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REVIEW

Real-World Outcomes of Trilaciclib Among Patients with Extensive-Stage Small Cell Lung Cancer Receiving Chemotherapy

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ABSTRACT

Introduction: Trilaciclib was recently approved in the USA for reducing chemotherapy-induced myelosuppression (CIM) among adults with extensive-stage small cell lung cancer (ES-SCLC) when administered prior to chemotherapy. There is limited understanding of real-world outcomes of trilaciclib.

Methods: A comprehensive literature review was conducted using a keyword search in the MEDLINE, Embase, and conference abstracts. Additional studies were identified through communications with the authors of relevant studies. Published and unpublished real-world studies of trilaciclib- and comparable non-trilaciclib-treated patients with ES-SCLC were included. Evidence on myelosuppressive hematologic adverse events (HAEs), cytopenia-related healthcare utilization, and other reported outcomes (e.g., hospitalizations, dose reduction, and treatment delay) were synthesized. If feasible, outcomes were compared qualitatively between the trilaciclib and historical reference groups, and between first-line trilaciclib initiators and the overall trilaciclib population. Weighted averages were estimated for selected outcomes using sample size as the weight.

Results: The literature search identified five unique studies based on eight records—two included trilaciclib only, two non-trilaciclib only, and one both. In trilaciclib cohorts, the weighted average prevalence of grade ≥ 3 myelosuppressive HAEs in ≥ 1 lineage, ≥ 2 lineages, and all three lineages was 40.5%, 14.5%, and 7.5%, respectively. All rates were numerically lower compared to the historical non-trilaciclib cohorts (58.8%, 28.0%, 13.0%

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respectively). Cytopenia-related healthcare utilization was also lower in the trilaciclib cohorts. In general, first-line trilaciclib initiators had numerically lower myelosuppressive HAEs and cytopenia-related healthcare utilization than the overall trilaciclib patients.
Conclusions: The existing evidence suggests that trilaciclib may reduce single and multilineage grade ≥ 3 myelosuppressive HAEs and cytopenia-related healthcare utilization among patients with ES-SCLC in the real world. It is a promising new treatment for CIM prevention in ES-SCLC and may bring greater benefits to first-line trilaciclib initiators. Future studies are recommended to further evaluate the real-world effectiveness of trilaciclib.

Keywords: Extensive-stage small cell lung cancer; Chemotherapy-induced myelosuppression; Cytopenia; Real world; Supportive care; Trilaciclib

Key Summary Points

Trilaciclib is the first and only therapy that helps proactively protect hematopoietic stem and progenitor cells. It was approved to decrease the incidence of chemotherapy-induced myelosuppression among adults with extensive-stage small cell lung cancer (ES-SCLC) in 2021. Although clinical trials showed trilaciclib reduced grade ≥ 3 myelosuppressive hematologic adverse events (HAEs) among chemotherapy-treated patients with ES-SCLC, the real-world outcomes associated with trilaciclib are not well understood. The patient populations and treatment outcomes in real-world settings may be different from those observed in clinical trials.

Existing real-world studies consistently demonstrate that trilaciclib-treated patients had numerically lower prevalence of single and multilineage grade ≥ 3 myelosuppressive HAEs and lower cytopenia-related healthcare utilization, in reference to comparable historical non-trilaciclib cohorts that were identified in the same or different studies.

The real-world outcomes associated with trilaciclib are consistent with clinical trials, despite a higher proportion of elderly population, poorer performance status, and variation in timing of initiation of trilaciclib in real-world studies.

Future comparative effectiveness studies with a larger sample size are recommended to provide more robust real-world evidence on trilaciclib.

INTRODUCTION

Small cell lung cancer (SCLC) is a high-grade neuroendocrine carcinoma that accounts for 15% of lung cancer cases [1]. It is often diagnosed at a late stage with two-thirds of patients having distant metastasis at initial diagnosis [1]. Extensive-stage SCLC (ES-SCLC), which refers to disease beyond one hemithorax and one radiation port, has a particularly poor prognosis with a 30-month survival rate of less than 10% [1]. Chemotherapy has been the mainstay of the treatment for ES-SCLC. Recently, immuno-oncology (IO) agents were shown to improve survival when used in combination with chemotherapy, which led to the approval of atezolizumab and durvalumab for first-line treatment of ES-SCLC [2–4]. Despite these new treatments, the majority of patients experience relapse within 6 months [2]. The treatments for relapsed ES-SCLC are even more limited with suboptimal efficacy [5]. Topotecan was the only treatment approved for second-line ES-SCLC in the USA until June 2020 [2, 5]. Currently, the National Comprehensive Cancer Network (NCCN) guidelines recommend etoposide and carboplatin (EP) with and without an IO agent (atezolizumab or durvalumab) as first-line therapy and regimens containing topotecan or lurbinectedin as second-line therapy [6, 7].

