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Dynamics of eligibility criteria for central nervous system metastases in non-small cell lung cancer randomized clinical trials over time: A systematic review

Janna Josephus Anna Oda Schoenmaekers [a], Safiye Dursun [b], Charlotte Biesmans [c], Dirk Karel Maria De Ruysscher [d], Martinus Petrus Gertrudis Broen [e], Jordi Remon [f], Anne-Marie Clasina Dingemans [a,g], Lizza Elisabeth Lucia Hendriks [a,*]

[a] Dept. of Pulmonary Diseases, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Center+, Maastricht, the Netherlands
[b] Dept. of Pulmonary Diseases, Maastricht University Medical Center +, Maastricht, the Netherlands
[c] Maastricht University, Maastricht, the Netherlands
[d] Dept. of Radiation Oncology (MAASTRO), GROW - School for Oncology and Developmental Biology, Maastricht University Medical Center+, Maastricht, the Netherlands
[e] Department of Neurology, Maastricht University Medical Center+, Maastricht, the Netherlands
[f] Department of Medical Oncology, Centro Integral Oncológico Clara Campal (HM-CIOCC), Hospital HM Delfos, HM Hospitales, Barcelona, Spain
[g] Department of Pulmonary Diseases, Erasmus Medical Centre, Rotterdam, the Netherlands

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ABSTRACT

Although central nervous system (CNS) metastases frequently occur in patients with non-small cell lung cancer (NSCLC), historically these patients have been excluded from clinical trials. However, due to improving NSCLC prognosis, time to develop CNS metastases increases and information on CNS efficacy of systemic treatment is important. We performed a systematic PubMed review (2000–2020) to describe CNS related eligibility and screening criteria over time. Randomized phase III, and for tyrosine kinase inhibitors (TKIs) also randomized phase II trials enrolling advanced/metastatic NSCLC patients were included.

256/1195 trials were included. In 71 %, CNS metastases were eligible, but in only 3% regardless of symptoms/treatment. Only 37 % required baseline CNS screening (most often TKI and immunotherapy trials), without significant increase over time. A CNS endpoint was pre-specified in 4%.

Conclusion: CNS screening and eligibility criteria are heterogenous across trials, and CNS related endpoints are rare. These criteria and endpoints should be improved and harmonized.

1. Introduction

Central nervous system (CNS) metastases are a clinically relevant issue in patients with non-small cell lung cancer (NSCLC). Approximately 10–20 % of patients with wild type NSCLC present with CNS metastases at diagnosis, and 40–70 % of all patients with NSCLC will develop them during their disease (Huber et al., 2020; Moro-Sibilot et al., 2015; Yawn et al., 2003). Historically, patients with CNS metastases are underrepresented in clinical trials, as in a report published in 2015, only in 26 % of trials patients with NSCLC and CNS metastases were eligible regardless of CNS treatment (McCoach et al., 2016).

Two major improvements have changed the treatment paradigm in patients with NSCLC; the first is the discovery of oncogenic addicted tumors that can be treated with a personalized approach with tyrosine kinase inhibitors (TKI). The second is the introduction of the immune checkpoint inhibitors (ICI). These treatments resulted in a significantly improved 5-year survival rate in selected groups of patients with metastatic NSCLC, with 5-year survival rates in the first-line setting of over 30% to 60% (Huber et al., 2020; Camidge et al., 2019; Ramalingam et al., 2020; Reck et al., 2016; Gandhi et al., 2018; Mok et al., 2020; Reck

* Corresponding author at: Dept. of Pulmonary Diseases, GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center+, PO Box 5800, 6202 AZ, Maastricht, the Netherlands.
E-mail addresses: J.schoenmaekers@mumc.nl (J.J.A.O. Schoenmaekers), Safiye.dursun@mumc.nl (S. Dursun), charlotte.biesmans@student.maastrichtuniversity.nl (C. Biesmans), Dirk.deruysscher@maastro.nl (D.K.M. De Ruysscher), Martijn.broen@mumc.nl (M.P.G. Broen), jremon@hmhospitales.com (J. Remon), A.dingemans@erasmusmc.nl (A.-M.C. Dingemans), lizza.hendriks@mumc.nl (L.E.L. Hendriks).

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et al., 2021). This prolonged survival results in an increasing time and therefore risk to develop both CNS metastases as well as CNS related complications (Ramotar et al., 2020), and both can negatively impact quality of life (Peters et al., 2016). As a result, CNS related endpoints, such as intracranial progression or CNS disease free survival (DFS) are becoming increasingly relevant. Recent approaches with next-generation TKIs in oncogenic addicted tumors have improved outcomes, including a decreased risk of developing intracranial disease in the metastatic as well as in the early stage settings, endorsing that the prevention of CNS disease is a relevant endpoint in all disease settings. This is even more relevant as oncogenic addicted tumors seem to have an increased risk of CNS metastases compared with wild-type patients (Ramalingam et al., 2020; Wu et al., 2020; Gadgeel et al., 2018)

To optimise and stimulate inclusion of patients with CNS metastases in clinical trials, the Response Assessment in Neuro-Oncology (RANO) brain metastases (BM) working group provided detailed recommendations (2018) on eligibility criteria for patients with BM from solid tumors in clinical trials with systemic agents, depending on the likelihood of the CNS activity of the agent (Camidge et al., 2018a). Furthermore, they addressed trial design aspects unique to patients with BM, including appropriate CNS endpoints (Lin et al., 2015). The American Society of Clinical Oncology (ASCO) gave similar recommendations (2017) regarding clinical trial eligibility criteria to expand eligibility, and to include more patients with BM (Lin et al., 2017). Recently, the Food and Drug Administration (FDA) presented a guidance document on how to evaluate cancer drugs in patients with CNS metastases (US Food and Drug Administration, 2021). However, it is not clear whether in recent years clinical trials were more inclusive regarding patients with CNS metastases.

