Cancer Treatment Reviews 119 (2023) 102586

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Systematic or Meta-analysis Studies

Safety profile of cyclin-dependent kinase (CDK) 4/6 inhibitors with concurrent radiation therapy: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Breast cancer
CDK4/6 inhibitors
Radiotherapy
Toxicity
Systematic review
Meta-analysis

ABSTRACT

The cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) have become the standard of care for hormone receptor-positive (HR +) and human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer, improving survival outcomes compared to endocrine therapy alone. Abemaciclib and ribociclib, in combination with endocrine therapy, have demonstrated significant benefits in invasive disease-free survival for high-risk HR+/HER2- early breast cancer patients. Each CDK4/6i—palbociclib, ribociclib, and abemaciclib—exhibits distinct toxicity profiles. Radiation therapy (RT) can be delivered with a palliative or ablative intent, particularly using stereotactic body radiation therapy for oligometastatic or oligoprogressive disease. However, pivotal randomized trials lack information on concomitant CDK4/6i and RT, and existing preclinical

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https://doi.org/10.1016/j.ctrv.2023.102586
Received 16 May 2023; Received in revised form 9 June 2023; Accepted 10 June 2023
Available online 15 June 2023

and clinical data on the potential combined toxicities are limited and conflicting. As part of a broader effort to establish international consensus recommendations for integrating RT and targeted agents in breast cancer treatment, we conducted a systematic review and *meta*-analysis to evaluate the safety profile of combining CDK4/6i with palliative and ablative RT in both metastatic and early breast cancer settings.

Introduction

The cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) represent the current standard of care as first- or second-line treatment for patients with hormone receptor-positive (HR +) and human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer, demonstrating improved survival outcomes compared to endocrine therapy (ET) alone [1–3]. Moreover, both abemaciclib and ribociclib, when combined with ET, have demonstrated a significant improvement in invasive disease-free survival in patients with HR+/HER2- early breast cancer who are at high risk of recurrence [4]. Palbociclib, ribociclib, and abemaciclib are potent and specific inhibitors of CDK4/6 with a more favourable toxicity profile as compared to non-selective CDKi. The three drugs have a distinct toxicity profile. Neutropenia is the most commonly reported adverse event, observed in up to 80% of women receiving palbociclib or ribociclib, and up to 50% of women receiving abemaciclib. Diarrhoea is more commonly associated with abemaciclib, occurring in up to 80% of cases. Other toxicities include fatigue, nausea, increased liver enzymes, skin toxicities, and venous thromboembolism [1–5].

Radiation therapy (RT) represents one of most widely used local treatment options; it can be delivered both with a palliative or biologically ablative intent, especially using stereotactic body radiation therapy (SBRT) to treat de-novo oligometastatic or oligoprogressive disease [6,7]. The combination of palliative RT and CDK4/6i was only prospectively evaluated in a clinical setting for a subgroup of patients treated in the PALOMA trials [1,5,8], where it was recommended to suspend palbociclib from the day prior to RT, so no information regarding the combination of RT and CDK4/6i was available [1,8]. There are limited and conflicting preclinical and clinical data on the potential synergistic toxicities of RT and CDK 4/6i [9].

As part of the European Society for Radiotherapy and Oncology (ESTRO) Guidelines Committee's consensus recommendations on the integration of RT with targeted treatments for breast cancer, we conducted a systematic review and *meta*-analysis to assess the safety profile of combining CDK4-6i with palliative and ablative RT in both the metastatic and early breast cancer settings.

Materials and methods

Literature analysis and systematic review

A comprehensive literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. Two authors (CB and LV) independently conducted the review using a computer-assisted search of the Medline, Scopus, and Embase databases. The search covered the period from January 1, 2000, to November 1, 2022, as shown in Fig. 1.

A specific research string based on the following keywords was developed: "breast" OR "mammary" OR "breast cancer" OR "breast neoplas*", "radiotherapy", "irradiation", "radiation", "radio-therapy", "concurrent*", "concomitant*", "combin*", "associat*", "simultaneous*", "cyclin-dependent kinase 4/6 inhibitor", "palbociclib", "ribociclib", "abemaciclib". Keywords used were 'breast cancer', 'radiotherapy', 'concurrent', 'cyclin-dependent kinase 4/6 inhibitor', 'Palbociclib','Ribociclib','Abemaciclib'.

The primary endpoint of the present study was safety of the combination RT and CDK4/6i in HR+/HER2- breast cancer patients. Safety was assessed based on the occurrence of toxicities of grade 3 or higher (grade 3 +). Secondary outcomes included evaluating the association between RT and any grade of toxicity, the rate of CDK4/6i dose reduction, and the rate of CDK4/6i treatment discontinuation. In this study, irradiation was considered concomitant if the administration of CDK4/6i occurred within the five half-lives of the respective drugs (5.8 days for palbociclib, 6.7 days for ribociclib, and 3.8 days for abemaciclib).

For the inclusion of studies in the systematic review, specific criteria were applied. Studies were selected if they met the following criteria: (1) they involved cohorts of breast cancer patients with more than five consecutive patients, (2) they investigated the administration of CDK4/6i in combination with either palliative or ablative RT, (3) RT was delivered for intracranial or extracranial disease, (4) the study focused on the adjuvant or metastatic setting. If studies met these inclusion criteria, they were considered for inclusion in the *meta*-analysis. Data extraction was performed independently by two reviewers (CB and LV) to ensure consistency and accuracy. In case of disagreements, a third author (IM) resolved the discrepancies.

