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REVIEW

A systematic review of targeted agents for non-small cell lung cancer

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ABSTRACT

Background: advanced-stage non-small cell lung cancer (NSCLC) is characterized by having limited treatment options and thus a poor prognosis. However, new treatment options, in the form of targeted agents (TA), have emerged during recent years. This systematic review aims to provide an overview of the accessible literature in PubMed evaluating TA used on NSCLC patients, and the resulting survival outcomes.

Method: this systematic literature review was conducted by reviewing all relevant literature in PubMed. Six separate searches were performed: Three searches where controlled entry terms were used and three free text searches. Furthermore, other relevant publications were included manually. A total of seventy-two studies met the search criteria and were thus further analyzed and evaluated.

Results: In the included studies, various TAs and their effect on different molecular targets have been evaluated. Clinical responses vary considerably among the different genetic aberrations. The majority of studies evaluated TA for epidermal growth factor receptor (EGFR) mutations and TA for echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangements. Studies regarding the use of TA for Rat sarcoma (RAS), rapidly accelerated fibrosarcoma (RAF), ROS proto-oncogene 1 (ROS1) rearrangement, Receptor tyrosine-protein kinase erbB-2 (ERBB2), Phosphatidylinositol 3-kinase (PIK3CA)/v-akt murine thymoma viral oncogene homolog; protein kinase B(AKT)/Phosphatase and tensin homolog deleted on chromosome 10(PTEN), The mammalian target of rapamycin (mTOR), and Mesenchymal-epithelial transition factor (MET) were included as well. In general, studies comparing treatment outcomes in EGFR-mutated patients and EML4-ALK (ALK) rearranged patients after use of either TA or standard chemotherapy, present significant better results after TA.

Conclusions: This systematic review provides an overview of available literature in PubMed regarding NSCLC and TA. Included studies point toward that TA appears to be a promising therapeutic tool in treating NSCLC patients and use of TA is expected to result in improved treatment outcomes.

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Background

Non-small cell lung cancer (NSCLC) is the major cause of cancer-related deaths in the Western world [1], leading to about 80–85% of all lung cancer cases [2]. NSCLC is characterized by being a highly heterogeneous disease, harboring many genetic aberrations within the various subtypes [3]. Furthermore, a high mutation rate is seen, leading to resistance to treatment and thus resulting in a poor prognosis [3]. Another factor contributing to the unsatisfactory outcome for many NSCLC patients is the fact that as many as 35% of all NSCLC cases are stage IV at the time of diagnosis with distant metastases and where curative surgery is not possible [4].

Based on large phase III trials, the standard 1st line treatment of advanced NSCLC is a combination of platinum-based chemotherapies, which results in a median survival time of only 8–11 months and response rates of only 20–50% [2]. The accepted 2nd and 3rd line treatments have even less activity, and resistance to 1st line treatment is quickly developed [2]. Thus, it is obvious that there is a need for new and better treatment options [4]. Since cancer is considered as being a complex disorder on gene level, [3] introducing TA could pave the way for more effective treatment for this subgroup of cancer patients for whom current treatment options have proven to be unsatisfying [2]. Several previously conducted landmark studies such as the IPASS conducted by Mok et al. [5] and the study by Maemondo et al. [6], have shown convincing results after treatment with TA compared to standard chemotherapy. It is such revolutionary discoveries, which have been used as stepping-stones for this systematic review on TA in NSCLC, an area in rapid development. The aim of this systematic review is to provide a comprehensive overview of current, available literature regarding TA for NSCLC.

Methodology

In order to obtain a comprehensive literature search, a total of six searches were conducted in PubMed. Initially, a systematic literature search was performed (Figure 1). This was

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Supplemental data for this article can be accessed here.

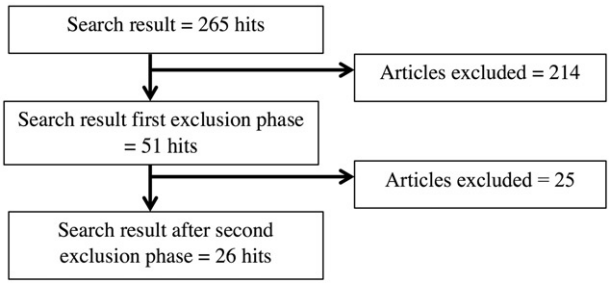

Figure 1. Depicts a flowchart of the search process for the systematic literature search.

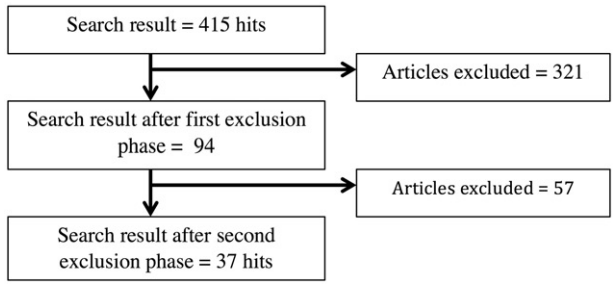

Figure 2. Depicts a flowchart of the search process for the free text search.

followed by a free text search (Figure 2). Both searches were conducted on the 7th November 2016. For the systematic literature search, only articles published between the 1st January 2013 and the 7th November 2016 were encompassed. For the free text search, only articles published between the 1st January 2015 and the 7th November 2016 was included. These time frames were applied in order to optimize the literature search with the newest data. In all searches, the filter 'humans' were used. Prior to the literature searches inclusion and exclusion criteria were set up. Inclusion criteria included that studies must be clinical studies and must concern TA applied on NSCLC patients. Moreover, the mutation status of patients had to be known, and the endpoint must be median overall survival (mOS), median progression free survival (mPFS) or overall response rate (ORR). If a study had only presented patients without specific mutations, had a nontransparent methodology, or was a review, systematic review or meta-analysis, it was excluded. The latter due to their non-empirical nature.