As recent data on CNS eligibility criteria and CNS related endpoints in clinical trials evaluating systemic therapy for NSCLC is lacking, we performed a systematic review. Our aims were to obtain a complete overview on 1) CNS eligibility criteria 2) required CNS screening methods 3) the implementation of CNS related endpoints and 4) the actual proportion of patients with CNS metastases enrolled in clinical trials over time. This was evaluated in relation to the time of trial initiation and taking into account the systemic therapy under evaluation. We hypothesized that with the introduction of systemic therapies with improved CNS activity (especially the next generation TKIs), there would be a change in CNS eligibility criteria and endpoints over time, with more recent trials having broader eligibility criteria and more CNS specific endpoints.

2. Methods

2.1. Study design

This systematic review was conducted according to the PRISMA guideline (preferred Reporting Items for Systematic reviews and Meta-Analyses) (Moher et al., 2009)

2.2. Outcomes

The main outcome measures were to assess the percentage of trials in which baseline CNS screening (mandatory versus only if clinically indicated) was required, and to assess the eligibility criteria for patients with CNS metastases. This was also evaluated over time (in blocks of 5 years according to start of enrollment, except the first block [8 years] due to the limited number of included trials, and the last block [7 years] due to the limited number of trials in the last 2 years). Based on different working mechanisms, and cerebral response rates, we divided the CNS eligibility criteria according to the different investigational drugs (a. immunotherapy (defined as ICI or vaccine studies), b. TKI or c. other). Furthermore, for all the included trials it was evaluated whether there were prespecified CNS related endpoints. The outcomes of these endpoints were also recorded. Last, for trials allowing patients with CNS metastases, the number of actually enrolled patients with CNS metastases was extracted.

2.3. Search strategy and selection criteria

A systematic literature search for publications between January 1st 2000 and November 11th 2020 (the search date) was carried out using the PubMed database according to the PICO (Patient, Intervention, Comparison, Outcome) method (supplemental Table 1). The full search terms are depicted in supplemental Table 2. The search was limited to full papers, published in English. Eligibility criteria were advanced/metastatic NSCLC, randomized interventional drug trials, phase III. In addition, for trials evaluating TKIs as trial drug, randomized phase II trials were eligible as some U.S. Food and Drug administration (FDA)/European Medicines Agency (EMA) approvals for TKI are based on (randomized) phase II trials. Detailed inclusion criteria are described in supplemental Table 3. Every included trial was counted only once; however all available related publications were searched to collect the required data. The publication with the primary endpoint analysis was included as reference. If CNS reported endpoints were reported in a separate publication, this publication was added also as a reference.

2.4. Study selection

Two authors independently selected papers for inclusion based on titles and abstracts (JS and LH), and full texts (JS and SD). A third author (LH) evaluated all papers with disagreement and consensus was sought through discussion.

2.5. Data extraction

The following data were extracted from eligible full texts: title; journal; year of publication; year of start enrollment; trial phase; study drug; if TKI, generation of TKI; eligible histological and molecular type (adeno, squamous, not otherwise specified, limited to oncogenic driver or not, and if oncogenic driver, specification of driver); screening for CNS metastases and if so, type of screening (magnetic resonance imaging [MRI] or computed tomography [CT]); eligibility of CNS metastases and specification of eligibility criteria (a: all CNS metastases eligible regardless of treatment/symptoms; b: untreated only eligible if asymptomatic, otherwise only if treated and stable; c: only eligible if treated and stable, all untreated excluded; d: strictly excluded; e: nothing specified); whether BM and leptomeningeal disease (LMD) were separately specified; intracranial response as prespecified study endpoint and whether/how this outcome was reported; number of patients enrolled including percentage of patients with CNS metastases; whether local treatment of isolated CNS progression with continuation of trial drug was allowed. If this data was not available in the full text, the trial register in which the trial was registered, and the protocol, if available, were screened.

2.6. Statistical analyses

Statistical analyses were performed with SPSS (version 23; SPSS Inc., Chicago, IL) and Microsoft Excel (version 2016). The baseline characteristics were analyzed using standard descriptive statistics. Groups were compared with the Chi Square test. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1. Included trials

The electronic literature search yielded a total of 1195 records, of which 250 fulfilled the eligibility criteria (Fig. 1). After reference checking, six additional records were included. Five additional