In the present study, the proportions of patients experiencing grade 3 + toxicities, both haematological and non-haematological toxicities, were calculated for each individual study. These proportions were then combined into summary proportions using the "metaprop" command in Stata. Prior to pooling, the proportions underwent a Freeman-Tukey double arcsine transformation, which helps to stabilize the variances. After pooling, the summary estimate was back-transformed to its original scale. To calculate the corresponding 95% confidence intervals (CI), the exact method was employed [11]. By means of this approach, proportions can be accommodated that are close or equal to 0%, which was a common occurrence in our data (see Results section). The heterogeneity across studies was quantified using the I^2 statistics, which can be interpreted as the proportion of the total variability of study estimates that is due to actual heterogeneity rather than mere chance. Using the Cochrane risk-of-bias tool for randomised trials (RoB 2) [12] and non-randomised studies (ROBINS-I) [13], risk-of-bias of each study was assessed by two independent reviewers (CB and LV). Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria [14]. Toxicity had to be either graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), or properly described. When toxicity was not graded according to the CTCAE grading system, the authors rated the toxicity accordingly.

This study was registered on PROSPERO (Registration No. CRD42023393367, https://www.crd.york.ac.uk/prospero/#recordDetails).

Consensus Development process

This systematic review and *meta*-analysis project is conducted as part of the ESTRO Guidelines Committee's consensus recommendations on the integration of RT with targeted treatments for breast cancer. It is an initiative led by a multidisciplinary panel of experts, including patient advocates, medical and clinical oncologists, radiation oncologists, and basic science specialists. The aim is to provide evidence-based guidance and recommendations regarding the use of RT in conjunction with targeted treatments for breast cancer, ensuring a comprehensive and well-informed approach to patient care.

Results

The systematic literature search initially identified 516 articles (as

shown in Fig. 1). After removing duplicates, a total of 340 articles were screened, and from those, 140 full texts were reviewed. Ultimately, eleven articles met all the eligible criteria for the systematic review and were included in the subsequent *meta*-analysis. The details of these articles are shown in Table 1 [15–25].

Study characteristics

The systematic review included eleven retrospective studies, which collectively evaluated a total of 382 patients who received concurrent RT for a total of 558 lesions. The median age of the patients was 57 years, ranging from 30 to 91 years. The reported median follow-up period across the studies was 12 months, with a range of 6 to 19 months.

All studies reported on patients affected by metastatic breast disease. No information was retrieved about the early breast cancer setting. Four studies included cohorts treated with exclusive CDK4/6i [25] or sequential RT [18,19,24]. Toxicity was reported according to CTCAE Version 4.0 or version 5.0 in six and five studies, respectively. Out of the ten studies that reported data on CDK4/6i dose reduction for the entire intention-to-treat population (510 patients), it was found that dose reduction was required in 145 patients, representing a rate of 29%. Regarding concurrent treatment, nine studies reported dose reduction in 21 out of 255 patients, accounting for 8.2%.

Regarding the RT setting, data from eleven studies were available. Among the reported treatment courses, 518 were classified as palliative and 93 as ablative. SBRT or Stereotactic Radio Surgery (SRS) was utilized in 96 patients, while intensity-modulated RT (IMRT) or Volumetric-modulated Arc Therapy (VMAT) was described in 79 patients, and 3-dimensional conformal radiation therapy (3DCRT) was utilized in 286 patients. However, data were missing for 64 patients. Detailed information on the main features of RT is summarized in Table 2.

Risk of bias and GRADE assessment

According to examined domains of risk-of-bias tools for non-randomized trials, most studies were judged at moderate overall risk [17–19,21,22,25], and only one study was deemed to be at low risk [24].