A PubMed database systematic literature search was conducted using the following search words: ((('Carcinoma, Non-Small-Cell Lung'(Mesh)) AND ((((((((((('Precision Medicine'(Mesh)) OR 'targeted medicine') OR 'person specific medicine') OR 'novel therapy') OR 'Genes, erbB-1'(Mesh)) OR 'Genes, erbB-2'(Mesh)) OR 'CMET') OR 'Proto-Oncogene Proteins p21(ras)'(Mesh)) OR 'Proto-Oncogene Proteins B-raf'(Mesh)) OR 'ALK') AND ((('Disease-Free Survival'(Mesh)) OR 'response rate') OR ((('Survival Rate'(Mesh)) OR 'overall survival'))). This provided 265 hits.

A PubMed database free text search was conducted using the following search words: (((('NSCLC*') OR 'non-small cell lung cancer*') OR 'non-small-cell lung carcinoma*')) AND ((((((((((('Personalized medicine*') OR 'targeted medicine*') OR 'novel therapy*') OR 'person specific medicine*') OR 'EGFR*') OR 'HER2*') OR 'CMET*') OR 'KRAS*') OR 'BRAF*') OR 'ALK*')) AND ((((((('Overall survival*') OR 'Survival rate*') OR 'Progression free survival*') OR 'Disease-free survival*') OR 'Progression-free survival*') OR 'response rate*'). This provided 415 hits.

The articles found in both the systematic literature search as well as the free text search underwent two exclusion phases: the first being based on title and abstract and the second being based on a thorough read-through (Figures 1 and 2). If an article did not fulfill the inclusion and exclusion criteria, it was discarded. This process resulted in 26 relevant articles in the systematic literature search and 37 relevant articles in the free text search.

After having conducted the first part of the literature search, four searches on two additional targets, mTOR and MET, were performed in an identical manner (Figures 1–4 in Supplementary data). This was done on the 28th April 2017. The reason for this later performed search was due to later awareness of the importance of these two targets. The search resulted in three articles being included. See search history in Supplementary data.

Furthermore, six articles with new or relevant data were added manually. Thus, the final number of relevant articles found was 72.

Results

EGFR

Table 1 lists studies, which have investigated EGFR mutations and the effect of TA.

EGFR TKI

An overview of the results is shown in Table 1. A total of 42 studies, included in the systematic review, have investigated TA and its effect on EGFR-mutated NSCLC patients (Table 1). This is reflecting that the EGFR historically has played a very central role within the field of TA and NSCLC. Moreover, several of these studies are phase III or IV studies stating that the drug development has already gone far. In the multicenter, open-label, randomized phase III LUX-LUNG 6 study by Wu et al. [10], the comparison of Afatinib to standard chemotherapy was conducted (Table 1). Herein Afatinib improved mPFS with a mPFS of 11.0 months compared to 5.6 months in patients treated with standard chemotherapy ($p < .0001$). Despite no statistical significance, ORR results for Afatinib was superior to standard chemotherapy, with ORR results of 66.9 and 23%, respectively. Another randomized, global, open-label, phase III, the LUX-LUNG 3, study presented by Sequist and colleagues [9] compared the activity of Afatinib with standard chemotherapy (Table 1). Here results supporting the beneficial use of TA were presented as well with mPFS results of 11.1 months in patients treated with Afatinib vs. 6.9 months in patients treated with standard chemotherapy ($p = .001$). Furthermore, ORR was also significantly higher in the Afatinib arm compared to the standard chemotherapy arm with ORRs of 56 and 23%, respectively ($p = .001$). A phase IV study is included in this systematic review as well, supporting the general idea that the use of EGFR TKIs is already well incorporated in the treatment regimens of

Table 1. EGFR.