Chemotherapy is known for associated myelosuppressive adverse events, resulting from direct damage to hematopoietic stem and progenitor cells (HSPCs) in the bone marrow or an indirect effect, such as reduced production of

erythropoietin [8]. Chemotherapy-induced myelosuppression (CIM) occurs because chemotherapy drugs not only target tumor cells but also normal HSPCs, both of which are in constant proliferation. It affects multiple lineages and often presents as neutropenia, anemia, and thrombocytopenia [8–11], which are the most common treatment-related adverse events reported for patients with SCLC in real-world studies [12]. Despite overall effort of improving cancer management, incidence of CIM in patients with SCLC remained consistent between 2012 and 2015 [13]. More recently, a study reported that over 55% of patients with ES-SCLC experienced grade $\geq$ 3 myelosuppressive hematologic adverse events (HAEs) after receiving chemotherapy in community practices, including approximately one-third with grade $\geq$ 3 myelosuppressive HAEs in two or more lineages [14]. Clinically, CIM is associated with an increased risk of infection, bleeding, and mortality [8, 10, 11]. Severe CIM often leads to dose reduction, treatment delay, or discontinuation [14–16], which may compromise treatment outcomes in patients with cancer, such as disease control and survival [15, 17, 18]. In addition, symptoms associated with the myelosuppressive HAEs can substantially reduce patients' quality of life (QoL) [19]. Therefore, CIM management is an important part of treatment of ES-SCLC. Treatment for CIM mainly consists of supportive care, e.g., granulocyte colony-stimulating factors (G-CSFs) for neutropenia and erythropoiesis-stimulating agents (ESAs) for anemia [9, 10]. For patients with severe myelosuppressive HAEs, red blood cell (RBC) or platelet transfusion and hospitalization may be required [6, 9, 11]. Treatments for CIM and its associated complications pose substantial economic burden to healthcare systems. In the USA, annual incremental costs associated with grade $\geq$ 3 myelosuppressive HAEs among patients with SCLC ranged from $22,251 for thrombocytopenia to $63,245 for neutropenia [20]. Moreover, healthcare resource utilization (HCRU) increased with the number of lineages involved [21]. The above evidence suggests that there remains substantial unmet need for new therapies that can effectively manage CIM in patients with ES-SCLC, improve patients' QoL, and reduce the economic burden borne by patients and healthcare systems.

Trilaciclib is the first and only therapy that helps proactively protect HSPCs, the source of all blood cell lineages [5]. Trilaciclib transiently arrests HSPC in the G1 phase of the cell cycle by inhibiting the activity of cyclin-dependent kinases (CDK) 4/6, an important factor in the process of the proliferation of HSPCs [22]. Trilaciclib, as an innovative transient CDK4/6 inhibitor, when used before the start of chemotherapy, can prevent HSPCs from proliferating in the presence of cytotoxic chemotherapy, thereby protecting multiple cell lineages from cytotoxic effects of chemotherapy [22]. In three randomized phase 2 clinical trials and the pooled analyses of these trials [23–28], trilaciclib has been shown to effectively reduce myelosuppression in multiple lineages and decrease cytopenia-related healthcare utilization. These effects have been demonstrated when trilaciclib was administered prior to EP or EP plus atezolizumab in the first-line setting and prior to topotecan-containing regimens in previously treated ES-SCLC. On the basis of these results, the US Food and Drug Administration (FDA) approved trilaciclib for decreasing the incidence of CIM among adults with ES-SCLC when administered prior to EP- or topotecan-containing regimens in February 2021 [29]. The NCCN guidelines also recommend trilaciclib as a prophylactic treatment to reduce the incidence of CIM in ES-SCLC [6, 7]. In addition to its clinical efficacy, trilaciclib has also been shown to reduce the overall healthcare costs and improve quality-adjusted life years among patients with ES-SCLC [30–32].