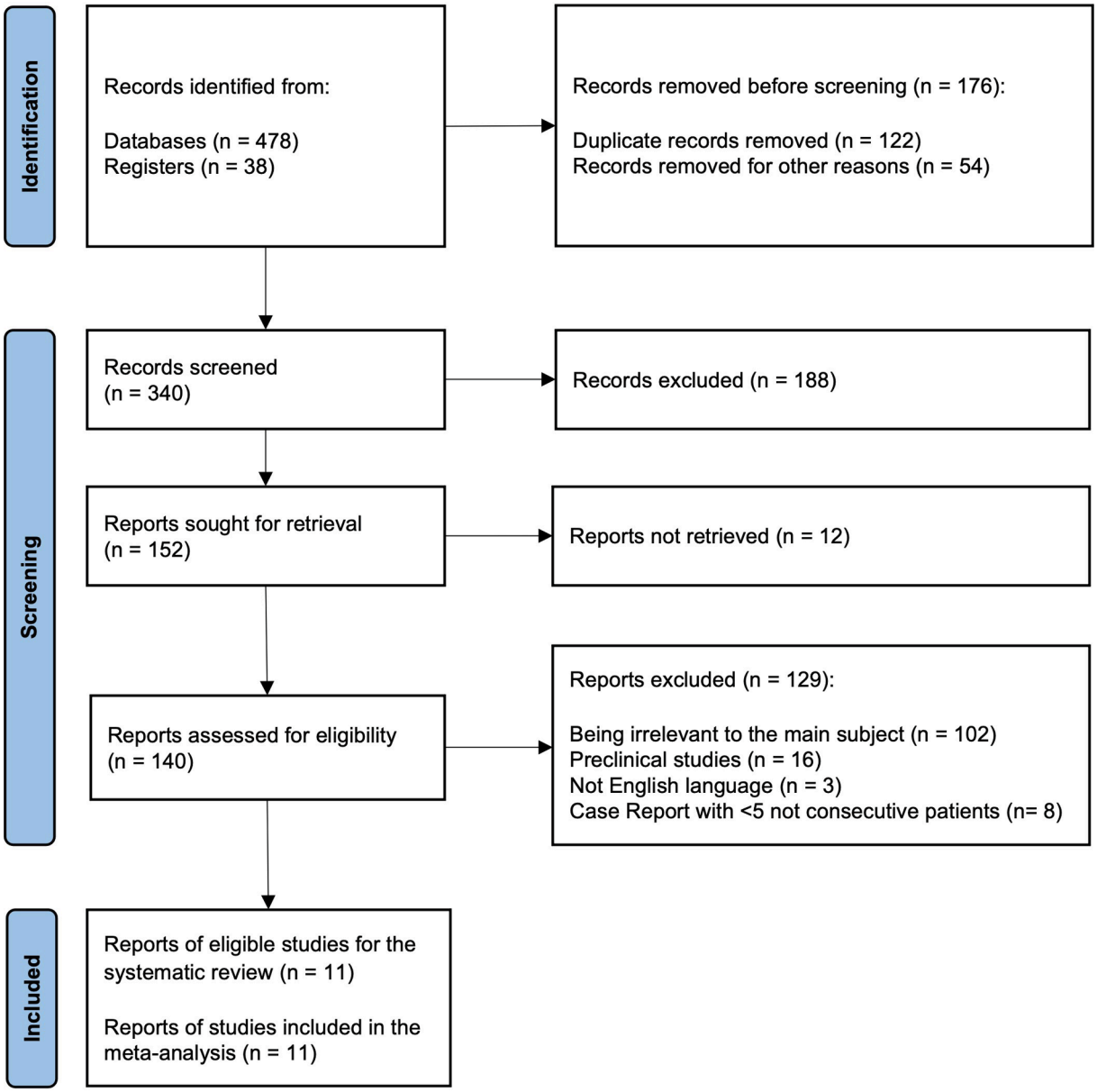

Fig. 1. PRISMA flow diagram depicting the search strategy in the systematic review literature search.

Table 1
Main characteristics of eligible studies included in the systematic review and *meta*-analysis.

Author, Year	No. of patients	CDK4/6i (No. of patients)	Site of radiation (No. of irradiated lesions)	RT timing with CDK4/6i * (%)	Median follow-up (months)	Median total dose and fractions (range)	TRAE G3+ (% of patients)	CDK 4/6i dose reduction (No. of patients)	CDK 4/6i discontinuation due to toxicity (No. of patients)
Hans S, et al. [15], 2018	5	Palbociclib (5)	Bone (4) Liver (1)	Concurrent (100)	NR	20 Gy (20–60) 5 fractions (5–10)	Neutropenia (40) Anaemia (20) Thrombocytopenia (20)	1	0
Meattini I, et al. [16], 2018	5	Ribociclib (5)	Bone (5)	Concurrent (100)	NR	20 Gy (20–30) 5 fractions (5–10)	Neutropenia (20) Diarrhoea, vomiting (20)	0	0
Ippolito E, et al. [17], 2019	16	Palbociclib (13) Ribociclib (3)	Bone (22) Breast/chest wall (2)	Concurrent (100)	6.3	30 Gy (20–60) 10 fractions (7–25)	Neutropenia (31.3)	1	0
Chowdhary M, et al. [18], 2019	16	Palbociclib (16)	Bone (11) Brain (4) Mediastinal nodes (1)	Concurrent (100)	17.6	30 Gy (18–36) 10 fractions (1–18)	None reported	0	0
Figura NB, et al. [19], 2019	15	Palbociclib (10) Abemaciclib (5)	Brain (42)	Concurrent (100)	9.2	20 Gy (18–20) 1 fraction	Radionecrosis (4.8)	0	0
Beddok A, et al. [20], 2020	30	Palbociclib (30)	Bone (25) Brain (1) Breast/chest wall (14)	Concurrent (100)	12.5	20 Gy (8–64) 5 fractions (1–26)	Pain (3.3) Radiodermatitis (3.3) Febrile neutropenia (3.3)	0	2
Ratosa I, et al. [21], 2020	46	Palbociclib (30) Ribociclib (15) Abemaciclib (1)	Bone (50) Brain (3) Breast/chest wall (2) Visceral (7)	Concurrent (100)	6	20 Gy (8–63) 5 fractions (1–26)	Diarrhoea (2.2) Neutropenia (13)	5	0
Guerini AE, et al. [22], 2020	18	Palbociclib (9) Ribociclib (6) Abemaciclib (3)	Bone (32)	Concurrent (100)	6	30 Gy (8–30) 10 fractions (1–10)	Enterocolitis (5.6)	2	0
Howlett S, et al. [23], 2021	42	Palbociclib (28) Ribociclib (6) Abemaciclib (6)	Bone (40) Brain (2)	Concurrent (100)	NR	NR	Neutropenia (9.5) Dermatitis (4.8)	NR	0
Al-Rashdan A, et al. [24], 2022	185 (n = 132 CDK4/6i + RT n = 53 RT only)	Palbociclib (124) Ribociclib (8)	Bone (157) Brain (20) Breast/chest wall (39) Lung, liver (9)	Concurrent n = 104 (46.2) Sequential n = 121 (53.8)	18	NR	Non haematological (3.7)	69 (12 in the concurrent cohort)	13 (1 in the concurrent cohort)
Visani L, et al. [25], 2022	132 (n = 57 CDK4/6i + RT n = 75 CDK4/6i only)	Palbociclib (NR) Ribociclib (NR) Abemaciclib (NR)	Bone (54) Brain (4) Breast/chest wall (4) Lung, liver (8)	Concurrent (100)	18.8	20 Gy (8–55) 5 fractions (1–10)	Asthenia (1.8) Nausea (1.8), diarrhoea (1.8) Anaemia (3.5), neutropenia (54.4), thrombocytopenia (1.8) Hypertransaminasemia (3.5)	67	1

Abbreviations: RT, radiation therapy; NR, not reported; TRAE, treatment-related adverse event; G3+, grade equal or more than 3.
* Irradiated lesions were considered treated concurrent with CDK4/6i if received irradiation within 5 half-lives of the CDK4/6i.

The remaining articles [15,16,20,23] were judged at serious overall risk-of-bias (Appendix, **Table S1**). The GRADE Working Group grades of evidence was reported in the Appendix (**Table S2**).

Toxicity profile

We extrapolate data regarding grade 3 + toxicity derived from concurrent treatment from all the studies. The pooled incidence of all grade 3 + toxicity was 22% (95% CI, 0.08—–0.39), with a substantial heterogeneity between the studies (I^2 90.7%) (Fig. 2**a**).

