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Exclusion of Patients with Brain Metastases From Early-Phase Systemic Therapy Trials: A Cross-Sectional Analysis of Eligibility Criteria

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Abstract

PURPOSE

Patients with brain metastases (BrM) are frequently excluded from early-phase clinical trials, limiting evaluation of central nervous system (CNS) efficacy of novel therapies. We aimed to determine the proportion of phase I systemic therapy trials for metastatic solid tumours that exclude patients with BrM.

METHODS

ClinicalTrials.gov was systematically searched in July 2024 using the term “cancer.” Phase I trials evaluating systemic therapies for advanced solid tumours, with publicly available protocols, were included. Trial characteristics and BrM eligibility criteria were independently abstracted by four reviewers.

RESULTS

Of 3,210 identified studies, 1,752 met inclusion criteria, and 873 trials were analysed. Lung cancer, breast cancer, and melanoma trials comprised 12.6%, 7.6% and 4.4% of studies, respectively, while 58.5% enrolled mixed tumour types. Investigational therapies included cytotoxic chemotherapy (5.0%), targeted therapy (15.0%), immunotherapy (43.8%), and combination regimens. Patients with BrM were eligible with stipulations in 70.3% of trials and excluded in 13.2%; BrM eligibility was unspecified in 16.5% of studies. Among trials permitting BrM enrolment (n = 614), patients with symptomatic (58.5%), active/unstable (84.0%), and previously untreated (75.9%) BrM were frequently excluded. Trials initiated between 2015 and 2019 more frequently permitted enrolment of patients with BrM than those initiated between 2010 and 2014 (72.8% vs. 66.2%). Cytotoxic chemotherapy trials more commonly excluded patients with BrM than targeted therapy or immunotherapy trials.

CONCLUSION

Inclusion of patients with BrM in phase I trials has improved over time, particularly when the investigational products involve immunotherapy and/or targeted therapies. However, restrictive eligibility criteria for symptomatic, untreated and/or active/unstable BrM remain common.

INTRODUCTION

Brain metastases (BrM) are a frequent and devastating neurological complication of metastatic malignancies, including melanoma, breast, and lung cancers [1, 2], and are associated with substantial neurologic morbidity and poor survival [3, 4]. Neurological manifestations, including increased intracranial pressure, seizures, and cognitive dysfunction, are common across tumour types and contribute to impaired quality of life and shortened survival; among patients with breast cancer BrM, for example, up to 80% have neurological symptoms at diagnosis [5]. Despite significant morbidity and mortality, patients with BrM remain underrepresented in clinical trials, raising concerns regarding the generalisability of trial findings to real-world populations [6, 7]. Although advances in targeted therapies and immunotherapy have improved systemic control, extended extracranial survival has correspondingly increased the opportunity for intracranial progression [1, 2]. Improvements in neuroimaging and surveillance

strategies have further contributed to increased detection of intracranial disease, including smaller or asymptomatic BrM that may previously have gone undiagnosed [2, 6].

Historically, patients with BrM have frequently been excluded from cancer clinical trials due to concerns regarding limited life expectancy, perceived risk of central nervous system (CNS) complications, and inadequate penetration of investigational agents across the blood-brain barrier [2, 6, 8]. However, the development of increasingly CNS-active systemic therapies has challenged these assumptions, with increasing evidence demonstrating meaningful intracranial activity in selected patients with BrM [2, 8, 9]. Despite these advances, clinical trial eligibility criteria frequently restrict enrolment to patients with “stable”, “treated”, or “asymptomatic” BrM [8, 10, 11, 12], often without standardised definitions [6, 13].

The FDA and ASCO–Friends of Cancer Research have both called for broader inclusion of patients with BrM in clinical trials [7, 8]. Characterising BrM inclusion in early-phase trials is particularly important, as initial signals of intracranial safety and efficacy may emerge and inform the design of future phase II/III trials [6, 7].

Prior analyses have characterised BrM eligibility in registrational trials [6], lung-cancer trials [10], and mixed-phase populations [9]. To our knowledge, no prior study has systematically described the granular protocol-level architecture of phase I trials, including corticosteroid thresholds, restrictions in the use of antiseizure pharmacotherapy, and specifications of radiographic stability. We sought to catalogue these criteria across phase I trials of systemic therapies for patients with advanced solid tumours and to characterise the gap between nominal inclusion and operational access.