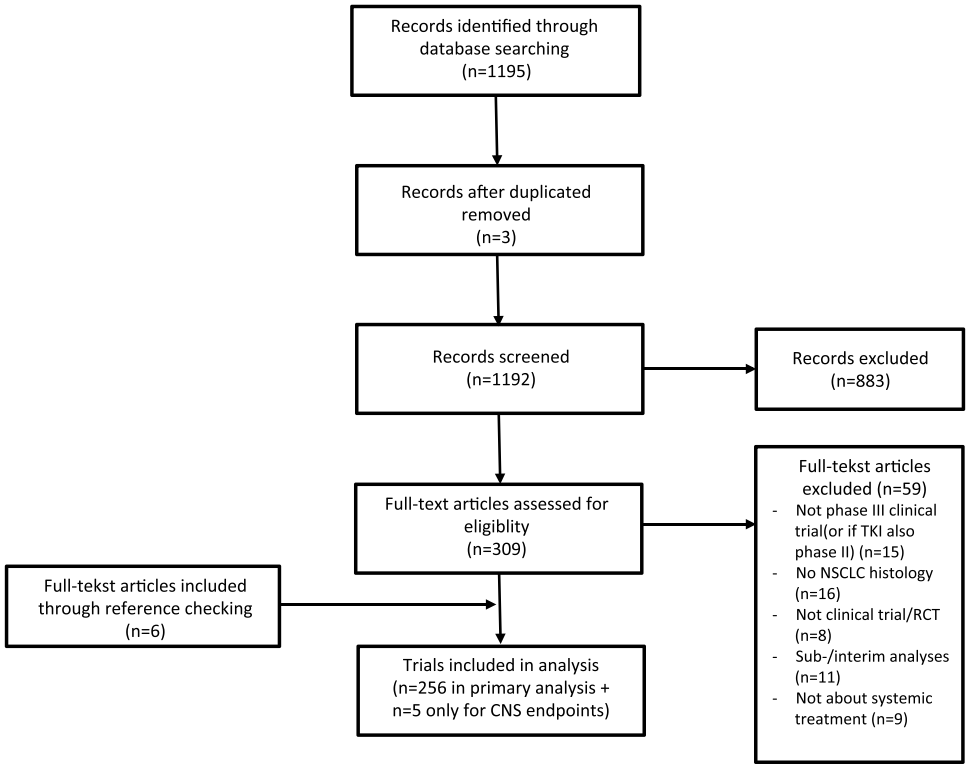

Fig. 1. Consort diagram excluded trials.
Abbreviations: n; number, TKI; tyrosine kinase inhibitor, NSCLC; non-small cell lung carcinoma, RCT; randomized controlled trial, CNS; central nervous system.

publications were also used for data extraction as they described more detailed CNS related outcomes compared to the original trial publication.

Table 1 provides an overview of the characteristics of the included trials (n = 256). Furthermore, in supplementary table 4 all included trials are shown, sorted according to study drug and time of start patient enrollment in the trial. Most trials (92 %) were randomized phase III trials, 79 % included all NSCLC subtypes, 4% included only adenocarcinoma, 3% only squamous cell carcinoma and 14 % non-squamous cell carcinoma. TKI was the study drug in 34 % of the trials, and immunotherapy was the treatment under investigation in 9% of the trials.

3.2. Eligibility of patients with CNS metastases

In 71 % of trials, patients with CNS metastases were eligible, whereas in 16 % of trials patients with CNS metastases were strictly excluded and in 11 % of trials nothing was specified. In trials allowing patients with CNS metastases, 3% allowed all CNS metastases regardless of CNS directed treatment or neurological symptoms, in 47 % patients with asymptomatic (including treated) CNS metastases were eligible, and in the remaining 50 % only those with stable and treated CNS metastases were eligible. There was no significant difference over time in the number of trials that strictly excluded CNS metastases ($p > 0.05$).

Fig. 2 shows a comparison between the different eligibility criteria for CNS metastases for the different study drug groups. No significant differences were found between the different study groups ($p > 0.05$).

In 71 % of the trials that allowed patients with CNS metastases (treated and stable; asymptomatic regardless of local treatment or, regardless of symptoms/treatment), the median actual percentage of patients with CNS metastases included was 12 % (range 0.4 %–69 %). This number increased over time, from 9% (range 2.0 %–28.8 %) in trials that started enrollment between 1996−2000, to 22 % (range 2.0 %–69.4 %) in trials started enrollment between 2011−2017 ($p < 0.02$). In the period 1987−1995 the actual percentage of patients with CNS metastases included is not mentioned.

Further analyses regarding leptomeningeal disease (LMD) criteria could not be performed, as except for 7 trials (strictly excluded in 3 trials, eligible when treated in 2 trials and also eligible when asymptomatic in the other 2 trials), in all other trials, eligibility criteria regarding LMD were not specifically addressed (i.e. BM and LMD separately addressed instead of the more general term CNS disease).

3.3. Baseline screening for CNS metastases

In 94 trials (37 %) baseline screening for CNS metastases was required, either when clinically indicated (N = 36/256, 14 %), or mandatory (N = 58/256, 23 %).

As is shown in Fig. 3, except for the time period 1987−1995, there was a non-significant increase in the percentage of trials in which mandatory baseline CNS screening was performed over time: from 18 % to 31 % in studies that started enrollment from 1996−2000 till 2011−2017, respectively ($p > 0.05$). However, up to 19 % of clinical trials that started enrollment between 2011−2017 still required CNS screening only if clinically indicated and screening was not required at all in approximately 50 % of trials. The recommended screening method changed to predominantly MRI in 24 % of trials that started enrollment in 2011−2017 and even in 75 % of trials that started enrollment in 2016–2017 in comparison with 0% in trials that started enrollment between 1987−1995.

3.3.1. TKI trials

In 86 (34 %) trials the study drug was a TKI. In only 30 % of these trials (26/86) brain imaging was required at baseline, in 9/86 (10 %) only when clinically indicated.

In 34/86 trials with a TKI as study drug, only patients with a pre-specified oncogenic driver (e.g. epidermal growth factor receptor *(EGFR),* anaplastic lymphoma kinase *(ALK)*), were eligible.

In 8/23 (35 %) EGFR-TKI trials, screening for CNS metastases was

Table 1
Characteristics of included trials.