Grade 3 + haematological toxicity was mostly represented by neutropenia (40/68; 58.8% of events). However, the onset of this toxicity rarely caused treatment discontinuation. Only four patients required definitive discontinuation of CDK4/6i treatment: one due to hematological toxicity (neutropenia) [25], one due to grade 3 radiodermatitis and febrile neutropenia, one due to grade 2 dysphagia [20], and one due to unspecified non-hematological toxicity [24]. In the study by Al-Rashdan A et al [24], the authors reported discontinuation of CDK4/6i

Table 2
Radiation details of patients included in the eligible studies.

Author	RT setting (No. of treated lesions)			RT technique (No. of treated patients)				RT Dose (Gy/fraction) (No. of treated lesions)	RT dose EQD2 (Gy) (No. of treated lesions) *		
	Adjuvant	Palliative	Ablative	SBRT/ SRS	IMRT/ VMAT	3DCRT	NR		≤32.5 Gy	>32.5 Gy	NR
Hans S, et al. [15]	0	4	1	0	0	0	5	20/5 (4); 60/10 (1)	4	1	0
Meattini I, et al. [16]	0	5	0	0	1	4	0	30/5 (1); 20/5 (4)	4	1	0
Ippolito E, et al. [17]	0	19	5	1	4	19	0	30/10 (11); 36/13 (1); 20/5 (6); 39.6/ 18 (1); 50/25 (2); 60/30 (1); 21/7 (1)	19	6	0
Chowdhary M, et al. [18]	0	16	0	3	2	15	3	30/3 (1); 25/5 (1); 35/14 (5); 36/18 (1); 18/1 (1); 30/10 (7)	9	7	0
Figura NB, et al. [19]	0	0	42	42	0	0	0	18/1 (5); 20/1 (9); 21/1 (8); 24/1 (4); 20/5 (3); 25/5 (8); 30/5 (5)	11	31	0
Beddok A, et al. [20]	0	34	1	1	10	24	0	20/5 (13); 30/10 (10); 8/1 (3); 18/1 (1); 50/25 (7); 64.4/26 (2)	25	10	0
Ratosa I, et al. [21]	0	62	0	7	1	41	13	Median total dose 20 Gy (8–63); median dose per fraction 4 (2–18)	0	0	62
Guerini AE, et al. [22]	0	30	2	0	2	29	1	20/5 (13); 30/10 (14); 8/1 (5)	32	0	0
Howlett S, et al. [23]	0	NR	NR	0	0	0	42	NR	0	0	42
Al-Rashdan A, et al. [24]	0	292	28	28	43	114	0	NR	222	42	52
Visani L, et al. [25]	0	56	14	14	16	40	0	45–54/3 (3); 30–55/5 (6); 21–24/3 (2); 30/10 (7); 20/5 (42); 8/1 (2); NR (8)	56	14	0

Abbreviations: RT, radiation therapy; NR, not reported; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiation surgery; IMRT, intensity. modulated radiation therapy; VMAT, Volumetric-modulated Arc Therapy; 3DCRT, 3-dimensional conformal radiation therapy; Gy, Gray; EQD2, equivalent. dose in 2 Gy fractions.
* a/b ratio of 10 for acute toxicity.

treatment due to toxicity in 13 patients, although only one patient was included in the concurrent cohort.

The resulting pooled incidence of grade 3 + hematologic toxicity rate was 14% (95% CI, 0.03——0.30), with a substantial heterogeneity between the studies (I^2 91.7%) (Fig. 2**b**). Regarding non-haematological toxicity, the pooled incidence of grade 3 + toxicity rate was 3% (95% CI, 0.01——0.05) with a minimal heterogeneity between the studies (I^2 0%) (Fig. 2**c**). Gastrointestinal toxicity was quite frequent, mostly represented by diarrhoea (4/19; 21% of events).

Use of concurrent RT on intracranial disease was reported in seven studies [18–20,23–26]. There was only one specific study on concurrent SBRT for intracranial lesions plus CDK4/6i [19]. All other studies did not specify radiation technique and/or fractionation for this setting of patients. Overall, intracranial treatments were performed in 13.6% of cases (76/558 total treatments), reporting a low incidence of radionecrosis (2.6%).

Discussion

To our knowledge this is the first registered systematic review and *meta*-analysis of the available literature to assess the safety of the concurrent use of CDK4/6i and RT in the early and metastatic breast cancer setting.

CDK4/6i currently represent the standard of care for the management of patients with advanced or metastatic HR+/HER2- breast cancer in combination with ET [1–3]. In addition, abemaciclib demonstrated a significant improvement in invasive disease-free survival in patients affected by early-stage high-risk disease [4].

In the metastatic setting, RT has been widely recognized for its safety and is considered an important component of palliative therapy, particularly for relieving bone pain caused by symptomatic lesions in cancer patients [27,28]. Additionally, prospective data has demonstrated that SBRT with an ablative intent can significantly improve local control and result in durable enhancements in progression-free and overall survival, especially in selected patients with oligometastatic disease, including those with breast cancer. Importantly, these benefits have been observed without significant negative impacts on health-related quality of life and with limited occurrence of major toxicity events [6,29,30]. As a result, there has been growing interest in exploring the safety profile of concurrent administration of RT with targeted agents for breast cancer in recent years.

The preclinical rationale suggesting that combining RT and CDK4/6i might be unsafe is derived from the cytostatic and immunomodulatory effects reported by studies testing combination therapy in vitro and in vivo models [31–36]. Selective inhibition of CDK4/6 affects the cell cycle by interfering with the transition from the G1 phase to the S phase, reducing retinoblastoma protein phosphorylation and inducing G1 cell-cycle arrest. Irradiation of the normal cells results in delayed progression through the G1, S, and G2 phases. Cells are more resistant to irradiation in G0, in early G1, and in the late S phase of the cycle and more radiosensitive in late G1, G2 and throughout the M phase of the cell cycle. When CDK4/6i are administered concurrently with RT, it is possible that a higher percentage of cells will be in the G2/M phase of the cell cycle. This suggests a potential synergistic effect between CDK4/6i and RT, as cells in the G2/M phase are more radiosensitive [33–36] (Fig. 3).