METHODS

We conducted a cross-sectional analysis of the ClinicalTrials.gov database, searched in July 2024. The search term “cancer” was queried with the following filters applied: study type, “interventional studies”; phase, “early phase 1” and “phase 1”; and study results, “studies with results.” Terminated trials were excluded at the database filter stage. Trials were subsequently screened to exclude those enrolling patients with haematologic malignancies, primary brain tumours, and interventions not evaluating anticancer efficacy. Trials registered between January 1, 2000, and June 30, 2024 that investigated a systemic therapy for patients with advanced solid tumours (unresectable, recurrent, locally advanced, refractory stage 3, or stage 4 disease) were included. Studies focused on leptomeningeal carcinomatosis in the absence of parenchymal BrM were excluded. For small cell lung cancer trials, extensive stage disease was classified as stage IV to maintain uniformity across data abstraction.

Where publicly available on ClinicalTrials.gov, full trial protocols were retrieved; trials without an accessible protocol were excluded from the final analysis. When multiple protocol versions existed, the most recent version accessible at the time of data abstraction was reviewed. Eligibility criteria related to BrM were abstracted directly from protocol inclusion and exclusion criteria, including any protocol-specific definitions or treatment restrictions pertaining to intracranial disease, corticosteroid use, antiseizure use, or prior brain-directed therapy. Trials that did not explicitly reference BrM within eligibility criteria were categorised as “not mentioned”. Abstraction was performed independently by two of four reviewers per trial (ND, EC, EZ, MK), with discrepancies resolved by a third reviewer (CZ). A standardised data collection instrument was developed prior to study initiation to ensure consistency across reviewers; in cases of ambiguous eligibility criteria, consensus was reached through discussion with senior study investigators (KJJ).

Abstracted variables included trial characteristics (location, cancer type, and investigational agent class) and BrM-specific eligibility parameters, including criteria related to symptomatic disease, leptomeningeal metastatic disease,

prior brain-directed therapy, radiographic stability, corticosteroid use, and antiseizure use; specific definitions and thresholds are reported in Results. We defined complete exclusion as protocol language explicitly disallowing enrolment of any patient with BrM, and conditional eligibility (or eligibility with stipulations) as protocols permitting enrolment of patients with BrM provided that one or more additional criteria were met (e.g., stable disease, prior local therapy, absence of symptoms, corticosteroid restrictions).

Categorical variables were expressed using frequency counts and percentages. A Chi-square goodness-of-fit test was used to examine the equality of proportions of inclusion or exclusion of patients with BrM across categories of each characteristic. A significant result indicates that the observed category proportions deviate from equal proportions. A two-sided p-value of less than 0.05 was considered statistically significant. All analyses were performed in R (version 4.4.1).

RESULTS

Trial Characteristics and Trends

An initial inquiry yielded 3,210 trials, of which 1,752 met inclusion criteria and 873 with available protocols were analysed. Trial characteristics are summarised in Table 1. Lung cancer (12.6%, n = 110), breast cancer (7.6%, n = 66), and melanoma (4.4%, n = 38) trials each accounted for a minority of studies, while genitourinary (GU) trials (17.0%, n = 148) and mixed tumour types (58.5%, n = 511) were more common. The majority of trials were registered after 2015 (72.9%, n = 636), evaluated immunotherapy as the investigational agent class (43.8%, n = 382), and were conducted in North America (63.0%, n = 552).

Table 1
Trials characteristics regarding the inclusion/exclusion/not mentioned of patients with brain metastasis in phase I trials, n = 873

Characteristic	Categorization	n = 873 No. (%)[1]	BrM included n = 614 (70.3%) No. (%)[1]	P-value[2]	BrM excluded n = 115 (13.2%) No. (%)[1]	P-value[2]	Not mentioned n = 144 (16.5%) No. (%)[1]
Study Start Year	2000–2004	2 (0.2)	1 (0.2)	< 0.001	0	< 0.001	1 (0.7)
	2005–2009	25 (2.9)	15 (2.4)		4 (3.5)		6 (4.2)
	2010–2014	210 (24.1)	139 (22.6)		32 (27.8)		39 (27.1)
	2015–2019	562 (64.4)	409 (66.6)		76 (66.1)		77 (53.8)
	2020 onwards	74 (8.5)	50 (8.14)		3 (2.6)		21 (14.6)
	Breast	66 (7.6)	48 (7.8)	< 0.001	5 (4.3)	< 0.001	13 (9.0)
	GU	148 (17.0)	76 (12.4)		39 (33.9)		33 (22.9)
Cancer Type	Lung	110 (12.6)	96 (15.6)		4 (3.5)		10 (6.9)
	Melanoma	38 (4.4)	33 (5.4)		1 (0.9)		4 (2.8)
	Any	511 (58.5)	361 (58.8)		66 (57.4)		84 (58.3)
Investigational Agent	Cytotoxic chemotherapy	44 (5.0)	18 (2.9)	< 0.001	14 (12.2)	< 0.001	12 (8.3)
	Targeted therapy	131(15.0)	87 (14.2)		14 (12.2)		30 (20.8)
	Immunotherapy	382 (43.8)	291 (47.4)		40 (34.8)		51 (35.4)
	Chemo + Targeted Therapy	56 (6.4)	36 (5.9)		7 (6.1)		13 (9.0)
	Chemo + immunotherapy	142 (16.3)	97 (15.8)		24 (20.9)		21 (14.6)
	Combination of chemo/immunotherapy	74 (8.5)	63 (10.3)		9 (7.8)		2 (1.4)
	Other systemic therapies	44 (5.0)	22 (3.6)		7 (6.1)		15 (10.4)
Location[3]	Asia	47 (5.4)	38 (6.2)	< 0.001	7 (6.1)	< 0.001	2 (1.4)
	Europe	53 (6.1)	31 (5.0)		6 (5.2)		16 (11.1)
	North America	552 (63.0)	361 (58.8)		85 (73.9)		106 (73.6)