	N (%)
Total number of trials	256
Type of trial	
Phase II	21 (8.2)
Phase III	235 (91.8)
Year of publication	
2000−2005	51 (20.0)
2006−2010	56 (21.9)
2011−2015	89 (34.8)
2016−2020	60 (23.4)
Start of enrollment (year)	
1987−1995	10 (3.9)
1996−2000	45 (17.6)
2001−2005	54 (21.1)
2006−2010	77 (30.1)
2011−2017	58 (22.7)
Not mentioned	12 (4.7)
Histological type eligible	
All NSCLC	203 (79.3)
Adenocarcinoma	9 (3.5)
Squamous cell carcinoma	7 (2.7)
Non-squamous cell carcinoma	36 (14.1)
Non-adenocarcinoma	1 (0.4)
Eligibility based on presence of oncogenic driver	
No	218 (85.2)
Yes	38 (14.8)
- EGFR	−27 (10.5)
- ALK	−10 (3.9)
- KRAS	−1 (0.4)
Study drug	
Chemotherapy	107 (41.7)
Targeted therapy	86 (33.6)
Immunotherapy	22 (8.6)
Anti-angiogenic therapy	13 (5.1)
Combination	6 (2.3)
Other*	22 (8.6)
Eligibility of CNS metastases	
Eligible	185 (72.3)
- All CNS metastases regardless of treatment/symptoms	- 6 (3.2)
-Untreated if asymptomatic, otherwise treated and stable	- 87 (47.0)
-Treated and stable (no untreated)	- 92 (49.7)
Strictly excluded	42 (16.4)
Nothing specified	29 (11.3)

Abbreviations: N; number, NSCLC; non-small cell lung cancer, CNS; central nervous system, EGFR; epidermal growth factor receptor, ALK; anaplastic lymphoma kinase, KRAS; Kirsten rat sarcoma, RET; Rearranged during transfection; * Simvastatin, celecoxib, nitroglycerin etc.

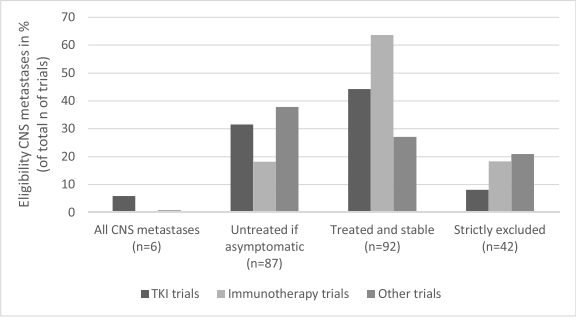

Fig. 2. Eligibility CNS metastases compared between trials with different study drugs.
*In the untreated if asymptomatic group, patients with treated and stable CNS metastases were eligible as well. *29 trials did not specify eligibility of CNS metastases. Abbreviations: CNS; central nervous system, TKI; tyrosine kinase inhibitor.

part of the baseline assessment and was mandatory in 4/23 (17 %). CNS screening was mandatory in 9 out of 10 (90 %) ALK-TKI trials. Screening criteria over time for TKI trials in which only patients with an oncogenic driver were included, are depicted in Fig. 4 a, with a statistically significant increase (p = 0.02) in required CNS screening in the period 2011−2017 compared with 2006−2010.

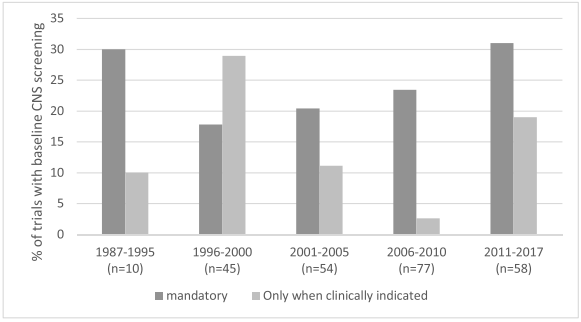

Fig. 3. Percentage of trials with required screening for CNS metastases at baseline; sorted from the date of start enrolment.
*of 12 trials the start of enrolment is not mentioned and therefore these trials are missing in this figure.
** 63 % of trials did not screen or did not mention screening in the trial methods Abbreviations: n; number (total number of trials that period), CNS; central nervous system.

3.3.2. *Immunotherapy trials*

In 22 (9%) of the trials, immunotherapy was the study drug. In 13 (59 %) of these trials baseline screening was required, in 8/22 (36 %) mandatory. Fig. 4 b shows that there is no significant difference in baseline screening for CNS metastases over time (2011−2017 compared to 2006−2010).

3.3.3. *Other study drugs trials*

In 148 (57 %) of the trials the study drug was either chemotherapy, anti-angiogenic therapy, multiple types of therapy combined or other (such as simvastatin, celecoxib, nitroglycerin etc.). In 55 (37 %) trials baseline CNS screening was required and in 22/148 (15 %) this was only required when clinically indicated. In most of the trials (n = 93, 63 %) screening was not mandated. Fig. 4 c shows that there is no trend towards more CNS screening over time.

3.4. *CNS related endpoints*

In 10/256 (4%) of the trials (all TKI trials for oncogenic driven NSCLC), a CNS endpoint (intracranial response) was prespecified, for the first time in a study that started enrollment in 2011 (Table 2). In 8 out of these 10 trials BM was a stratification factor. In 5 of these trials, continuation of the study drug was allowed upon CNS progression (at the discretion of the treating physician). None of the trials specified whether local treatment was allowed upon oligoprogression in the CNS. 90 % of these trials had prespecified follow up imaging of the CNS.

In 32/256 trials (13 %) the presence of BM was a stratification factor (i.e. regardless of whether a CNS related endpoint was included). In 16 (50 %) of these trials screening at baseline was specified, this was mandatory in 12 (38 %), and only required if neurologically symptomatic in the others. In most of these trials however, only pretreated, stable and asymptomatic BM were eligible. In 3 trials there were no CNS restrictions, and in 10 trials BM were allowed if asymptomatic, regardless of local treatment.