The combination of palliative RT and CDK4/6i was firstly prospectively evaluated in a clinical setting for a subgroup of patients enrolled in the PALOMA trials (NCT01740427, NCT01942135), where it was planned to suspend palbociclib from the day prior to RT to the seventh day following RT, so no information regarding the combination of RT and CDK4/6i was available [1,8]. In the MONALEESA trials (NCT01958021, NCT02422615, NCT02278120), palliative RT was permitted if used solely for relief of bone pain, while all metastatic patients requiring RT should be permanently discontinued from the MONARCH trials (NCT02107703, NCT02246621). Details on RT reported in the study protocol of the main CDK4/6 pivotal trials are summarised in the Appendix (**Table S3**).

Adjuvant treatment

Abemaciclib combined with ET was the first CDK4/6i to receive approval for the adjuvant treatment of high-risk node-positive HR+/HER2- breast cancer patients, based on the results of the pivotal

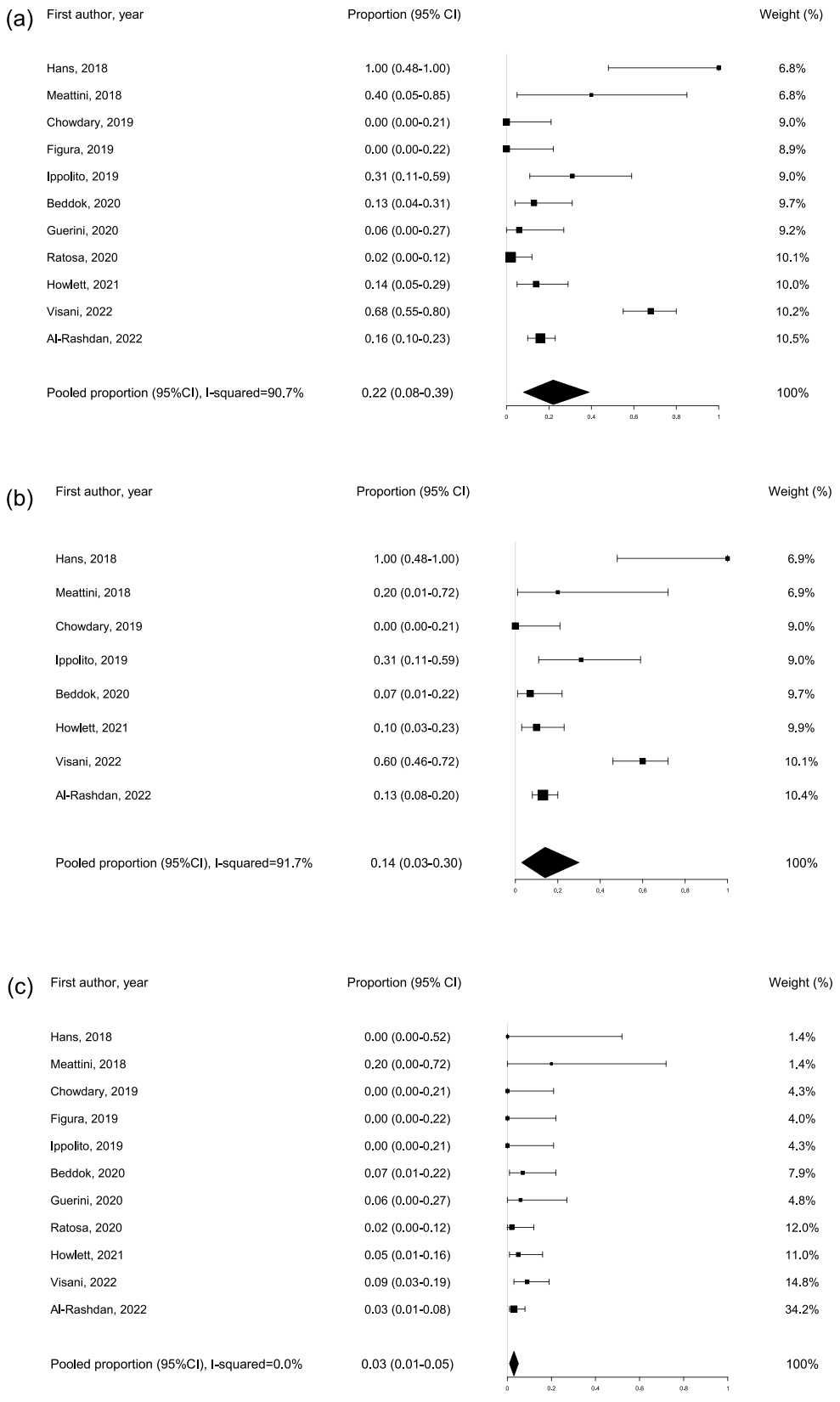

Fig. 2. Meta-analysis results concerning any toxicity of grade 3+ (**a**), haematological toxicity of grade 3+ (**b**), and non-haematological toxicity of grade 3+ (**c**).