Study	Year	Study type	Mutation status	Population treated (total population)	Treatment	ORR *n* (%)	PR *n* (%)	CR *n* (%)	mPFS (months)	mOS (months)
[7]	2014	Phase IV	EGFR	106 (1060)	Gefitinib	74 (69.8%)	72	2	9.7	19.2
[8]	2013		EGFR	(5)	Gefitinib	(72.7%)	39	1	13.8	29.1
[9]	2013	Phase III	EGFR	230 (1269)	Afatinib	(56%)	–	–	11.1	–
	–		EGFR	115 (1269)	Standard chemotherapy	(23%) ($p = .001$)	–		6.9 ($p = .001$)	–
[10]	2014	Phase III	EGFR	242 (910)	Afatinib	162 (66.9%)	159 (65.7%)	3 (1.2%)	11.0	22.1 (estimated)
			EGFR	122 (910)	Standard chemotherapy	28 (23%)	28 (23%)	0 (0%)	5.6 ($p < .0001$)	22.2 (estimated)
[11]	2014	–	EGFR	188 (188)	Erlotinib or Afatinib or Gefitinib		–	–	15.1	31.2
[12]	2015	–	EGFR	50 (88)	Erlotinib or Gefitinib	11 (20.4%)	11 (20.4%)	0 (0%)		
		–	EGFR	54 (88)	Erlotinib or Gefitinib				2.6	12.7
[13]	2014	–	EGFR	119 (168)	Gefitinib	(61%)	–		9.8	22.2
		–	EGFR	49 (168)	Gefitinib	(58%)	–		15.8	51.1
[14]	2015	–	EGFR	34 (773)	Gefitinib	(44.8%)	11 (37.9%)	2 (6.9%)	10	
[15]	2015	Phase II	EGFR	15 (481)	Erlotinib	(60%)	9		11.3	25.7
[16]	2015	–	EGFR	109 (5738)	EGFR TKI	(60.6%)	–		15.9	32
[17]	2015	Phase III	EGFR	242 (364)	Afatinib		–		11	–
			EGFR	122 (364)	Standard chemotherapy		–		5.6 ($p < .0001$)	–
[18]	2015	Phase II	EGFR	8 (23)	Sorafenib + Erlotinib	(62.5%)	–		11	26.12
[19]	2015	Phase II	EGFR	32 (32)	Erlotinib	(56.3%)	18 (56.3%)	0 (0%)	15.5	–
[20]	2015	Phase III	EGFR	54 (185)	Afatinib	(61.1%)	–		13.8	46.9
			EGFR	28 (185)	Standard chemotherapy	(20.7%) ($p = .0007$)	–		6.9 ($p = .0014$)	35.8
[21]	2015		EGFR	75 (75)	Gefitinib	(69.4%)	50 (66.7%)	2 (2.7%)	11.5	26.7
[22]	2015		EGFR	30 (36)	EGFR TKI				8.2	–
[23]	2015		EGFR	62 (62)	Gefitinib	(61.3%)	32	6	13.2	19
[24]	2015		EGFR	19 (37)	EGFR TKI	–	13	–	9.3	–
[25]	2015	Phase II	EGFR	45 (80)	Erlotinib + MK-2206		–	–	4.4	–
[26]	2015	Phase III	EGFR	133 (287)	Gefitinib + Standard chemotherapy	42 (32%)	–	–	5.4	14.8[a]
			EGFR	132 (287)	Placebo + Standard chemotherapy	45 (34%)	–	–	5.4	17.2[a]
[27]	2015	Phase III	EGFR	110 (217)	Erlotinib	(62.7%)	–	–	11.0	26.3
			EGFR	107 (217)	Standard chemotherapy	(33.6%)			5.6 ($p < .0001$)	25.5
[28]	2015	Phase III	EGFR	82 (165)	Erlotinib	–	–	–	–	22.8
			EGFR	72 (165)	Standard chemotherapy	–	–	–	–	27.2
[29]	2015	Phase II	EGFR	33 (34)	Erlotinib	(66.7%)	22 (66.7%)	0 (0%)	9.5	28.5
[30]	2015	Phase II	EGFR	26 (26)	Gefitinib + Standard chemotherapy	(84.6%)	22	0	18	–
[31][b]	2015		EGFR	153 (153)	Gefitinib	(66.7%)	–	–	9	–
[32][b]	2015		EGFR	44 (56)	Gefitinib or Erlotinib	(29.5%)	–	–	6.7	–
[33]	2015	Phase II	EGFR	20 (97)	Bevacizumab + Erlotinib	(70%)	11	3	14	23.4
[34]	2015	Phase II	EGFR	42 (42)	Gefitinib + Bevacizumab	31 (73.8%)	29 (69%)	2 (4.7%)	14.4	Not reached
[35]	2015	Phase II	EGFR	35 (35)	Gefitinib + Standard chemotherapy + S-1	(85.7%)	28	2	17.6	Not reached
[36]	2015	Phase II	EGFR	12 (24)	Erlotinib	7 (58.33%)	7 (58.33%)		6.9	14.5
[37]	2015		EGFR	104 (160)	Erlotinib or Gefitinib	(68%)			10.8	–
[38]	2015	Phase II	EGFR	41 (41)	Afatinib	–	13 (38%)	6 (18%)	–	–
[39]	2015	Phase III	EGFR	15 (79)	Gefitinib	–	–	–	–	46.87
			EGFR	15 (79)	Standard chemotherapy	–	–	–	–	20.97
[40]	2015		EGFR	64 (64)	Gefitinib	44 (69%)	42 (66%)	2 (2%)	16.1	37.1
[41]	2015	Phase I	EGFR	13 (24)	Patritumab + Erlotinib		1	–	107 d	–
[42]	2015		EGFR	24 (24)	EGFR TKI + Bevacizumab	(13%)	3 (13%)	0 (0%)	4.1	13.5
[43]	2016	Phase II	EGFR	46 (56)	Erlotinib		26 (57%)	1 (2%)	11	23
[44]	2016		EGFR	200 (293)[c]	EGFR TKI		–	–	–	21
			EGFR	53 (293)[d]	EGFR TKI					26
[45]	2016		EGFR	35 (35)	Gefitinib	29 (82.9%)	28	1	10	25
[46]	2016		EGFR	25 (53)	Afatinib	5 (20%)	5 (20%)	0 (0%)	4.1	10.3
			EGFR	28 (53)	Erlotinib	2 (7.1%)	2 (7.1%)	0 (0%)	3.3	10.8
[47]	2015	Phase I–II	T790M	46 (130)	Rociletinib	2 (78.59%)	27 (59%)		13.1 (estimated)	–
			T790M WT	17 (130)		5 (29%)	5 (29%)		5.6	