To date, there is limited evidence on the real-world outcomes associated with trilaciclib use in ES-SCLC. The patient populations and treatment outcomes in real-world settings may be different from those observed in clinical trials. To enhance our understanding of the real-world outcomes of trilaciclib, the current study was conducted to comprehensively review the current literature and synthesize the effectiveness of trilaciclib in real-world settings. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

METHODS

Literature Review Approach

A comprehensive literature search of the MEDLINE, Embase, and Northern Light Life Sciences Conference Abstract databases was performed on November 28, 2022, using the following keyword combinations: ("small-cell lung cancer" or "SCLC") and ("trilaciclib" or "Cosela"). To be included in the review, a study must have met the following inclusion criteria: (1) focused on the ES-SCLC population; (2) included patients receiving trilaciclib; (3) included one of the key outcomes of interest related to CIM, such as myelosuppressive HAEs or cytopenia-related resource utilization; (4) was a real-world observational study; and (5) was published in English. The review included full-text articles published from the inception of MEDLINE or Embase to the search date and conference abstracts from 3 years prior to the search date. Clinical trials, narrative reviews, and any type of publication other than original research were excluded. In addition, a search was conducted by hand to identify relevant reviews and studies not included in the electronic databases. As trilaciclib is a relatively new drug, the co-authors of the relevant studies provided additional data that were unpublished (but accepted for future publication or presentation) as of the search date. Moreover, additional unpublished data on file for the published or presented studies was solicited from the authors to enhance our understanding of these studies.

Following the Centre for Review and Dissemination (CRD) guidance [33], two levels of screening were performed. Level 1 screened titles and abstracts identified from the literature search and level 2 screened full-text articles identified as possibly relevant studies from the level 1 screening. Each level of screening was performed by two independent reviewers and discrepancies were resolved by a third reviewer. After eligible studies were identified, data extraction was conducted to extract information on study design, data source, baseline characteristics, and outcomes of interest from each included study.

To facilitate the interpretation of the real-world outcomes of trilaciclib-treated patients with ES-SCLC, the study also strived to identify comparable non-trilaciclib studies that evaluated similar outcomes among patients with ES-SCLC who did not receive trilaciclib from the same data sources. Similar data extraction was performed for each of the identified non-trilaciclib studies.

Outcomes of Interest

The main outcomes of interest for this review were myelosuppressive HAEs and cytopenia-related healthcare utilization. Specifically, myelosuppressive HAEs included any grade ≥ 3 anemia, neutropenia, and thrombocytopenia, as confirmed by laboratory tests. The study included outcomes for a single lineage (overall and by grade) as well as multiple lineages (i.e., two or three lineages). Cytopenia-related healthcare utilization included G-CSF, ESAs, RBC and platelet transfusions, and intravenous (IV) hydration. G-CSF use was evaluated within the first 3 days following the index date and during the defined outcome observation period (Table 1), with the former used as a proxy measure for prophylactic G-CSF use. Other outcomes (e.g., hospitalizations, dose reduction, and treatment delay) reported in eligible studies were also extracted and summarized.

Evidence Synthesis

Identified eligible trilaciclib studies were first synthesized qualitatively. Specifically, key study design elements, including study year, sample selection criteria, sample size, index date, and follow-up period were summarized for each study, along with their similarities and differences. Baseline characteristics were summarized and compared qualitatively across studies. Definitions of the outcomes of interest were evaluated, and if they were similar, a quantitative synthesis was conducted by estimating weighted averages of the outcomes using sample size as the weight. The analysis was conducted separately for the trilaciclib and historical non-trilaciclib cohorts. Depending on availability,

Table 1 Study design of real-world trilaciclib studies and historical non-trilaciclib studies