MonarchE trial, showing a significant benefit in terms of invasive disease-free survival as compared to ET alone [4,37]. In the study, nearly all patients (95.4%) had received postoperative RT. However, radiation should have been completed prior to enrolment, and a washout period of at least 14 days was required between the end of RT and the trial randomization. A patient reported outcomes analysis of the MonarchE trial conducted at a median follow-up of 27 months found the observed rates of radiation pneumonitis in patients previously treated

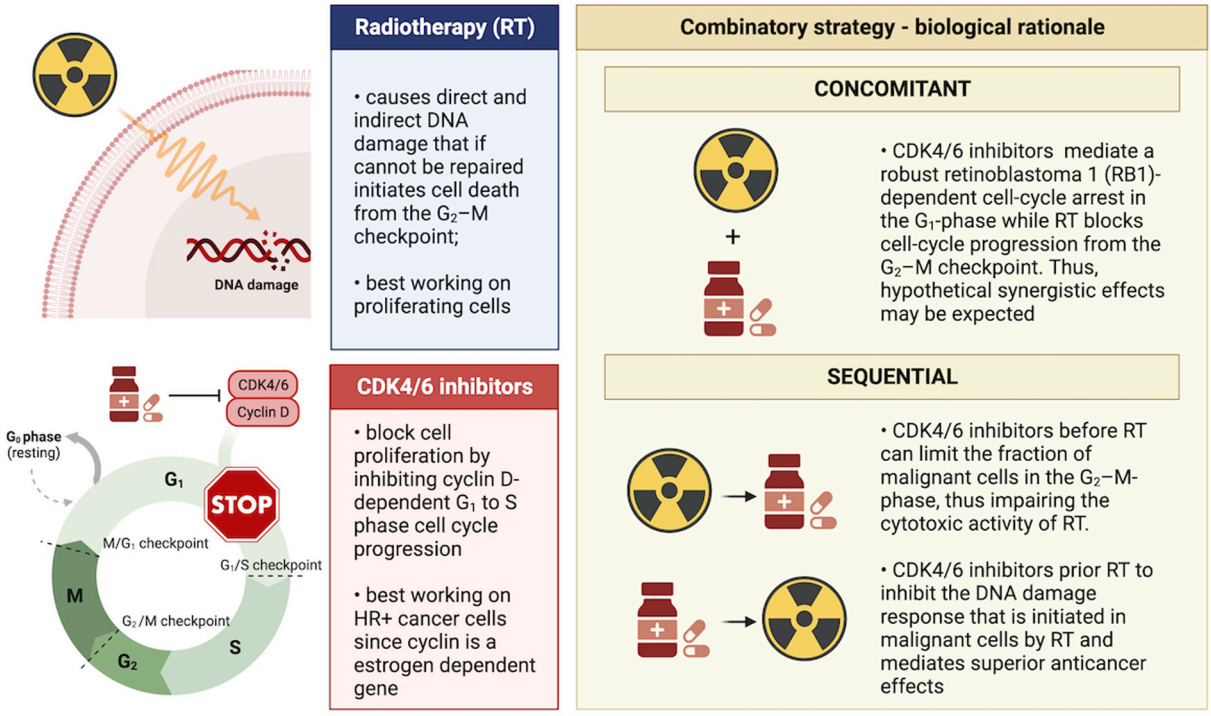

Fig. 3. Biological rationale of CDK4/6 inhibitors and irradiation combinatory strategy.

with RT were comparable between the two treatment arms [38]. The concurrent administration of RT during adjuvant abemaciclib may be an option in the future but requires further investigation.

The addition of ribociclib to standard-of-care ET has shown a statistically significant and clinically meaningful improvement in invasive disease-free survival, along with a well-tolerated safety profile. The NATALEE study (NCT03701334) is a phase III trial that demonstrates the benefits of this combination in a diverse population of patients with stage II and III HR+/HER2- early breast cancer who are at risk of recurrence, including those without nodal involvement. In this trial, postoperative RT was administered sequentially as part of the treatment approach [39].

The PALLAS study (NCT02513394) aimed to determine whether adding palbociclib to adjuvant ET improves invasive disease-free survival in early HR+/HER2- breast cancer. Adjuvant RT was administered to 2558 patients (88.7%) in the palbociclib group and 2560 patients (89%) in the placebo group. However, it is important to note that patients who underwent breast, axilla, or postmastectomy RT should have completed the entire treatment course and experienced sufficient resolution of side effects before participating in the study [40].

The PENELOPE-B study (NCT01864746) was a double-blind, placebo-controlled, phase III trial conducted in women with HR+/HER2- primary breast cancer who did not achieve a pathological complete response after receiving taxane-containing neoadjuvant chemotherapy and were at high risk of relapse. These patients were randomly assigned to receive 13 cycles of palbociclib or placebo in addition to ET. The primary endpoint of the study was invasive disease-free survival. Nearly all patients in the study had already received an anthracycline-taxane-based chemotherapy (98.6%), undergone adjuvant RT (98.8%), and had started ET before enrolling in the study (89.4%). Concurrent RT was not permitted during the active treatment phase of the study. Adjuvant RT should have been completed before patients entered the study. If a patient required RT during the active treatment phase, they were discontinued from the active treatment phase and entered the follow-up phase [41].

The WSG-ADAPTcycle (EudraCT: 2018–003749-40) is an additional phase III trial that aims to evaluate the use of a CDK4/6i (ribociclib) in combination with standard ET versus (neo-)adjuvant chemotherapy in HR+/HER2- early breast cancer. In the ADAPTcycle trial, RT may be administered in parallel or sequentially to either ribociclib or the standard of care treatment, based on the investigator's decision. This will enable the analysis of the tolerability of both approaches in a total collective of more than 1600 patients.

Due to the current lack of both prospective and retrospective data, the combination of CDK4/6i and RT in the adjuvant setting should be further investigated within the context of clinical trials or registration cohorts.

Metastatic intracranial disease

Out of the 11 retrospective studies included in this analysis, a total of 76 patients underwent concurrent radiotherapy (RT) for intracranial disease while receiving CDK4/6 inhibitors (CDK4/6i). One study reported two cases of grade 3 radionecrosis out of 42 patients who were treated with SRS, resulting in an incidence of 4.8% [19]. This finding is consistent with the overall incidence of symptomatic radionecrosis reported in the existing literature [42]. However, there is no available data regarding the irradiated bone volume and hematological toxicity in these studies.

Due to the small number of patients included in this pooled analysis who were treated for brain metastases, it is not possible to draw definitive conclusions regarding the safety of the combined approach of CDK4/6i and SRS at this time. Further research is needed to investigate the association between CDK4/6i and SRS in this specific scenario. It is worth noting that the combination of CDK4/6i and whole brain RT may potentially carry a lower risk of radionecrosis due to a lower total dose of radiation, although larger irradiated volumes and different disease contexts should be considered when comparing to SRS. However, the analysed studies lack specific details regarding the delivery of whole brain RT.