4. Discussion

In this systematic review we showed that approximately ¾ of NSCLC trials allowed patients with CNS metastases, although in half of these trials, only those with treated and stable metastases were allowed. We also found that in recently published trials (with start of enrollment between 2011−2017) only 31 % required mandatory CNS screening at

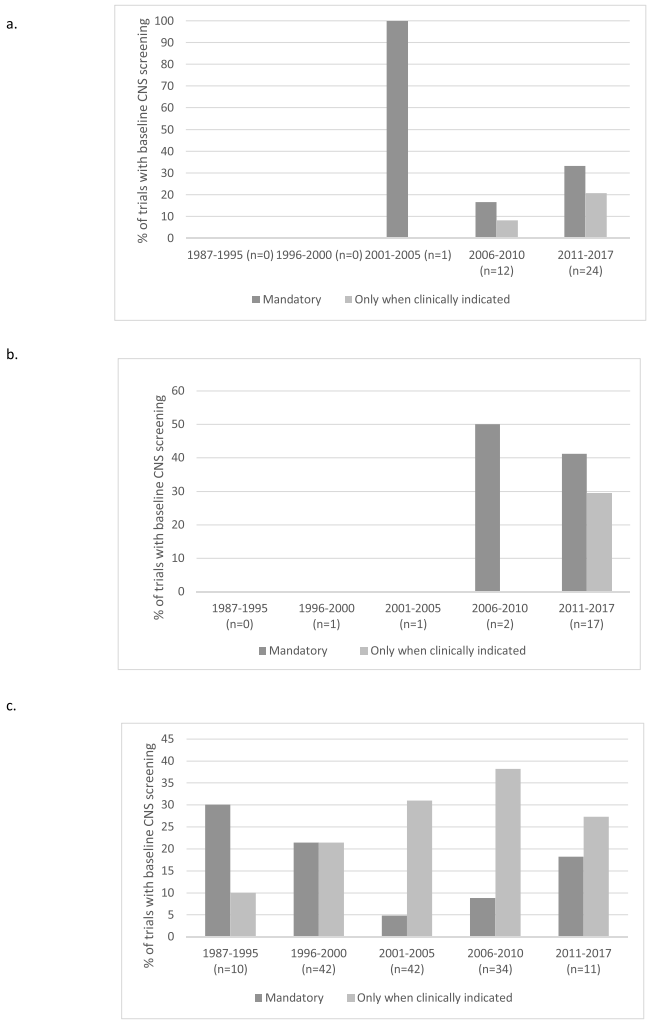

Fig. 4. Screening at baseline for CNS metastases in trials with different study drugs, sorted from the date of start enrollment.
a) TKI trials with an oncogenic driver as eligibility criterium.
* of one trial the start of enrolment is not reported and therefore missing in this figure.
** 50 % of the above mentioned TKI trials did not screen or did not mention screening in the trials methods Abbreviations: TKI; tyrosine kinase inhibitor, n; number
b) Trials with immunotherapy.
*41 % of the immunotherapy trials did not screen or did not mention screening in the trial methods.
Abbreviations: n; number.
c) Trials with other study drugs.
* Of 9 trials the start of enrolment is not mentioned and therefore missing in this figure.
**63 % of the other drug trials did not screen or did not mention screening in the trials methods.
abbreviations: n; number.

baseline. In contrast to our hypothesis, compared with older trials no significant increase in mandatory screening for CNS metastases over time was observed although a numerical increase occurred. Furthermore, only a minority of trials (4%, all TKI trials for oncogenic driven NSCLC) included prespecified CNS related endpoints in their trial design. In 90 % of these trials baseline screening for CNS metastases was required, and in 70 %, baseline CNS metastases was a stratification factor. Furthermore, 90 % of these trials mandated follow up of the CNS with brain imaging. The actual enrolled patients with BM increased from 9% in trials that started enrollment between 1996−2000, to 22 % in trials started enrollment between 2011−2017.

Although the presence of BM has been recognized as a poor prognostic factor (Roughley et al., 2014), only 13 % of all trials used presence of BM as a stratification factor. Importantly, in 2/3 of these trials no mandatory baseline CNS imaging was required. Nowadays, survival of NSCLC is increasing, and new treatment strategies are not limited to advanced disease (Wu et al., 2020; Antonia et al., 2017), meaning that control or even prevention of CNS metastases is becoming increasingly important. To evaluate the best systemic treatment strategy for CNS metastases, clinical trials should clearly specify the CNS eligibility criteria, the baseline CNS screening methods, and predefine CNS related outcome measures. For analysis of preplanned CNS related outcomes, stratification according to presence of CNS disease, and regular CNS imaging is required. Importantly, the description of eligibility criteria concerning CNS metastases in the trials included in this review was far from uniform and prevents comparison of trial data. Preferably, CNS eligibility criteria and response assessments are tailored to the expected CNS efficacy of a certain drug as specified in the RANO criteria and these criteria should be used in future trials (Camidge et al., 2018a). In 2018 the RANO-BM working group provided recommendations for clinical trial design in patients with CNS metastases. This guideline provided the optimal way to incorporate or exclude patients with CNS metastases in systemic therapy trials considering three scenarios, depending on the likelihood of CNS activity of the evaluated agents. The recommendation stresses that for a drug that is considered to have a high likelihood of CNS efficacy, patients with untreated CNS metastases (including symptomatic patients) should be eligible. However, if a drug is very unlikely to have CNS efficacy only patients with treated or stable CNS metastases should be eligible (Camidge et al., 2018a).

Historically, patients with CNS metastases were excluded from clinical trials, and clinicians have been reluctant to perform baseline screening for CNS metastases, as asymptomatic CNS metastases jeopardized trial eligibility. However, with the possible broadening of the eligibility criteria for CNS metastases over time (especially after the publication of the RANO criteria), the resistance to (the incorporation of) baseline screening could decrease.