Characteristic	Categorization	n = 873 No. (%)[1]	BrM included n = 614 (70.3%) No. (%)[1]	P-value[2]	BrM excluded n = 115 (13.2%) No. (%)[1]	P-value[2]	Not mentioned n = 144 (16.5%) No. (%)[1]
	Oceania	2 (0.2)	1 (0.2)		0		1 (0.7)
	Intercontinental	170 (19.5)	145 (23.6)		14 (12.2)		11 (7.6)
	Not Mentioned	49 (5.6)	39 (6.4)		3 (2.6)		7 (4.9)

[1] Column percentages.

[2] P-value corresponds with a Chi-square goodness-of-fit test.

[3] P-value calculated based on studies with known location.

Restrictive BrM Eligibility Criteria Persist Across Phase I Trial Protocols

Patients with BrM were completely excluded in 13.2% (n = 115/873) and eligible with stipulations in 70.3% (n = 614/873) of trials; inclusion criteria related to BrM were not specified in 16.5% (n = 144/873) of trials (Table 1). The exclusion of patients with BrM occurred less frequently in trials for lung cancer (3.5%), breast cancer (4.3%), and melanoma (0.9%), compared to genitourinary trials (33.9%) (Table 1, Fig. 2). Recent trials (2015–2019 and 2020 onward) were more likely to include patients with BrM compared to trials conducted between 2010–2014 (72.8% and 67.6% vs. 66.2%) (Fig. 1). Among trials with eligibility stipulations for patients with BrM, immunotherapy trials were most likely to include patients with BrM (47.4%, n = 291/614), followed by chemotherapy plus immunotherapy (15.8%, n = 97/614) and targeted therapy (14.2%, n = 87/614) (Table 1, Fig. 3). Trials testing cytotoxic chemotherapy were least likely to include patients with BrM (2.9%, n = 18/614). Trial inclusion of patients with BrM differed significantly by study era, cancer type, investigational agent class, and trial location (all $p < 0.001$). Trials conducted across multiple continents (85.3%) and those based exclusively in Asia (80.9%) more frequently permitted enrolment of patients with BrM than trials conducted in North America (65.4%) or Europe (58.5%). Most trials did not address the population of patients with leptomeningeal metastatic disease (63.6%, n = 555/873); however, 33.7% (n = 294/873) of trials excluded patients with leptomeningeal disease and a small minority explicitly allowed their inclusion (2.7%, n = 24/873).

Although 70.3% (n = 614/873) of trials nominally permitted enrolment of patients with BrM, most imposed restrictive criteria excluding symptomatic, untreated, and/or active/unstable disease (Table 2). Among these 614 trials, 58.5% (n = 359/614) excluded patients with symptomatic BrM; notably, none of the protocols in our analysis provided objective, symptom-based definitions to support this criterion. An additional 34.2% (n = 210/614) did not address symptomatic status within eligibility criteria (Table 2). Similarly, 84.0% (n = 516/614) excluded patients with active, unstable, or progressing disease; of these trials, 38.3% (n = 235/614) required more than four weeks of radiographic stability prior to enrolment, while 4.2% (n = 26/614) required four weeks or less (range: 1 week to 1 year) (Table 2). Only six trials (1.0%, n = 6/614) explicitly permitted enrolment of patients with active or progressing BrM. Most trials (75.9%, n = 466/614) excluded patients with previously untreated BrM (Table 2).

