusions. Moreover, c-MET status in these trials was not determined which might "dilute" results seen in this analysis. On the other hand, c-MET mutations are rare and only seen in 2% - 4% of NSCLC patients suggesting that they are negligible in this regard. Third, only two studies, albeit retrospective, addressed this issue (Table 4), however, number of patients again was low. As the t test applied in our study basically assigns the same weight to each estimate, it cannot be ruled out that some studies may be more precise (and reliable) than others since larger larger studies could have more "influence" than smaller ones. To address this point, a meta-analysis is currently conducted by our group.

Finally, with the evident clinical activity of c-MET inhibitors such as capmatinib or tepotinib combination of c-MET inhibitors with immune checkpoint inhibitors might be a promising treatment strategy for first-line treatment of NSCLCs harbouring c-MET exon 14 skipping mutations. With the confirmation of c-MET exon 14 skipping mutations as a *bona fide* target in NSCLC, careful consideration on sequencing and combining therapies becomes crucial. A treatment algorithm based on the results presented here is shown in Figure 2.

Accordingly, there are also ongoing trials to address these questions. Phase II trials of capmatinib after resistance to prior c-MET tyrosine kinase inhibitors (NCT02750215) and capmatinib in combination with immunotherapy with spartalizumab (NCT04323436) are examples of currently recruiting or planned trials.

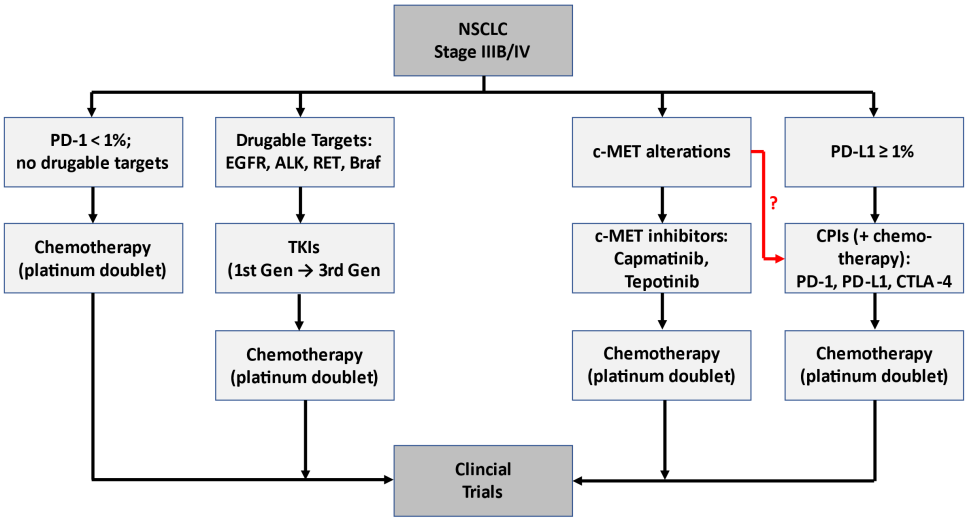

Figure 2. Treatment algorithm for advanced or metastatic NSCLCs based on the results of this analysis (CPI: checkpoint inhibitor).

5. Conclusion

The novel and highly selective c-MET inhibitors capmatinib and tepotinib are promising novel treatment options for patients with c-MET-dysregulated NSCLC primarily in the first-line setting. Based on the current data, the routine testing of c-MET exon 14 skipping mutations in stage IV non-squamous NSCLC is strongly recommended as the GEOMETRY mono-1 data, which clearly showed higher response rates with capmatinib in treatment-naive than in pretreated patients, indicating that c-MET exon 14 skipping mutations should preferably be molecularly assessed at baseline. C-MET exon 14 skipping mutations are, therefore, clear biomarkers of response to c-MET inhibitors.

Conflicts of Interest

Drs. Dempke, Bassim, and Murphy are employees of Worldwide Clinical Trials Inc. Dr. Reuther has no conflicts of interest to declare.

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