(*continued*)

Table 1. Continued

Study	Year	Study type	Mutation status	Population treated (total population)	Treatment	ORR *n* (%)	PR *n* (%)	CR *n* (%)	mPFS (months)	mOS (months)
[48]	2015	Phase I–II	T790M	138 (222)	Osimertinib	–	–		9.6	
			T790M	127 (222)	–	78 (61%)	–		2.8	
			T790M WT	62 (222)	–	13 (21%)	–		–	
			T790M WT	61 (222)	–	–	–		–	

[a]Not conclusive,
[b]Abstract only,
[c]1st line therapy with EGFR TKI,
[d]2nd line therapy with.

advanced-staged NSCLC patients (Table 1) [7]. This open-label, single-arm, phase IV, multicenter study demonstrated an ORR in 74 out 106 patients (69.8%) after treatment with Gefitinib. mPFS and mOS were 9.7 and 19.2 months, respectively. Furthermore, this phase IV study also evaluated the safety and tolerability concerning the use of Gefitinib, showing that only 1.9% of the patients developed serious adverse effects. However, no fatal adverse effects observed were found to be associated to Gefitinib [7].

Despite promising responses to treatment with 1st and 2nd generation EGFR TKIs, resistance often develops due to the T790M mutation [48]. Consequently, new EGFR TKIs targeting this specific mutation have been developed. Two phase I–II studies have evaluated the efficacy of these 3rd generation EGFR TKIs. In the multicenter study conducted by Jänne et al. [48], treatment outcomes in T790M mutation positive patients were compared to T790M WT patients after treatment with Osimertinib (Table 1). The mPFS was 9.2 and 2.8 months in mutation positive patients and WT patients, respectively. Regarding ORR Osimertinib also showed improved efficacy in mutation positive patients compared to WT patients with ORRs of 61 vs. 21%. Other important endpoints from this study include dose escalation and safety. None dose-limiting toxic effects were seen in the evaluation period lasting 28 d. Moreover, only 6% of the 22% who experienced serious adverse events was recognized as being treatment-related. However, only one out of seven fatal adverse events was considered to be due to treatment [48]. In the other phase I–II, multicenter study conducted by Sequist et al. [47], the 3rd generation EGFR TKI, Rociletinib, showed higher efficacy in T790M mutation positive patients compared to T790M WT patients with a mPFS of 13.1 and 5.6 months and an ORR of 59 and 29%, respectively (Table 1). Despite these convincing results the development of the Rociletinib has been stopped [49].

ALK

Table 2 lists studies, which have investigated the ALK-rearrangement and the effect of TA.

The ALK-rearrangement is another genetic alteration found in NSCLC patients [41]. Various TKIs for NSCLC patients with ALK-activation have been developed during recent years with Crizotinib being a 1st generation drug and Ceritinib and Alectinib being 2nd generation drugs. In this systematic review, an open-label phase III study conducted by Solomon et al. [56] evaluated the efficacy of Crizotinib in comparison with standard chemotherapy (Table 2). Treatment with Crizotinib showed a significantly improved mPFS of 10.9 months compared to 7.0 months in patients treated with standard chemotherapy ($p < .001$). Moreover, ORR was significantly higher in the Crizotinib arm compared to the standard chemotherapy arm (Table 2). Due to development of resistance to Crizotinib, 2nd generation ALK TKIs have recently been developed [62]. Results from an open-label, multicenter phase II study conducted by Ou et al. [62] conferred an ORR of 50% and a mPFS of 8.9 months after treatment with Alectinib (Table 2). Another 2nd generation ALK TKI, Ceritinib, has been assessed in the recent multicenter, open-label phase I ASCEND-1 study presented by Kim et al. [63]. Here an ORR and mPFS was found to be 72% and 18.4 months for ALK-inhibitor naïve patients while being 56% and 6.9 months for ALK-inhibitor pretreated patients (Table 2).

RAS

Table 1 of Supplementary data lists studies, which have investigated RAS mutations and the effect of TA. KRAS acts downstream of the EGFR and is mutated in 20–25% of all NSCLC patients [64,65]. Thus, it plays a pivotal role in the development of cancer in a great subgroup of NSCLC cancer cases [66]. In a randomized, open-label, multicenter, two-armed phase II study, conducted by Blumenschein et al. [65], treatment with the MEK1/MEK2 inhibitor, Trametinib, was used to treat KRAS-mutated patients (Supplementary Table 1). ORR was similar between the two treatment arms with ORRs of 12% each. The mPFS was 12 weeks and 11 weeks in the Trametinib arm and the standard chemotherapy arm, respectively. Another MEK inhibitor, which is currently being tested against RAS-mutated NSCLC patients, is Selumetinib. Two studies in this review investigated the efficacy of Selumetinib.

In the study by Jänne et al. [64] the efficacy of Selumetinib + Docetaxel was compared to Docetaxel + placebo. The results were convincing with ORR of 37 and 0%, respectively ($p < .0001$) (Supplementary Table 1). Moreover, mPFS and mOS results favor treatment with Selumetinib (Supplementary Table 1).