Corticosteroid and Antiseizure Use Frequently Restrict Enrolment of Patients with BrM

Among the 614 trials conditionally permitting BrM enrolment, 19.2% (n = 118/614) completely excluded patients receiving corticosteroids, 53.7% (n = 330/614) applied conditional criteria regarding steroid use, and 27.0% (n = 166/614) did not address steroid use (Table 2). Among trials with conditional steroid criteria, 86.4% (n = 285/330) mandated timing requirements; of these, 98.2% (n = 280/285) excluded patients who had received steroids within four weeks of trial commencement, while the remaining 1.8% (n = 5/285) excluded use beyond four weeks. Antiseizure use was not permitted in 9.3% (n = 57/614) of trials, was permitted with restrictions in 8.6% (n = 53/614) and not addressed in 82.1% (n = 504/614) of trials (Table 2). Among trials that permitted antiseizure use with stipulations (n = 41), timing restrictions were most common (75.6%, n = 31/41); 87.1% (n = 27/31) excluded antiseizure use within four weeks of trial commencement, and 12.9% (n = 4/31) excluded use beyond four weeks.

Table 2
Trials characteristics among the eligible patients with brain metastasis in phase I trials, n = 614

Characteristic	No. (%)
Symptomatic Exclusion	
Yes, excluded if they have symptomatic disease	359 (58.5)
No, no symptomatic criteria	45 (7.3)
Not Mentioned	210 (34.2)
Previous treatment for BrM	
Yes, no previous treatment for BrM and excluded from trial	466 (75.9)
No, no previous treatment for BrM and included in trial	34 (5.5)
Not Mentioned	114 (18.6)
Active, Unstable, or Progressing BrM	
Yes, patients with Active/Unstable/Progressing BrM are excluded from trial	516 (84.0)
No, patients with Active/Unstable/Progressing BrM are included in trial	6 (1.0)
Not Mentioned	92 (15.0)
Stability Timeline Requirement	
$\leq$4 Weeks	26 (4.2)
> 4 Weeks	235 (38.3)
NA	353 (57.5)
BrM at Initial Diagnosis	
Yes, patients with BrM at initial diagnosis were excluded from trial	2 (0.3)
No, patients with BrM at initial diagnosis were included in trial	0
Not Mentioned	612 (99.7)
Complete Steroid Exclusion	
Yes, any use of steroids is strictly forbidden, not enrolled in trial	118 (19.2)
No, either conditional or allowed all together in trial	330 (53.7)
Not Mentioned	166 (27.0)
Conditional Steroid Exclusion	
Yes, patients on steroids are conditionally allowed into trial	328 (53.4)
No, no conditional criteria for steroids	120 (19.5)
Not Mentioned	166 (27.0)
Steroid Timing	

Characteristic	No. (%)
Symptomatic Exclusion	
≤4 Weeks	280 (45.6)
> 4 Weeks	5 (0.8)
NA	329 (53.6)
Complete Antiseizure Medication Exclusion	
Yes, any use of antiseizure medication is strictly forbidden, not enrolled	57 (9.3)
No, either conditional or allowed all together in trial	53 (8.6)
Not Mentioned	504 (82.1)
Antiseizure Medications Conditionally Excluded	
Yes, patients on antiseizure medications are conditionally allowed into trial	41 (6.7)
No, no conditional criteria for antiseizure medication	69 (11.2)
Not Mentioned	504 (82.1)
Antiseizure Medication Timing	
≤ 4 Weeks	27 (4.4)
> 4 Weeks	4 (0.7)
NA	583 (95.0)

DISCUSSION

Most phase I trial protocols nominally permitted enrolment of patients with BrM; however, eligibility was frequently restricted. This pattern of restrictive conditional eligibility was not uniform across cancer types. Genitourinary trials were more likely to exclude patients with BrM than trials in lung cancer, breast cancer, or melanoma, a pattern that may reflect the lower incidence of intracranial metastases among patients with genitourinary malignancies, particularly those with prostate and bladder cancers [14, 15]. In addition, protocols commonly invoked terms such as “symptomatic,” “active,” or “progressing” without objective clinical definitions. Together, these findings suggest that formal inclusion may mask functional exclusion. Notably, the 34.2% of trials permitting conditional enrolment of patients with BrM did not address symptomatic status at all. In the absence of explicit guidance, investigators may default to conservative decisions, such that silence on symptomatic status may function as de facto exclusion in clinical practice. This matters because a substantial proportion of patients with BrM present symptomatically at diagnosis, including approximately 30% of those with melanoma BrM [3] and up to 80% of those with breast cancer BrM [5].