Study design	Study population	iKM network	iKM non-network	FCS	Integra Connect
Data source		iKnowMed EHR structured data from the US Oncology Network	iKnowMed EHR structured data from non-network community oncology practices	Florida Cancer Specialists & Research Institute structured EMR database	The Integra Connect Structured & Curated EMR and Claims database
Geographic location		USA	USA	Florida	USA
Patient identification period	Trilaciclib	Feb 2021–Apr 2022		Feb 2021–May 2022	Jan 2017–Dec 2021
	Non-trilaciclib	Jan 2015–Dec 2019		Sep 2013–Nov 2020	Jan 2015–Mar 2021
Index date	Trilaciclib	Date of trilaciclib initiation with LOT1 or LOT2+			Date of chemotherapy initiation when trilaciclib was used in the initial chemotherapy regimen
	Non-trilaciclib	Date of chemotherapy initiation			
Time horizon for outcome observation for myelosuppressive HAEs, cytopenia-related healthcare utilization, and dose reduction and treatment delay	Trilaciclib	From index date to 14 days after last trilaciclib administration of index chemotherapy regimen		During chemotherapy cycles when trilaciclib was used	From index date to end of follow-up[a]
	Non-trilaciclib	From index date to end of follow-up[a]			
Outcome measures[b]					
Grade ≥ 3 myelosuppressive HAEs[c]		Grade ≥ 3 myelosuppressive HAEs were identified using laboratory values based on CTCAE v5.0 definitions			
		All studies reported the myelosuppressive HAE rates by lineage and grade			
Cytopenia-related healthcare utilization		Included G-CSF and ESAs			
RBC or platelet transfusion		Based on lab proxy, i.e., hemoglobin < 8 g/dL; platelets < 10,000/μL			Transfusions occurred

Table 1 continued

Study design	Study population	iKM network	iKM non-network	FCS	Integra Connect
Dose reduction and dose delay		Dose reduction was defined as a decrease in dosage compared to the baseline or previous dose. A dose reduction of at least one drug was counted as an event for dose reduction Dose delay was defined as a gap of less than 60 days without treatment		Not available	Not available
Hospitalization		Not available		Not available	Hospitalization rates between day 8 and 16 and between day 1 and 21 LOS
IV hydration		IV hydration was determined on the basis of the structured EHR, if captured in the database			Not available
Subgroup analysis of trilaciclib	LOT1 trilaciclib initiators	Defined as initiation of trilaciclib before LOT1 cycle 1		Defined as initiation of trilaciclib at LOT1	Not available

FCS Florida Cancer Specialists and Research Institute, *EHR* electronic health record, *EMR* electronic medical record, *LOT* line of therapy, *HAE* hematologic adverse event, *iKM* iKnowMed, *CTCAE* Common Terminology Criteria for Adverse Events, *G-CSF* granulocyte colony-stimulating factors, *ESAs* erythropoiesis-stimulating agents, *RBC* red blood cell, *IV* intravenous, *LOS* length of stay

[a]Follow-up ends at date of death, last EMR activity date, or end of the study period, whichever occurs first

[b]Outcome measures were defined in the same way for the trilaciclib study and the corresponding non-trilaciclib group study from the same database

[c]In the FCS studies, myelosuppressive episodes were defined as all events of the defined type occurring within 21 days of the first event, with the highest observed grade assigned to that episode, while in the iKM-based and Integra Connect studies reported two separate episodes if two events of different grades occurred within 21 days

treatment outcomes were further compared qualitatively between trilaciclib- and non-trilaciclib-treated patients (i.e., directionality) on the basis of the results from individual studies and the quantitative synthesis. In addition, results for subgroups of trilaciclib-treated patients (who initiated trilaciclib before or during first line of therapy [LOT1]) were also summarized, if available.

RESULTS

Literature Search Results

The literature search yielded one published journal article [14] and four conference presentations [34–37] as of the search date. Communications with the authors of the identified studies produced one unpublished manuscript