RAF

Table 3 lists studies, which have investigated RAF mutations and the effect of TA.

The RAF-kinase plays a part in the EGFR pathway as well, acting downstream of RAS. The mutation subtype BRAF is considered a relatively rare mutation in NSCLC patients with

Table 2. ALK.

Study	Year	Study type	Mutation status	Population treated (total population)	Treatment	ORR *n* (%)	PR *n* (%)	CR *n* (%)	mPFS (months)	mOS (months)
[50]	2013		ALK	8 (208)	EGFR TKI	0 (0)	–	–	–	–
[51]	2013	Phase III	ALK	173 (347)	Crizotinib	(65%)	112 (65%)	1 (1%)	7.7	20.3
	–	–	ALK	174 (347)	Standard chemotherapy	(20%) ($p < .001$)	34 (20%)	0 (0%)	3 ($p < .001$)	22.8
[52]	2013	–	ALK	194 (414)	Crizotinib	–	–	–	–	21.9
[53]	2014	Phase I–II	ALK	44 (47)	Alectinib	24 (55%)	14 (32%)	1 (2%)	–	–
[54]	2014	–	ALK	45 (166)	Crizotinib	–	–	–	7.6	–
[55]	2015	–	ALK	73 (73)	Crizotinib	–	–	–	8.2	–
	–	–	ALK	73 (73)	Ceritinib	–	–	–	7.8	–
			ALK	73 (73)	Crizotinib →Ceritinib[a]	–	–	–	17.4	–
[56]	2015	Phase III	ALK	172 (343)	Crizotinib	74%	125 (73%)	3 (2%)	10.9	17.4 (estimated)
			ALK	171 (343)	Standard chemotherapy	45% ($p < .001$)	74 (44%)	2 (1%)	7 ($p < .001$)	16.7 (estimated)
[57]	2015	Phase I	ALK	19 (20)	Ceritinib	10 (53%)	10	–		–
[58]	2015	–	ALK	69 (69)	Crizotinib or Ceritinib[b]	42 (60.9%)	–	–	12	40
			ALK	22 (69)	Ceritinib or Alectinib[c]	19 (86.4%)	–	–	7	22
[59]	2015	–	ALK	18 (487)	Crizotinib	–	–	–	–	21.2
		–	ALK	22 (487)	Standard chemotherapy	–	–	–	–	19.1
[60]	2015	–	ALK	67 (72)	Crizotinib	52.2%	34 (50.8%)	1 (1.5%)	10.3	–
[61][d]	2015	–	ALK	21 (146)	Crizotinib	(61.9%)	–	–	–	–
[62]	2015	Phase II	ALK	138 (138)	Alectinib	–	–	–	8.9	–
			ALK	122 (138)	Alectinib	61 (50%)	–	–	–	–
[63]	2016	Phase I	ALK	83 (255)	Ceritinib[e]	60 (72%)	59 (71%)	1 (1%)	18.4	Not reached
	–	–	ALK	163 (255)	Ceritinib[f]	92 (56%)	89 (55%)	3 (2%)	6.9	16.7

[a]Sequential treatment,
[b]1st line treatment,
[c]2nd line treatment,
[d]Abstract,
[e]ALK-inhibitor naïve patients,
[f]ALK-inhibitor pretreated patients.

studies reporting a frequency of only 1.6% [69]. From the systematic review, two studies evaluated TA in BRAF-mutated patients. In the ongoing, open-label, multicenter, phase II study conducted by Planchard et al. [68], the two agents Dabrafenib + Trametinib are applied as combination therapy. Here an ORR of 63% and a mPFS of 8.6 months are presented (Table 3).

In the multicenter phase II study, Hyman et al. [67] investigated the efficacy of the selective BRAF inhibitor Vemurafenib (Table 3). The ORR was found to be 42% and the mPFS was 7.3 months.

ROS1

Table 2 of Supplementary data lists studies, which have investigated the ROS1-rearrangement and the effect of TA.

ROS1-rearrangement is another genetic alteration found in NSCLC patients. However, it is rare and only 1–2% harbor this rearrangement [70,71]. It has been found that the ROS1-kinase shares some similarities with the ALK-kinase [71]. Thus, the ALK-inhibitor Crizotinib has been applied to ROS1-rearranged patients [71]. In the study conducted by Maziéres et al. [71], 29 patients were treated with Crizotinib, which conferred an ORR of 80% and a mPFS of 9.1 months (Supplementary Table 2). Crizotinib's efficacy in 50 ROS1-rearranged patients was also investigated in the Phase I study by Shaw et al. [70] where ORR was 72% and mPFS was 19.2 months (Supplementary Table 2).

MET

Table 3 of Supplementary data lists studies, which have investigated MET mutations and the effect of TA.

The MET receptor tyrosine kinase is involved in many signal transduction pathways affecting the cell proliferation and angiogenesis [72]. In Table 3 of Supplementary data, results from the multi-national, randomized, double-blind, placebo-controlled phase III study testing Tivantinib + Erlotinib in patients with cMET high expression levels is depicted [72]. Treatment with Tivantinib + Erlotinib resulted in a mPFS of 3. 7 months, and a mOS of 9.3 months, while treatment with Erlotinib + placebo conferred a mPFS of 1.9 months and mOS of 5.9 months (Supplementary Table 3).