Approximately one in five trials permitting conditional enrolment of patients with BrM completely excluded patients requiring corticosteroids. The vast majority of trials that limited participation based on corticosteroid use required that steroids be discontinued for at least four weeks prior to trial enrolment. Given that corticosteroids are central to the management of neurologic symptoms among patients with BrM [16], such restrictions may functionally exclude a

substantial proportion of patients in the real-world setting. Similar restrictions were frequently imposed for antiseizure use, with the most common time period for exclusion being the use of antiseizure medication within 4 weeks of trial enrolment, a time period which is often prohibitory when considering enrolment in an early-phase clinical trial.

CIMARa is an international group of clinician investigators actively working to develop consensus definitions and standardised terminology for BrM subgroups, including objective criteria for “symptomatic” disease and thresholds for including patients requiring supportive pharmacotherapy in clinical trials [1]; in the meantime, definitional variability across existing trials limits cross-study interpretation. For example, CheckMate 204, a phase II study evaluating combined nivolumab and ipilimumab in melanoma BrM, demonstrated intracranial response rates of 53.5% versus 16.7% in the asymptomatic versus symptomatic cohort, underscoring the prognostic importance of symptom status classification [17, 18]. In contrast, the TRICOTEL study operationalised symptomatic disease using explicit clinical and treatment-based criteria, including seizures, headache, neurologic deficits, corticosteroid exposure, and antiseizure use, illustrating that standardised definitions are feasible in prospective trial design [19].

Prior analyses of phase III clinical trials have shown that a substantial proportion of studies in lung cancer, breast cancer, and melanoma exclude patients with BrM or permit conditional enrolment [12, 13], suggesting that restrictive practices persist across phases of drug development. The justification for these practices, however, has been challenged by direct safety data. An analysis of 1,181 oncology patients enrolled in phase I clinical trials, including 93 with BrM, demonstrated that although BrM patients had shorter survival and lower response rates compared to patients without BrM, there was no significant difference in time-to-treatment failure or grade 3 and 4 toxicity, including neurologic toxicities [20]. ASCO published recommendations in 2017 advocating for strategies to improve BrM inclusion, including dedicated expansion cohorts and tailored dose-limiting toxicity criteria [7]. Our findings of increased BrM permissiveness in more recent trials is consistent with a 2012–2022 time-series analysis showing that the proportion of phase I–III trials not excluding BrM rose from 11.5% to 17.3% in the post-recommendation period, though industry-sponsored trials showed less pronounced change [9]. Recent analyses of lung cancer clinical trials have similarly demonstrated persistent exclusion of patients with active BrM and leptomeningeal disease despite evolving ASCO and FDA recommendations [10].

As systemic therapies have improved extracranial disease control, more patients live long enough to develop intracranial progression. For example, among patients with metastatic HER2-positive or triple negative breast cancer at least one-third develop BrM during their lifetime [21], expanding the population in whom BrM eligibility criteria carry clinical relevance [15, 22]. For HER2-positive metastatic breast cancer, intracranial efficacy of small molecule tyrosine kinase inhibitors such as tucatinib [23] and antibody drug conjugates like trastuzumab deruxtecan [24] provides reassurance that systemic therapy has potential to meaningfully improve outcomes of patients with and without BrM [25].

The value of early-phase BrM inclusion is illustrated by precedent. Early-phase studies of alectinib enrolled patients with BrM and demonstrated meaningful CNS activity [26], generating the rationale for BrM inclusion in subsequent phase III development; the ALEX trial ultimately reported an 81% intracranial overall response rate in patients with measurable CNS disease, an outcome that would have remained uncharacterised had patients with BrM been excluded from early development [27]. Phase I trials therefore represent a critical opportunity to generate early intracranial safety and efficacy signals; inclusion of patients with BrM, even in small well-defined cohorts, may facilitate earlier characterisation of CNS activity and inform the design of subsequent trials, particularly in tumour types with a high BrM incidence [15, 21].

Limitations

This study has several limitations. First, analysis was restricted to trials with publicly available protocols retrieved from ClinicalTrials.gov. Trials whose full protocols were available only through peer-reviewed publications or sponsor websites were not captured, which may have disproportionately affected industry-sponsored studies. Second, eligibility criteria as written may not fully reflect real-world enrolment practices at individual sites. Finally, publicly available protocols may not capture subsequent amendments that alter BrM-specific criteria. Nonetheless, the use of protocol-level data provides a more granular assessment of eligibility criteria than prior registry-based analyses.