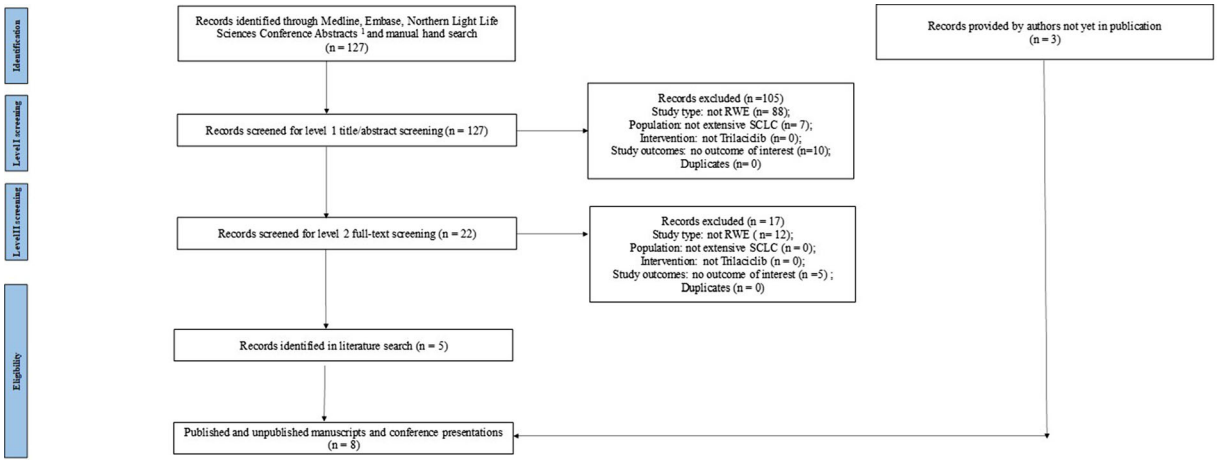

Fig. 1 PRISMA diagram based on the literature search. *PRISMA* Preferred Reporting Items for Systematic Literature Review and Meta-analysis, *RWE* real-world evidence, *SCLC* small cell lung cancer. The literature search was conducted in MEDLINE, Embase, and Northern Light Life Sciences Conference Abstract databases on November 28, 2022. The literature search was supplemented by the unpublished studies identified through author communications

as of the search date but published at the time of manuscript development [38] and two accepted conference presentations [39, 40]. Therefore, a total of eight manuscripts and conference presentations were identified [14, 34–40] (Fig. 1), of which, six reported five unique original studies [14, 34–38] and two presented results from the additional analyses of three original studies [39, 40]. Of the five unique studies, one included a trilaciclib cohort and a historical non-trilaciclib cohort [37]; two focused on trilaciclib only [34, 35]; and the rest included the corresponding historical non-trilaciclib cohorts for the trilaciclib-only studies [14, 36, 38]. In total, the five studies reported the results for eight distinctive cohorts of trilaciclib and historical non-trilaciclib users. In addition, there were three subgroups of LOT1 trilaciclib users (Table 1).

Description of Included Studies

Data Sources

All five studies [14, 34–38] were retrospective cohort studies based on four existing oncology databases in the USA: the US Oncology Network's electronic health record (EHR) system, iKnowMed (iKM), the Florida Cancer Specialists and Research Institute (FCS) structured electronic medical record (EMR) database, and the Integra Connect Precision De-Identified Structured & Unstructured EMR and Claims database (Table 1). The US Oncology iKM database is implemented across the US Oncology Network ("network") and non-network community oncology practices ("non-network") made up of approximately 80 clinics that have adopted iKM EHRs. Thus, they were considered as two separate databases. All patients in the databases were de-identified.

Study Design

Among the three trilaciclib studies, the patient identification period in the iKM-based sources and FCS studies covered the post-approval period only [34, 35], while the patient identification period in the Integra Connect study spanned both pre- and post-trilaciclib approval eras [37] (Table 1). The non-trilaciclib studies using the iKM-based sources and FCS databases included only the pre-trilaciclib approval period [14, 36, 38], while the Integra Connect non-trilaciclib group [37] had a follow-up period that extended up to March 31, 2021, i.e., 1 month after trilaciclib approval.

All five studies [14, 34–38] employed a retrospective longitudinal study design with some

variations in the definition of index date and outcome observation period (Table 1). The index date for the iKM-based sources and FCS trilaciclib studies was defined as the date of trilaciclib initiation [34, 35], while the index date for the Integra Connect trilaciclib study was designated as the date of chemotherapy initiation when trilaciclib was used in the initial chemotherapy regimen [37]. All studies for the historical non-trilaciclib cohorts defined the index date as the date of the first chemotherapy initiation during the identification period following diagnosis of ES-SCLC [14, 36–38]. The outcome observation period for the key outcomes of interest (i.e., myelosuppressive HAEs, cytopenia-related healthcare utilization, and dose reduction and treatment delay) also varied across the trilaciclib studies. The two iKM-based studies followed up patients from the index date to 14 days after the last trilaciclib administration of the index chemotherapy regimen [34]; the FCS study followed up patients from the index date until the last chemotherapy cycle when trilaciclib was administered [35]; the Integra Connect study followed up patients until the end of the study period, last EMR activity date or death, whichever occurred first [37]. However, despite the variations, the mean follow-up time was similar between the iKM-based and FCS studies (the two studies reporting such information). The outcome observation period for myelosuppressive HAEs was consistent across the historical non-trilaciclib studies [14, 36–38], which had the same definition as the Integra Connect trilaciclib study [37].