The actual implementation of the RANO recommendations (published in 2018), should become clear in the upcoming years, as trials that could have fully incorporated these recommendations are still ongoing.

Interestingly, even though patients with CNS metastases at baseline were eligible in 72 % of trials, the percentage of included patients with CNS metastases was often low (although increasing in recent years) and does not necessarily reflect the incidence of CNS metastases in the general NSCLC population (Huber et al., 2020; Moro-Sibilot et al., 2015; Yawn et al., 2003). Because screening at baseline often was not mandatory in the trials, patients with asymptomatic CNS metastases could have been included in the trials, and therefore the percentage could be underestimated. In daily practice 24–33 % of patients with CNS disease are asymptomatic (Nieder et al., 2019; Steindl et al., 2020). Importantly, the patients with BM included in clinical trials do not reflect the general population, as the majority is neurologically symptomatic and/or requires steroids, both factors are often an exclusion criterium for clinical trial participation (Nieder et al., 2019; Steindl et al., 2020; Hendriks et al., 2019).

In 2015, the same RANO group published recommendations for standard BM response and progression criteria in clinical trials (Lin et al., 2015). They stressed that it is important to assess intracranial responses separately from extracranial responses, as the response of these two compartments can be differential (bi-compartmental model), for example due to inadequate drug penetration (Metro et al., 2017), differences in tumor microenvironment (Schulz et al., 2019), and tumor heterogeneity (Wang et al., 2019; Suh et al., 2020). CNS response should be assessed according to the RANO-BM criteria and non-CNS response according to the RECIST 1.1 criteria (Eisenhauer et al., 2009). It is recommended that protocols also include a plan for patients who progress in one compartment only (for example, for CNS progression, is local treatment [stereotactic radiotherapy/whole brain

Table 2
Trials that included intracranial endpoints in their trial design.

Trial, drug, journal, year of publication, trial register number	Year of start enrollment	Baseline screening for CNS mets	CNS mets eligible	FU brain imaging	CNS endpoints	Evaluation of CNS	CNS Primary endpoint Yes/No	% of pts with CNS mets included	CNS results endpoint	Continuation study drug allowed upon CNS PD only
PROFILE 1014, crizotinib, NEJM 2014 and JCO 2016	2011	Yes, mandatory (MRI/CT)	Only treated, stable BM	Brain scanning every 12 weeks	IC-TTP. IC-PD and IC-DCR (after 12−24 weeks, evaluated post hoc)	RECIST V1.1	No	22.6 %	ITT population: 15 % (51/343) IC-PD, median IC-TTP not reached for crizo, 17.8 m for chemo. Treated BM at baseline (tBM): 27 % (21/79)IC-PD, median IC-TTP 15.7 vs 12.5 m (crizo vs chemo). No BM at baseline: 11 % (30/263) IC-PD, median IC-TTP nr.	yes
NCT01154140 (Takeda et al., 2013; Wolf et al., 2020)					Presence of BM stratification factor				Crizo non statistically significant improvements in IC-TTP (ITT population HR 0.60 (p = 0.069); tBM present: HR 0.45 (P = 0.063); BM absent: HR 0.69 (p = 0.323) IC DCR: tBM at 12 weeks 85 % vs 45 % (p=<0.001), 24weeks 56 % vs 25 % (p = 0.006)	
J-ALEX, alectinib, Lancet 2017 AND Lung cancer 2018	2013	Not mentioned	Stable, treated, or asymptomatic (untreated) BM	Not mentioned	IC-TTP in patients with BM at baseline; time to onset of BM in patients without BM at baseline	RECIST v1.1	No	22.7 %	BM-TTP (BM at baseline) HR 0.19	Not mentioned
JapicCTI-132,316 (Solomon et al., 2014; Hida et al., 2017)					Presence of BM not a stratification factor				Time to onset of BM (no BM at baseline) HR 0.51	
									1-year CIRs of CNS PD 16.8 % vs 5.9 % (crizotinib vs alectinib)	
AURA, osimertinib,	2014	Yes, only if clinically indicated (brain imaging)	Stable, treated or asymptomatic (untreated) BM	Every 6 weeks if BM are present at baseline, with same modality as baseline	Predefined subgroup analyses; Duration of PFS	RECIST v1.1	No	34.4 %	Osimertinib vs chemotherapy	Not mentioned
N Eng J Med 2017 AND J Clin Oncol 2018 NCT02151981 (Nishio et al., 2018; Mok et al., 2017)					Presence of BM not a stratification factor at baseline				CNS ORR 70 % vs 31 %	
									Median DOR 8.9 m vs 5.7 m Median CNS PFS 11.7 m vs 5.6 m	
Alex, alectinib, N Eng J Med 2017 and Ann Oncol 2018	2014	Yes, mandatory (brain imaging)	Treated and stable, or Asymptomatic (untreated) BM or LMD.	Every 8 weeks with MRI	Time to CNS progression, rate of CNS response, Duration of CNS response presence of CNS mets Stratification factor	RECIST v1.1 AND RANO	No	40.3 %	Endpoints alectinib vs crizo	yes

(*continued on next page*)

Table 2 (*continued*)