CONCLUSION

While formal inclusion of patients with BrM in phase I trials has increased, restrictive and inconsistently defined eligibility criteria continue to limit meaningful participation. Despite formal inclusion in many early phase clinical trials, patients with brain metastases are often unable to participate due to restrictive criteria related to symptomatic disease, corticosteroid use, radiographic stability, and lack of prior brain-directed therapy. Standardisation of BrM-related eligibility criteria across trial phases is required to ensure broader and more representative enrolment of this patient population in early-phase oncology trials. Future efforts to harmonise eligibility criteria will be essential to expand patients' access to investigational therapies and generate the prospective intracranial efficacy data that a growing proportion of patients with BrM now require.

Declarations

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CONFLICT(S) OF INTEREST:

K.J.J. has acted as a consultant and/or adviser of Amgen, AstraZeneca, Apo Biologix, BioCon, Daiichi Sankyo, Eli Lilly, Esai, Genomic Health, Gilead Sciences, Knight Therapeutics, Merck, Myriad Genetics, Novartis, Organon, Pfizer and Roche; and has received research support from AstraZeneca, BioCon, Eli Lilly, and Pfizer. A.S. has acted as a consultant and/or adviser of AstraZeneca, BrainLab, CarboFIX, Cerapedics, Elekta AB, Seagen Inc, Servier and Varian; and has received research grants from BrainLab and Elekta AB and travel support from Elekta AB, BrainLab and Seagen. C.Z., I.F., N.D.S., I.K., E.C., E.Z., M.K., F.T., M.S., M.J.L.F. have no conflicts to report.

ETHICS APPROVAL:

This study involved analysis of publicly available clinical trial protocols registered on ClinicalTrials.gov and did not involve human participants, human tissue, or identifiable patient data. As such, institutional review board approval and informed consent were not required, and no ethics committee review was sought. The study was conducted in accordance with the principles of the Declaration of Helsinki.

HUMAN ETHICS AND CONSENT TO PARTICIPATE:

Not applicable.

CONSENT FOR PUBLICATION:

Not applicable.

DATA AVAILABILITY:

All data generated and analysed in this study are provided within the manuscript and tables. The datasets analysed during this study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS:

Conceptualization – K.J.J., I.F., C.Z.

Methodology – K.J.J., C.Z., N.D.S., F.T.

Data curation – N.D.S., E.C., E.Z., M.K., C.Z.

Formal analysis – F.T., I.F., C.Z.

Writing (original draft) – C.Z., I.K., E.C.

Writing (review & editing) – C.Z., I.F., N.D.S., I.K., E.C., E.Z., M.K., M.S., M.J.L.F., A.S., K.J.J.

Supervision – K.J.J.