ERBB2

Table 4 of the Supplementary data lists studies, which have investigated ERBB2 mutations and the effect of TA.

Table 3. RAF.

Study	Year	Study type	Mutation status	Population treated (total population)	Treatment	ORR *n* (%)	PR *n* (%)	CR *n* (%)	mPFS (months)	mOS (months)
[67]	2015	Phase II	BRAF	19 (20)	Vemurafenib	8 (42%)	8 (42%)	0 (0%)	7.3	–
[68]	2016	Phase II	BRAF	57 (59)	Dabrafenib + Trametinib	36 (63%)	36 (63%)	0 (0%)	8.6	–

The ERBB2 mutation is a mutation with a low incidence [15]. In this systematic review, only two studies investigated TA for this mutation. The ongoing, multi-arm, open-label, non-randomized phase II study by Lopez-Chavez et al. [15] investigated the efficacy of Lapatinib in patients with ERBB2 mutations. However, the results were disappointing with an ORR of 0% and no results for mOS or mPFS (Supplementary Table 4). In the other included study, various ERBB2 TAs were investigated. Trastuzumab in combination with standard chemotherapy resulted in an ORR of 50% and a mPFS of 5.1 months. Moreover, this combination with an addition of T-DM1 resulted in an ORR of 50.9%, a mPFS of 4.8 months and mOS of 13.3 months (Supplementary Table 4). The remaining treatment arms presented various efficacy results [73].

PIK3CA/AKT/mTOR/PTEN

Table 5 of Supplementary data lists studies, which have investigated mutations within the PIK3CA/AKT/mTOR/PTEN pathway and the effect of TA.

Mutations in the PIK3CA/AKT/mTOR/PTEN pathway are like the ERBB2 rarely found [15]. In the systematic review, three studies investigated TA for mutations within this pathway. Two studies tested the effect of Everolimus, however mutational status was not known. In the phase II study by Ramalingam et al. [74] Everolimus was combined with Docetaxel and presented PR, CR and mOS of 8, 0 and 9.6 months, respectively (Supplementary Table 5). In the study by Deutsch et al. [75], Everolimus was combined with radiotherapy and resulted in PR of 41%, CR of 0% and mPFS and mOS of 8 and 21 months, respectively (Supplementary Table 5).

Discussion

EGFR

Eight phase III studies and one phase IV study concerning the use of EGFR TKIs were found in the systematic literature search. This reflecting that the development of EGFR TKIs has already gone far. In 2003, 1st generation EGFR TKIs obtained approval for use in clinical practice [76] while the 2nd generation EGFR TKI, Afatinib, was FDA and EMA approved in 2013 [77]. Current NCCN and ESMO guidelines recommend the 1st and 2nd generation EGFR TKIs as 1st line treatment for EGFR mutation-positive patients [78,79]. Despite of a well-established beneficial outcome after treatment with these TKIs, progression will often develop [48]. In both guidelines, treatment algorithms exist when patients progress upon 1st line treatment with 1st/2nd generation EGFR TKIs. The procedure upon progression consists of a re-biopsy testing for the T790M mutation. In the latest version of the NCCN guidelines version 3.2017 (National Comprehensive Cancer Network, Fort Washington, PA, USA), it has been implemented that if a patient is T790M positive, Osimertinib is recommended as treatment [79]. This is in accordance with the ESMO guidelines [78]. In the systematic review, one study investigated the clinical outcomes after treatment with Osimertinib in T790M positive and T790M WT patients and found that mPFS as well as ORR were markedly improved in mutation positive patients (Table 1) [48]. This underlining the importance of rebiopsying and subsequent establishment of whether a T790M mutation exists before treatment decisioning.

In another study, published after the time frame of this systematic review, Mok et al. investigated the potential beneficial use of Osimertinib compared to Pemetrexed + platinum based chemotherapy in T790M mutation positive patients [80]. A total of 419 patients were assigned to receive either Osimertinib or standard chemotherapy in a 2:1 ratio. Regarding mPFS and ORR, treatment with Osimertinib showed significantly improved outcomes when compared to outcomes after treatment with standard chemotherapy [80]. These results also support the recommendations in the NCCN and ESMO guidelines stating that if a T790M mutation is present, Osimertinib should be the drug of choice [78,79].

The other 3rd generation EGFR TKI, Rociletinib, showed promising results in the phase I–II study conducted by Sequist et al. [47], which is included in this review. Nevertheless, after disappointing results from a randomized phase II–III study, FDA accelerated approval was not achieved, and the enrollment of patients was ended in 2016 [81].

ALK

In 2011, Crizotinib was FDA approved as treatment for ALK-rearranged NSCLC patients [82]. This is in great accordance with the fact that two phase III studies included in this review both presented convincing results [51,56]. Both studies found that treatment with Crizotinib did confer significant better mPFS and ORR results when compared to standard chemotherapy. These substantial results are in agreement with the fact that Crizotinib is recommended as 1st line treatment for ALK positive patients in current NCCN and ESMO guidelines [78,79].