Metastatic extracranial disease

Neutropenia is the most frequent adverse event associated with

CDK4/6 inhibitors, with a higher incidence observed with palbociclib and ribociclib compared to abemaciclib. However, it is important to note that neutropenia is reversible upon discontinuation of the inhibitor, and the rates of febrile neutropenia and intercurrent infections are low [43,44].

In our systematic review and *meta*-analysis, we found that the most frequently reported toxicity was hematologic, with neutropenia being the predominant adverse event, accounting for 58.8% of grade 3 + hematologic toxicity events. However, the overall pooled incidence of grade 3 + hematologic toxicity was moderate, with a rate of 14%. Importantly, this level of hematologic toxicity did not significantly impact the continuation of CDK4/6 inhibitor treatment.

There have been concerns regarding the potential risk of increased pulmonary severe toxicity when combining RT and CDK4/6 inhibitors, particularly in the context of thoracic or locoregional breast irradiation. This is attributed to the inhibition of the cell cycle and subsequent senescence, which can lead to an increased recruitment of inflammatory response cells at the bronchoalveolar level [45,46]. However, it is worth noting that in pivotal clinical trials of CDK4/6 inhibitors, the incidence of interstitial lung disease, a severe pulmonary toxicity, was low, ranging from 1% to 3% [47,48]. These findings suggest that the risk of significant pulmonary toxicity with the combination of RT and CDK4/6 inhibitors may be relatively low based on available clinical data.

A retrospective large series conducted on metastatic breast cancer patients treated with CDK4/6i, with or without RT, reported no evidence of increased pulmonary toxicity in patients receiving SBRT for lung or bone metastases, specifically in the thoracic vertebrae [25]. Overall, 18 patients received spinal bone RT to thoracic vertebral lesions, 15 treated with palliative schedules and three with bone SBRT; the toxicity profile was safe with no evidence of additional RT-related acute and late pulmonary adverse events. Two out of three patients treated with bone SBRT reported grade 1–2 asthenia. Three patients received SBRT to lung metastases (54 and 55 Gy in 3 and 5 fractions, respectively, and 60 Gy in 8 fractions for a centrally located lesion). The authors did not report SBRT-related pneumonitis or esophagitis [25]. Findings regarding lung toxicity were not reported in other studies selected for this *meta*-analysis. Given the limited numbers of patients, definitive conclusions cannot be reached especially for those receiving lung or thoracic bone SBRT. However, available data are encouraging and where there are limited treatment volumes with lung doses maintained as low as reasonably achievable, the combination might be acceptable.

Another major point of discussion revolves around the risk of increased gastrointestinal adverse events, particularly when irradiating large target volumes. However, few cases of gastrointestinal toxicity have been reported following concurrent treatment with CDK4/6 inhibitors, predominantly palbociclib, and palliative RT [49,50]. In the study by Guerini et al [22], one case of grade 3 ileitis was reported ten days after the end of RT with concurrent palbociclib on a bulky pelvic bone localization which resolved completely after 20 days. Since 30 Gy in 10 fractions is well below the common bowel radiation tolerance dose, palbociclib might act as a radiosensitizer on normal intestinal tissue [51] as palliative RT or palbociclib as exclusive treatments are very unlikely to cause severe gastrointestinal side effects. In vivo data showed conflicting results, as palbociclib exposure resulted in both reduction and increase of acute gastrointestinal radiation syndrome in murine models, depending on irradiation schedule [52–54].

Among studies included in our *meta*-analysis, only two cases of grade 1 esophagitis were reported for patients treated to cervical spinal bone lesions with palliative schedules. Overall, 22 patients experienced diarrhoea, of those only four case of grade 3 was reported. A total of five patients were treated with liver ablative SBRT, reporting only one case of grade 2 nausea.

In four studies [16,22,24,55], the authors reported gastrointestinal toxicities of grade 3 + within the irradiated volume, affecting a total of 5 patients. Among these patients, data from 2 individuals were obtained from studies analysing concurrent administration of palbociclib, ribociclib, and abemaciclib [22,55], while the remaining 3 patients were from studies analysing concurrent administration of palbociclib and ribociclib [16,24]. Due to the limited number of events, it is challenging to determine a more toxic association between the drugs. However, all the reported toxicities appeared to be related to the RT treatment field. Out of the 11 studies included in the analysis, 8 of them have reported a correlation between irradiation and the timing of grade 3 + toxicity [16,17,19–24]. While the incidence of grade 3 + events reported in these studies does not exceed that of the events reported in randomized trials, the heterogeneity of the data makes it challenging to definitively determine the contribution of the combination of CDK4/6i with RT to these toxicities.

To conclude, in case of concurrent CDK4/6i administration, the use of highly conformal techniques (such as IMRT) and plan optimization are recommended to maintain the dose to the gastrointestinal mucosa as low as reasonably achievable, especially in cases of large target volumes located in abdominal and pelvic areas and for patients that experienced previous gastrointestinal toxicity. The distinct toxicity profile of the available CDK4/6i should be also considered in the concurrent treatment toxicity assessment.

Ongoing trials

Several ongoing trials are currently evaluating the combination of CDK4/6i and RT in breast cancer (refer to Table 3). The majority of these studies have been designed using palbociclib, while one study focuses on assessing the effectiveness of ribociclib and ET in combination with hypofractionated RT specifically for elderly patients with locally advanced inoperable disease. Additionally, a small phase I/II single-arm trial has been designed to investigate the intracranial progression-free survival in patients receiving abemaciclib and concurrent SRS for either intact brain metastases or postoperative cavities. Preliminary results from these trials are expected to become available in the coming years, providing additional evidence regarding the safety of concurrently administering CDK4/6i and RT.