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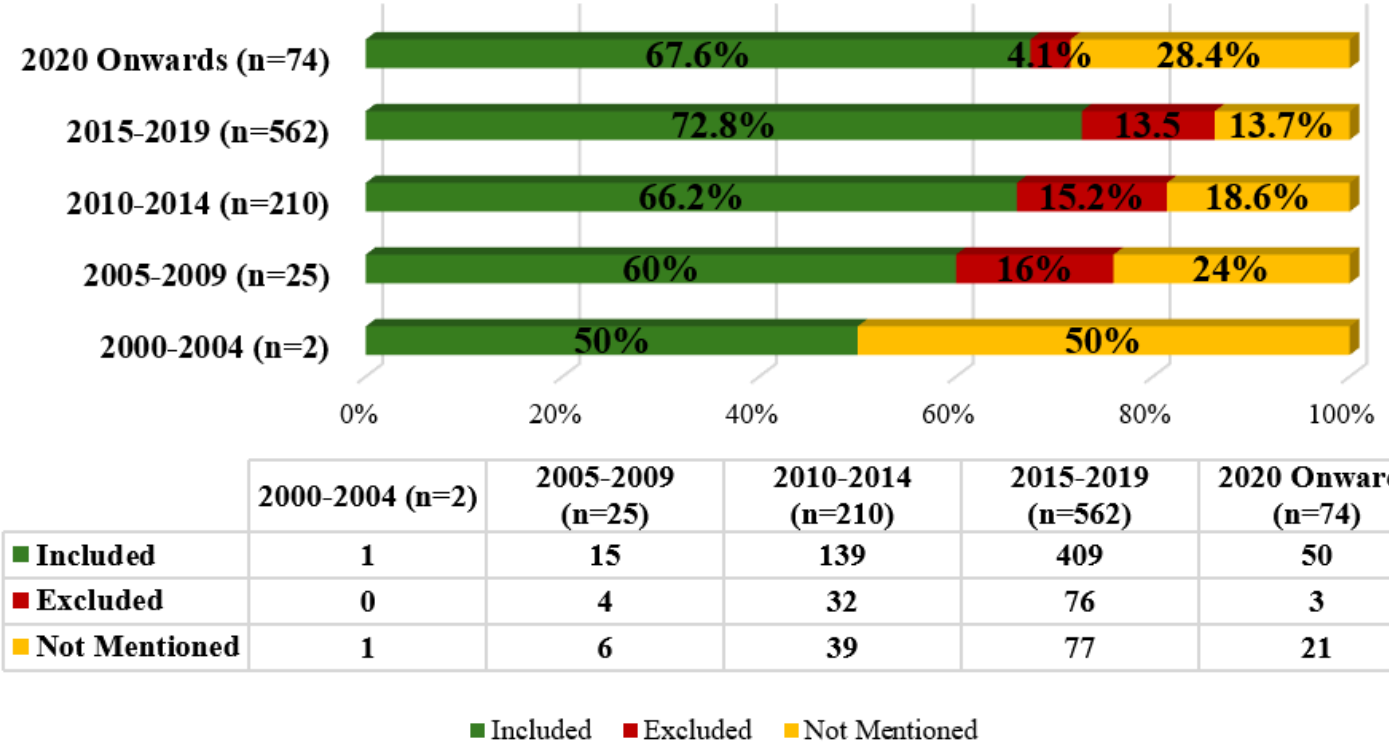
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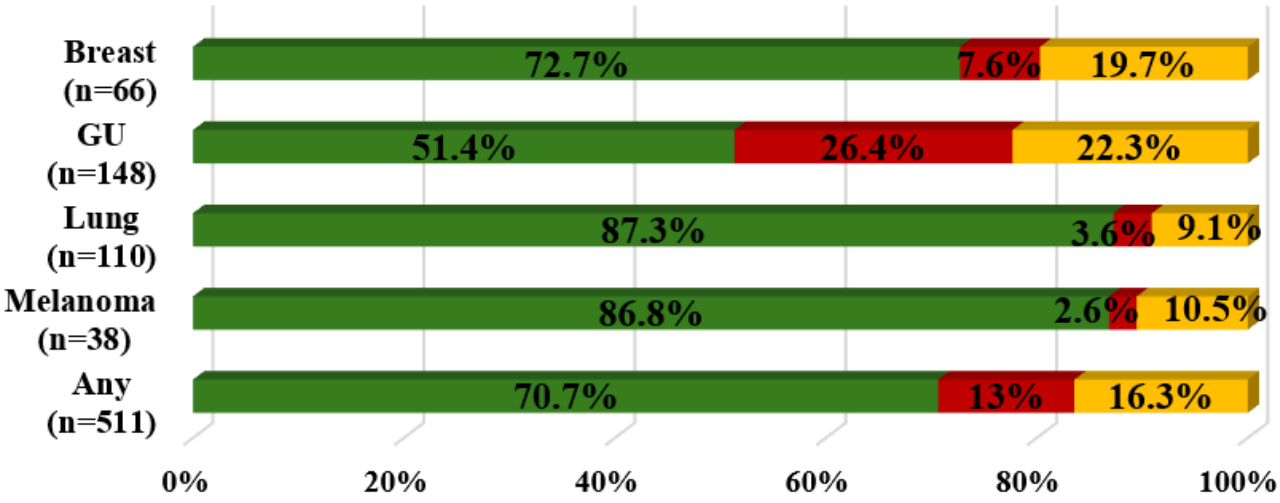
Figures



	2000-2004 (n=2)	2005-2009 (n=25)	2010-2014 (n=210)	2015-2019 (n=562)	2020 Onwards (n=74)
Included	1	15	139	409	50
Excluded	0	4	32	76	3
Not Mentioned	1	6	39	77	21