Unfortunately, patients will progress on Crizotinib treatment [41]. As a result, two 2nd generation ALK inhibitors, Alectinib and Ceritinib, have been developed [83]. Regarding Ceritinib, the phase I study, ASCEND-1, investigated the efficacy of Ceritinib in both ALK inhibitor-naïve and ALK inhibitor-pretreated patients [63]. Based on the durable responses reported, the potent ALK-TKI Ceritinib is suggested as a potential alternative to Crizotinib as 1st line treatment [63]. Moreover, treatment with Ceritinib showed antitumor activity as well as clinical responses in ALK-inhibitor pretreated patients, who previously have progressed on

Crizotinib [63]. It was on the bases of the results from ASCEND-1, Ceritinib was implemented as standard treatment upon progression on Crizotinib in both the ESMO and NCCN guidelines [78,79].

In addition, results regarding the efficacy of Ceritinib compared to standard chemotherapy have recently been presented in the ASCEND-4 study [84]. Herein, it was shown that Ceritinib is significantly superior compared to standard chemotherapy with mPFSs of 16.6 and 8.1 month, respectively ($p < .0001$) [84]. While ASCEND-4 tested Ceritinib in ALK inhibitor-naïve patients [84], the more recently published ASCEND-5 study by Shaw et al. [85], tested Ceritinib vs. standard chemotherapy in a 2nd line setting which adds upon the results from the ASCEND-1. An improved PFS was found after treatment with Ceritinib upon progression on Crizotinib + standard chemotherapy with a mPFS of 5.4 months for Ceritinib compared to 1.6 months for standard chemotherapy [85]. Hence, Ceritinib might represent a promising option for patients who have already progressed on 1st generation ALK inhibitors where standard chemotherapy previously has been the treatment of choice [85].

Moreover, Ceritinib has proven good intracranial activity, which further underlines the great potential of this drug [84].

In this systematic review, one phase II study and one phase I/II study investigated the efficacy of the other 2nd generation ALK inhibitor Alectinib and presented ORRs of 50 and 55%, respectively [53,62].

After the completion of the systematic literature search, two phase III studies based on the ALEX and J-ALEX trials have compared treatment outcomes after treatment with either Alectinib or Crizotinib [86,87]. Both studies presented results where treatment with Alectinib showed improved survival outcomes [86,87]. In the ALEX study conducted by Peters et al. [87], mPFS was 25.7 and 10.4 months and ORR results were 82.9 and 75.5% for Alectinib and Crizotinib, respectively. A similar tendency was seen in the J-ALEX study presented by Hida et al. [86] where mPFS was 10.2 months for Crizotinib while it was not reached after treatment with Alectinib. The ORRs were 92 and 79% for Alectinib and Crizotinib, respectively.

Furthermore, in both studies, Alectinib showed improved intra-cranial activity as well as a lower toxicity compared to Crizotinib [86,87].

The results from of the interim analyses of the data from the J-ALEX trial, were so convincing that they were used as a part of the foundation for recommending Alectinib as a 2nd line treatment option, like Ceritinib, in the ESMO guidelines even before publication of the final data [78].

Despite the substantial results after treatment with 2nd generations ALK TKIs, some patients develop resistance [83]. In order to overcome this, the next-generation ALK inhibitor, Brigatinib, have been tested in Crizotinib-refractory patients in a phase II study conducted by Kim et al. [83]. Here, doses of either 90 or 180 mg of Brigatinib was administered. The survival outcomes favor a dose of 180 mg with a mPFS of 12.9 months and an ORR of 54% [83]. The findings in this study have accelerated the FDA approval for Brigatinib [88]. Thus, it is now a promising alternative for patients previously progressed on 1st and 2nd generation ALK TKIs.

RAS

In this review, five studies investigated TAs efficacy on RAS-mutated patients. Especially the phase II study conducted by Jänne et al. [64] presented promising results with statistical significant ORRs favoring the Selumetinib + chemotherapy treatment arm. This formed the bases for the phase III, double-blind, randomized SELECT-1 study, also conducted by Jänne et al. [89]. In this first prospective trial regarding KRAS-mutated NSCLC patients, 510 patients were administered to either Docetaxel + Selumetinib or Docetaxel + placebo [89]. However, against all expectations, combination therapy with Selumetinib + Docetaxel did not improve either OS, PFS or ORR significantly compared to Docetaxel + placebo [89]. These discouraging findings underline the very urgent need for new TAs for this subgroup of NSCLC patients. The lack of solid results in this subset of patients, is reflected in both the ESMO and NCCN guidelines, where no treatment algorithms currently are found [78,79]. Furthermore, no screening for this specific mutation is routinely performed. This might be because screening has not much purpose due to the very limited effective treatment options [89]. However, due to new diagnostic tools, such as next generation sequencing that contains a panel that detects RAS mutations, the mutation status is often given nevertheless [90].

RAF

In the ESMO and NCCN guidelines, no routine testing for RAF mutation is included [78,79]. However, in the NCCN guidelines, emerging treatment options are noted [79]. This being Vemurafenib, Dabrafenib or Dabrafenib in combination with Trametinib [79]. The recommendation of the latter mentioned relies on the phase II study from 2016, which is also included in this review, where the two drugs are applied on V600E BRAF-mutated NSCLC patients [68]. Here, an ORR of 63% is presented [68]. Still, more robust evidence needs to be presented in order to include the combination of Dabrafenib and Trametinib in the standard guidelines.