All studies [14, 34–38] included outcomes related to grade ≥ 3 myelosuppressive HAEs (such as rates of any grade ≥ 3 myelosuppressive HAE, neutropenia, anemia, and thrombocytopenia overall and by severity, and rates of grade ≥ 3 myelosuppressive HAEs based on the number of lineages involved) and cytopenia-related healthcare utilization (i.e., G-CSF and ESAs) (Table 1). RBC or platelet transfusions were also reported in all studies but were based on lab proxies (i.e., RBC or platelet transfusion eligibility) in the iKM-based and FCS studies [34, 35]. Other outcomes, including IV hydration, dose reduction, treatment delay, and hospitalization, were only reported in some studies.

Subgroup analysis among LOT1 trilaciclib initiators was conducted in two out of three trilaciclib studies [39, 40], with some variation in the definition (Table 1). The iKM-based study defined LOT1 trilaciclib initiators as patients who initiated trilaciclib before the first cycle in the first-line treatment [39], while the FCS study defined them as patients who initiated trilaciclib during the first-line treatment, due to lack of cycle information in the database [40]. The Integra Connect database did not have the LOT information and thus did not include this subgroup analysis.

Baseline Characteristics

The sample size for trilaciclib studies ranged from 21 in the Integra Connect study [37] to 50 in the FCS study [35] (Table 2). Comparatively, the corresponding historical non-trilaciclib studies had a substantially larger sample size, ranging from 959 in the iKM non-network study to 3277 in the Integra Connect study [14, 36–38]. The baseline demographics were similar across the trilaciclib studies, with the mean age in the overall trilaciclib cohorts ranging from 67.1 to 70.0 years and 44.0% to 51.6% male patients (Table 2). The age and gender distribution were also similar between the trilaciclib cohorts and their corresponding historical non-trilaciclib cohorts. Performance status based on the Eastern Cooperative Oncology Group (ECOG) score showed that the majority of patients were in ECOG 0 or 1 in the trilaciclib and historical non-trilaciclib cohorts in the FCS and Integra Connect studies. As a result of a high proportion of missing values, ECOG was not reported in the iKM-based studies.

Trilaciclib was used in LOT1 in 66–68% of the patients, which was consistent across the two studies with available LOT information [34, 35] (Table 2). However, the proportions were considerably lower than the historical non-trilaciclib cohorts, in which 94–100% patients had the index chemotherapy in LOT1 [14, 36, 38]. Most of patients in the "all trilaciclib" cohort and LOT1 trilaciclib initiations (80–100%) received trilaciclib in combination

Table 2 Baseline characteristics of real-world trilaciclib studies and non-trilaciclib studies

Baseline characteristics	Study population	iKM network *n* = 31 (all trilaciclib) *n* = 19 (LOT1 trilaciclib initiators[b]) *n* = 1574 (non-trilaciclib)	iKM non-network *n* = 35 (all trilaciclib) *n* = 18 (LOT1 trilaciclib initiators[b]) *n* = 959 (non-trilaciclib)	FCS *n* = 50 (all trilaciclib) *n* = 32 (LOT1 trilaciclib initiators[b]) *n* = 1239 (non-trilaciclib)	Integra Connect *n* = 21 (all trilaciclib) *n* = 3277 (non-trilaciclib)
Age as of the index date (years), mean (SD)	All trilaciclib	67.1 (7.3)	67.7 (7.9)	67.8 (8.3)	70.0 (8.3)
	LOT1 trilaciclib initiators[b]	68.6	67.0	68.5	–
	Non-trilaciclib	67.8 (9.1)	67.4 (8.9)	66.9 (9.3)	68.0 (9.1)
Age $\geq$ 65 years, %	All trilaciclib	61.3	48.6	64.0	81.0
	LOT1 trilaciclib initiators[b]	73.7	44.4	68.8	–
	Non-trilaciclib	61.2	60.6	62.7	67.1
Male, %	All trilaciclib	51.6	45.7	44.0	47.6
	LOT1 trilaciclib initiators[b]	52.6	44.4	46.9	–
	Non-trilaciclib	47.6	49.0	49.7	50.4
ECOG score 0 or 1[a], %	All trilaciclib	–	–	82.6	85.7
	LOT1 trilaciclib initiators[b]	–	–	82.8	–
	Non-trilaciclib	–	–	77.3	76.5