Trial, drug, journal, year of publication, trial register number	Year of start enrollment	Baseline screening for CNS mets	CNS mets eligible	FU brain imaging	CNS endpoints	Evaluation of CNS	CNS Primary endpoint Yes/No	% of pts with CNS mets included	CNS results endpoint	Continuation study drug allowed upon CNS PD only
NCT02075840 (Gadgeel et al., 2018; Wu et al., 2018)									Time to CNS PD in pts with CNS metastases; HR 0.18, in pts without CNS metastases at baseline HR 0.14 Event of CNS PD 12 % vs 45 %. 12 m CIR of CNS PD in pts with CNS metastases at baseline 16 vs 58.3 %, in pts without CNS mets at baseline 4.6 vs 31.5 % CNS ORR (BM at baseline) 81 % vs 50 %.	
ASCEND-4, ceritinib, Lancet, 2017	2013	Yes, mandatory (MRI/CT brain)	Treated, stable or asymptomatic (untreated).	If BM present at baseline, follow up imaging (CT or MRI) every 6 weeks until 33 weeks and every 9 weeks thereafter	Overall IC-RR, IC-DCR, IC-DOR; IC clinical benefit rate, presence of BM is stratification factor	Modified RECIST v1.1	No	32.2 %	Median IC-DOR 17.3 m vs 5.5 m BM at baseline ceritinib: 31/59 PD (48 % IC only, 42 % EC only, 10 % both.) In pt without BM ceritinib: 81/130 PD, 30 % IC only, 69 % EC only, 1 % both Median PFS BM+10.7 m vs 6.7 m (HR 0.70) Overall IC-RR: BM + 72.7 % in ceritinib and 27.3 % in chemo. Median IC-DOR 16.6 m in ceritinib group. IC clinical benefit rate at 24 weeks or longer was 86.4 % vs 50 % (ceretinib vs chemo)	Yes
NCT01828099 (Peters et al., 2017)										
ASCEND-5, ceritinib, Lancet, 2017	2013	Yes, mandatory (MRI/CT brain)	Treated, stable or asymptomatic (untreated) CNS mets.	Brain imaging (CT or MRI) every 6 weeks (if BM at baseline, history of BM or clinically indicated) until 18 months and every 9 weeks thereafter	IC-RR, IC-DCR, IC-DOR	Modified RECIST v1.1	No	58 %	BM at baseline median PFS 4.4 m vs 1.5 m; HR 0.54 Ceritinib (BM+); 68 % PD, 51 % IC PD only, 41 % only EC PD and 7% both.	Not mentioned
NCT01828112 (Solomon et al., 2016)					Presence of BM is Stratification factor				Ceritinib (BM-): 62 % PD, 15 % only IC PD, 85 % EC PD only Chemo (BM+): 45 (76 %) of 59 pts progressed, with 30 (67 %) of 45 progressing in the brain. chemo (BM-), 39 (68 %) of 57 pts progressed. Of these 39 pts, 4 (10 %) had IC PD only, 32 (82 %) had EC PD only, and 3 (8%) had both. Overall IC-RR 35 % vs 5% Median IC-DOR 6.9 m (ceritinib)	
ALTA-1 L, brigatinib, N Eng J Med, 2018	2016	Yes, mandatory (MRI)	Treated or asymptomatic untreated and treated BM	Every 8 weeks MRI brain	IC-ORR	Modified RECIST criteria	No	29 %	BM + IC-ORR 78 % briga and 29 % crizo.	Yes

(*continued on next page*)

Table 2 (*continued*)

Trial, drug, journal, year of publication, trial register number	Year of start enrollment	Baseline screening for CNS mets	CNS mets eligible	FU brain imaging	CNS endpoints	Evaluation of CNS	CNS Primary endpoint Yes/No	% of pts with CNS mets included	CNS results endpoint	Continuation study drug allowed upon CNS PD only
NCT02737501 (Shaw et al., 2017)					Presence of BM at baseline stratification factor				IC-OR 83 % briga vs 33 % crizo. 9% in briga group and 33 % in crizo group had IC-PD as the first site of PD(alone or with systemic PD). BM-: 1% (briga) vs 5% (crizo) had IC-PD Estimated rate of 12 m survival without IC-PD BM + 67% (briga) vs 21% (crizo). In ITT group 79% (briga) vs 61 % (crizo)	
ALESIA, alectinib, Lancet Respir Med, 2019	2016	Yes, mandatory (MRI)	Treated or asymptomatic untreated and treated BM, LMD included	Every 8 weeks untill disease progression with brain MRI	Time to CNS progression, % of pts with CNS ORR, CNS DOR	RECIST v1.1 and RANO	no	33 %	CNS ORR 73 % (alectinib) vs 22 % (crizo)	Pts with asymptomatic disease progression in the CNS were permitted to continue study drug after disease progression
NCT02838420 (Soria et al., 2017)					CNS metastases at baseline stratification factor				PD CNS 10 % (alectinib) vs 36 % (crizo)(cause specific HR 0.14) Median DOR crizo/alectinib 3.7 months /NE	
RELAY; Ramucirumab Lancet Oncol, 2019	2016	Yes, mandatory (MRI)	CNS mets	Imaging of CNS if clinically indicated	Time to diagnosis of CNS mets	RECIST v1.1	No	0%	Analysis not done because only ten events	Not mentioned
NCT02411448 (Zhou et al., 2019)					Presence of CNS mets not a stratification factor					
ALTA 2; Brigatinib J Thorac Oncol 2017 + 2020	2017	Yes, mandatory (MRI)	Asymptomatic BM included	Brain MRI every 8 weeks in patients with CNS metastases at baseline	IC-PFS, IC-ORR	RECIST v1.1	No	69 %	IC-ORR briga 90 mg 50 % briga 180 mg 67 %. Median IC-DOR briga 90 mg 9.4 months, briga 180 mg 16.6 months. Median IC-PFS 18.4 months	
NCT02094573 (Nakagawa et al., 2019; Kim et al., 2017)					CNS mets is stratification factor					