Figure 1

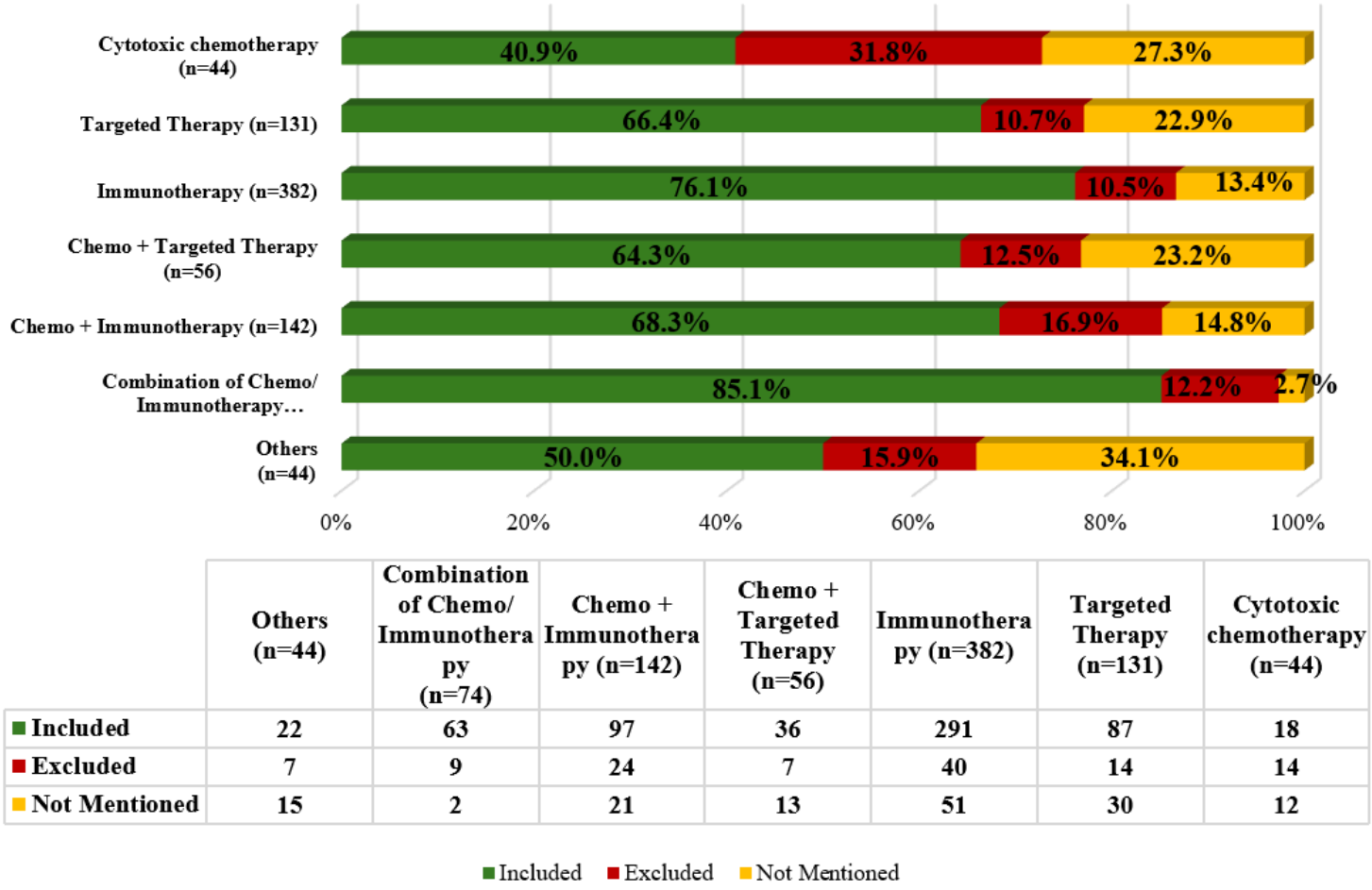
Proportion of phase I trials including, excluding, or not mentioning patients with brain metastases, stratified by study start year (n=873). Each bar represents the percentage of trials within that time period; categories are Included, Excluded, and Not Mentioned.



	Any (n=511)	Melanoma (n=38)	Lung (n=110)	GU (n=148)	Breast (n=66)
Included	361	33	96	76	48
Excluded	66	1	4	39	5
Not Mentioned	84	4	10	33	13

Figure 2

Proportion of phase I trials including, excluding, or not mentioning patients with brain metastases, stratified by cancer type (n=873). Each bar represents the percentage of trials within that cancer type; categories are Included, Excluded, and Not Mentioned.



	Others (n=44)	Combination of Chemo/ Immunotherapy (n=74)	Chemo + Immunotherapy (n=142)	Chemo + Targeted Therapy (n=56)	Immunotherapy (n=382)	Targeted Therapy (n=131)	Cytotoxic chemotherapy (n=44)
Included	22	63	97	36	291	87	18
Excluded	7	9	24	7	40	14	14
Not Mentioned	15	2	21	13	51	30	12

Figure 3

Proportion of phase I trials including, excluding, or not mentioning patients with brain metastases, stratified by investigational agent class (n=873). Each bar represents the percentage of trials within that agent class; categories are Included, Excluded, and Not Mentioned.