Study limitations.

The main limitation of this work is the relatively small number of included studies and the wide range of patient numbers within each study. The heterogeneity observed in the primary outcome, which is Grade 3 + toxicity, further complicates the interpretation of the results. These factors highlight the need for caution in drawing definitive conclusions from the *meta*-analysis. The limited number of studies and the heterogeneity suggest that more research is needed to provide a comprehensive understanding of the safety profile of combining CDK4/6i with RT in breast cancer patients. Additionally, the retrospective nature of the included studies introduces inherent limitations such as selection bias, incomplete data, and confounding factors. Prospective, randomized controlled trials with larger sample sizes are necessary to provide more robust evidence and address these limitations.

Conclusions

Published data on the feasibility of concurrent RT and CDK4/6i are based on a low level of evidence derived from small retrospective series. These studies exhibit heterogeneity in reporting RT doses to targets and organs at risk, schedules, techniques, and treatment intent. There is currently no available data on the safety or efficacy of concurrent RT and CDK4/6i in the early breast cancer setting, and therefore, it is advisable to avoid such combination. However, in cases of metastatic disease, it may be possible to consider administering them on a case-by-case basis, taking into consideration factors such as the total dose and irradiated volumes, and carefully weighing the risks and benefits in collaboration with the patient. It is important to note that reliable reporting of RT details and toxicity is essential for both early and advanced settings when combining new agents with RT.

Table 3
Main ongoing studies investigating concomitant CDK4/6 inhibitors and radiation therapy.

Study Identifier	Molecule	Title	Design and Phase	N° of patients	End Of Study	Primary Objective	RT
NCT03691493 (ASPIRE)	Palbociclib	Radiation Therapy, Palbociclib, and Hormone Therapy in Treating Breast Cancer Patients With Bone Metastasis	II	46	10/08/2023	3-month response rate	RT (either 30 Gy/10 fractions or 20 Gy/5 fractions) for up to 4 separate anatomic regions containing bone metastases defined by 4 separate and not overlapping radiation plans.
NCT03870919 (PALATINE)	Palbociclib	Locoregional Treatment and Palbociclib in de Novo, Treatment Naive, Stage IV ER+, HER2- Breast Cancer Patients	NA	200	23/10/2026	OS	After 6 courses of systemic treatment initiation, the loco-regional treatment of the primary tumour will be performed: surgery (conservative or mastectomy) with or without RT, or exclusive RT.
NCT03750396 (CLEAR)	CDK4/6 inhibitors mTOR inhibitors	Local Treatment in ER-positive/HER2-negative Oligo-metastatic Breast Cancer	II	110	31/07/2025	PFS	Surgery, SBRT (57–97.5 Gy/6–10 fractions), or radiofrequency ablation.
NCT04563507 (CIMER)	Palbociclib	CIMER: Combined Immunotherapies in Metastatic ER + Breast Cancer	II	102	31/10/2025	PFS	SBRT (50 Gy in 5 fractions). Patients will add palbociclib on day 21, after completion of SBRT.
NCT05664893 (CALHYS)	Ribociclib	Study to Determine the Safety and Efficacy of Ribociclib in Combination With Hormone Therapy and Hypofractionated Radiotherapy in Breast Cancer, With Positive Hormone Receptors and Negative HER2 Status, in Newly Diagnosed, Not Immediately Operable Elderly Patient	I/II	85	31/03/2032	Phase I: MTD and RP2D determination Rate of non-progression at 24-month	Hypofractionated RT.
NCT04923542	Abemaciclib	Stereotactic Radiation & Abemaciclib in the Management of HR+/HER2- Breast Cancer Brain Metastases	I/II	31	31/12/2024	Intracranial PFS	Single session SRS to intact brain metastases and postoperative cavities. For intact brain metastases, this will be 15 Gy to lesions between 31 and 40 mm, 18 Gy to 21—30 mm, and 24 Gy to lesions measuring $\leq$ 20 mm.

Abbreviations: CDK, cyclin-dependent kinases; mTOR, mammalian target of rapamycin; NA, not available; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery; MDT, maximal tolerated dose; RP2D, recommended Phase II dose.

CRediT authorship contribution statement

Carlotta Becherini: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Luca Visani:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Saverio Caini:** Writing – original draft, Writing – review & editing. **Indrani S. Bhattacharya:** Writing – original draft, Writing – review & editing. **Anna M. Kirby:** Writing – original draft, Writing – review & editing. **Gustavo Nader Marta:** Writing – original draft, Writing – review & editing. **Gilberto Morgan:** Writing – original draft, Writing – review & editing. **Viola Salvestrini:** Writing – original draft, Writing – review & editing. **Charlotte E. Coles:** Writing – original draft, Writing – review & editing. **Javier Cortes:** Writing – original draft, Writing – review & editing. **Giuseppe Curigliano:** Writing – original draft, Writing – review & editing. **Evandro de Azambuja:** Writing – original draft, Writing – review & editing. **Nadia Harbeck:** Writing – original draft, Writing – review & editing. **Clare M. Isacke:** Writing – original draft, Writing – review & editing. **Orit Kaidar-Person:** Writing – original draft, Writing – review & editing. **Elisabetta Marangoni:** Writing – original draft, Writing – review & editing. **Birgitte Offersen:** Writing – original draft, Writing – review & editing. **Hope S. Rugo:** Writing – original draft, Writing – review & editing. **Andrea Morandi:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Matteo Lambertini:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Philip Poortmans:** Writing – original draft, Writing – review & editing. **Lorenzo Livi:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Icro Meattini:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Authors would like to acknowledge Tessa Piazzini and Alida Daniele (Biblioteca Biomedica, University of Florence, Florence, Italy) for their contribution to the literature search. Research data are stored and will be shared upon request to the corresponding author. Charlotte E. Coles CEC is funded by the National Institute of Health and Social Care Research (NIHR) and supported by the NIHR Cambridge Biomedical Research Centre; the views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2023.102586.

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