Abbreviations: CNS; central nervous system, mets: metastases; v: version; BM; brain metastases, LM; leptomeningeal, LMD; leptomeningeal disease, PD; progressive disease, MRI; magnetic resonance imaging, CT; computed tomography, IC; intracranial, EC; extracranial, TTP; time to progression, DCR; duration of cranial response, PFS; progression free survival, RR; response rate, DOR; duration of response; ORR; objective response rate, ITT; intention to treat, crizo; crizotinib, chemo; chemotherapy, briga; brigatinib, m; months, HR; hazard ratio, NE; not evaluable, CIRs; cumulative incidence rates, Pts; patients, RECIST; response evaluation criteria in solid tumors, RANO; response assessment in neuro-oncology.

radiotherapy/surgery] allowed with continuation of the systemic study drug, if a patient progresses only intracranially). For trials evaluating ICI, separate criteria have been developed as with ICI pseudoprogression can occur (Seymour et al., 2017). The FDA recently (2021) also published a guidance document on how to assess patients with CNS metastases in clinical drug trials. They also endorsed the importance of the bi-compartmental model, as described above. Furthermore, they advised to describe all prior CNS-directed treatments and specify at least one appropriate stratification factor, to incorporate baseline CNS screening (preferably with gadolinium-contrast MRI), to apply standard response criteria, and to prespecify appropriate endpoints (US Food and Drug Administration, 2021).

This review showed that in most of the trials no recommendations were given for the treatment of CNS oligoprogression (e.g. whether local treatment with continuation of study drug was allowed), although this oligoprogression frequently occurs especially with the first generation TKI, but also with the next generation TKI and ICI (Gadgeel et al., 2018; Takeda et al., 2013; Solomon et al., 2016; Shaw et al., 2017; Camidge et al., 2018b; Schmid et al., 2019; Rheinheimer et al., 2020; Goldberg et al., 2020).

A possible limitation of this review is that we did not search other electronic databases, or conference proceedings. Therefore, completed but not fully published trials will not have been identified and this could have introduced bias in the results. However, as we aimed to evaluate detailed trial design criteria and outcomes, it is expected that these data could not have been extracted from abstract publications.

Moreover, our search for full publications was executed in November 2020. Most of the recently published trials started enrolling several years ago (latest 2017, i.e. the protocols were written even before 2017). Several of the next generation TKI trials, and the newer ICI trials have not been published yet. This could be a possible explanation for not identifying a higher percentage of mandatory baseline screening. Possibly, currently enrolling trials have more mandatory screening, broadened eligibility criteria and more specified CNS related endpoints. Therefore, it would be interesting to evaluate in the future whether mandatory screening increased and whether eligibility and CNS related endpoints were better defined in these trials. Last, we did not include single arm phase I/II trials evaluating TKI for patients with NSCLC and an oncogenic driver, while some TKI for rare drivers are approved upon completions of these early phase trials (Solomon et al., 2018; Paik et al., 2020; Drilon et al., 2020; Planchard et al., 2017; Wolf et al., 2020). In all these trials BM were eligible if asymptomatic (including untreated) or stable when treated (Solomon et al., 2018; Paik et al., 2020; Drilon et al., 2020; Planchard et al., 2017; Wolf et al., 2020).

5. Future directions and conclusion

Our systematic review clearly shows the need for improving and harmonizing CNS related eligibility criteria and the specification of CNS related endpoints.

Future trials should not only be designed according to the RANO recommendations (Camidge et al., 2018a; Lin et al., 2015), and include prespecified CNS related endpoints, but also prespecify specific actions that are allowed upon CNS oligoprogression should be addressed. Furthermore, although outside of the scope of this review, the best sequence of treatments (systemic treatment followed by local CNS treatment upon CNS progression versus CNS local treatment followed by systemic therapy) should be evaluated, as well as the clinical efficacy and toxicity of local treatments concurrent with systemic treatments. Last, as the 5-year survival rate is improving, prolonged low grade CNS related toxicity, and long-term CNS toxicity should be considered.

Authorship

As is clear from the author contributions above, all authors made substantial contributions to the following (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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Author contributions

J Schoenmaekers: conceptualization, data curation, formal analysis, investigation, methodology, resources, software, project administration, writing original draft.

S Dursun: data curation, formal analysis, investigation, resources, review and editing.

S Biesmans: data curation, investigation, resources.

D De Ruysscher: investigation, resources, validation, review and editing.

M Broen: investigation, resources, validation, review and editing.

J Remon: investigation, resources, validation, review and editing.

A Dingemans: conceptualization, formal analysis, investigation, methodology, resources, supervision, validation, visualisation, writing original draft, review and editing.

L Hendriks: conceptualization, data curation, formal analysis, investigation, methodology, resources, supervision, validation, visualisation, writing original draft, review and editing.

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Appendix A. Supplementary data

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J. Schoenmaekers pulmonologist, specialized in thoracic oncology with a special interest in brain metastases.

S. Dursun pulmonologist, specialized in thoracic oncology with a special interest in brain metastases.

C. Biesmans medical student, in training to become a physician-researcher.

D. De Ruysscher radiation oncologist, specialized in thoracic oncology (professor), special interest in brain metastases and their treatment, including neurocognitive complications.

M. Broen neurologist, main interest brain metastases and primary brain tumors and their treatment, and neurocognition.

J. Remon medical oncologist, specialized in thoracic oncology, special interest in brain metastases and their treatment (mainly TKI and ICI).

A. Dingemans pulmonologist, specialized in thoracic oncology (professor), main interested targeted therapies.

L. Hendriks pulmonologist, specialized in thoracic oncology and brain metastases treatment (including neurocognitive complications).