Hyman and colleagues [67] presented treatment outcomes after treatment with the other evolving drug, Vemurafenib. In this phase II study an ORR of 42% was presented [67]. Treatment outcomes after treatment with Vemurafenib have been investigated elsewhere in the literature. An example is given by a retrospective study conducted by Gautschi and colleagues [91] where an ORR of 54% was presented. Thus, varying efficacy results have been presented regarding BRAF-mutated NSCLC patients and the use of Vemurafenib. Therefore, it could be suggested that more research within this field should be conducted in order to obtain enough evidence regarding the potential use of Vemurafenib.

ROS1

The ROS1-kinase shares molecular similarities with the ALK-kinase [79]. For that reason, Crizotinib is considered as the 1st line treatment for ROS1-rearranged patients according to the NCCN guidelines [79]. Three studies investigating the use of Crizotinib was included in the systematic review.

These studies showed good results with high ORRs >70% [1,70,71]. Additionally, the phase I study be Shaw et al. presented a mPFS of 19.2 months [70]. These positive findings are in line with the fact that screening for ROS1-rearrangement has been incorporated in the 1.2017 version update for the NCCN guidelines and that the subsequent recommended treatment is Crizotinib [79]. Crizotinib as treatment for patients harboring ROS-1 rearrangements was FDA approved in 2016 [92]. The European Commission approval for Crizotinib in this patient group came shortly after the latest version of the ESMO guidelines was written [93]. This is the reason why these recommendations are not incorporated in the guidelines. This approval was based on the results presented by Shaw et al. [70] from 2014. There is now a routine screening for ROS-1 in lung cancer patients in Europe as well and a following recommendation for Crizotinib as standard treatment [93].

MET

The study by Scagliotti et al. [72] investigated the potential use of Tivantinib in the combination with an EGFR TKI compared to an EGFR TKI + placebo [72]. Since MET is recognized to contribute to the development of resistance to EGFR TKIs, this dual inhibition of MET and EGFR by using Tivantinib and Erlotinib is an approach which is of great clinical relevance [72].

Subgroup analyses were conducted for a cMET high tumor expression group and a cMET low tumor expression group. No substantial efficacy improvement was noted in the cMET low tumor expression group. Regarding the cMET high tumor expression group, the combination of Tivantinib and Erlotinib resulted in improved mPFS and mOS [72]. Thus, based from this study combination therapy could represent a treatment approach for this group of NSCLC patients [72]. However, in a more recent phase III study, survival outcomes when combining Erlotinib with another agent, here being the antibody Onartuzumab, showed disappointing survival outcomes with a mOS of only 6.8 months compared to a mOS of 9.1 months after treatment with Erlotinib + placebo [94]. ORR plus mPFS outcomes were similar between the two treatment arms [94]. Hence, based upon these two studies, there are some contradictions with regards to combination therapy in patients with MET mutations [72,94]. Thus, it is an area which could benefit from more research.

ERBB2 and PIK3CA/AKT/mTOR/PTEN

Both the ERBB2 mutation and mutations within the PIK3CA/AKT/PTEN pathway are rarely present in NSCLC patients [15,69]. In this review, two studies investigated the ERBB2 mutation. The use of Lapatinib was investigated by Lopez-Chavez et al. [15], and presented poor results. Lapatinib was also tested by Mazières et al. [73], where all treated patients experienced progressive disease already when the first response assessment was conducted. Thus, Lapatinib does not seem as a durable treatment option [73]. However, other TAs were tested in this study including the monoclonal antibody Trastuzumab. This was tested in combination with chemotherapy and showed an encouraging ORR of 50% and a mPFS of 5.1 month [73]. Based on these results, Trastuzumab could be a possible treatment option for ERBB2 patients. One patient received T-DM1 and treatment outcomes from this pooled with treatment outcomes from Trastuzumab + chemotherapy resulted in an ORR of 50.9%, a (m)PFS and mOS of 4.8 and 13.3 months, respectively [73]. Furthermore, the patient who received T-DM1 alone experienced a rapid response [73]. This effect has been reported elsewhere in the literature [95].

Concerning the PIK3CA/AKT/mTOR/PTEN pathway, Everolimus either in the combination with standard chemotherapy or with radiotherapy have been tested. Neither of the studies presented results with statistical significance, which might point toward a low activity of Everolimus in this subgroup of patients [74,75].

No recommendations for ERBB2 and PIK3CA/AKT/mTOR/PTEN mutations are found in the ESMO and NCCN guidelines [78,79]. This could be a consequence of the rarity of these mutations.

In the guidelines, it is advised that a wider screening for rare mutations like these should be done [78,79] in order to detect them and possibly recruit them in future clinical trials in hopes of developing effective treatment options for this group of patients [78,79].

From searching the literature, it is evident that the development within the field of TA has already gone far. However, some challenges still lies ahead, since it is well established that acquired resistance to therapy in many cases eventually develop [41,48]. In order to overcome this resistance, noninvasive biomarkers, such as plasma-samples, should be implemented to analyze driver mutation status and monitor the tumor development. Being able to monitor tumor status could help ensure that the targeted therapy would always be directed at the specific mutation responsible for the tumorigenesis. Thus, creating the possibility of applying the most effective treatment for each individual patient at any given time point of their disease. Introducing biomarkers as a part of the standard treatment could hold great hope for the future of NSCLC patients, where currently treatment is still limited.

Disclosure statement

The authors report no conflict of interest.

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