Table 2 continued

Baseline characteristics	Study population	iKM network *n* = 31 (all trilaciclib) *n* = 19 (LOT1 trilaciclib initiators[b]) *n* = 1574 (non-trilaciclib)	iKM non-network *n* = 35 (all trilaciclib) *n* = 18 (LOT1 trilaciclib initiators[b]) *n* = 959 (non-trilaciclib)	FCS *n* = 50 (all trilaciclib) *n* = 32 (LOT1 trilaciclib initiators[b]) *n* = 1239 (non-trilaciclib)	Integra Connect *n* = 21 (all trilaciclib) *n* = 3277 (non-trilaciclib)
Index LOT, %					
LOT1	All trilaciclib	67.7	65.7	66.0	–
	LOT1 trilaciclib initiators[b]	100.0	100.0	100.0	–
	Non-trilaciclib	99.5	99.6	94.0	–
LOT2 or later	All trilaciclib	32.3	34.3	34.0	–
	LOT1 trilaciclib initiators[b]	0.0	0.0	0.0	–
	Non-trilaciclib	0.5	0.4	6.0	–
Index chemotherapy, %					
Platinum/etoposide-containing regimen with or without IO	All trilaciclib	93.5	85.7	80.0	100.0[c]
	LOT1 trilaciclib initiators[b]	100.0	100.0[c]	96.9	–
	Non-trilaciclib	95.2[c]	95.6[c]	86.7	87.8[c]
Topotecan-containing regimen	All trilaciclib	0.0	11.4	14.0	0.0[c]
	LOT1 trilaciclib initiators[b]	0.0	0.0[c]	0.0	–
	Non-trilaciclib	1.7[c]	0.0[c]	2.3	0.5[c]

Table 2 continued

Baseline characteristics	Study population	iKM network *n* = 31 (all trilaciclib) *n* = 19 (LOT1 trilaciclib initiators[b]) *n* = 1574 (non-trilaciclib)	iKM non-network *n* = 35 (all trilaciclib) *n* = 18 (LOT1 trilaciclib initiators[b]) *n* = 959 (non-trilaciclib)	FCS *n* = 50 (all trilaciclib) *n* = 32 (LOT1 trilaciclib initiators[b]) *n* = 1239 (non-trilaciclib)	Integra Connect *n* = 21 (all trilaciclib) *n* = 3277 (non-trilaciclib)
Myelosuppressive HAEs prior to the index date, %					
Grade 3 anemia	All trilaciclib	4.2	9.7	15.2	–
	LOT1 trilaciclib initiators[b]	0.0	0.0	10.3	–
	Non-trilaciclib	6.9	2.9	1.6	
Grade 3 neutropenia	All trilaciclib	8.7	4.8	15.2	–
	LOT1 trilaciclib initiators[b]	0.0	0.0	13.8	–
	Non-trilaciclib	3.5	3.6	2.0	–
Grade 3 thrombocytopenia	All trilaciclib	0.0	15.6	8.7	–
	LOT1 trilaciclib initiators[b]	0.0	0.0	10.3	–
	Non-trilaciclib	2.7	2.3	1.0	–
Grade 4 neutropenia	All trilaciclib	0.0	19.0	21.7	–
	LOT1 trilaciclib initiators[b]	0.0	9.1	24.1	–
	Non-trilaciclib	1.7	5.6	1.4	–

Table 2 continued

Baseline characteristics	Study population	iKM network *n* = 31 (all trilaciclib) *n* = 19 (LOT1 trilaciclib initiators[b]) *n* = 1574 (non-trilaciclib)	iKM non-network *n* = 35 (all trilaciclib) *n* = 18 (LOT1 trilaciclib initiators[b]) *n* = 959 (non-trilaciclib)	FCS *n* = 50 (all trilaciclib) *n* = 32 (LOT1 trilaciclib initiators[b]) *n* = 1239 (non-trilaciclib)	Integra Connect *n* = 21 (all trilaciclib) *n* = 3277 (non-trilaciclib)
Grade 4 thrombocytopenia	All trilaciclib	4.2	6.3	13.0	–
	LOT1 trilaciclib initiators[b]	0.0	0.0	10.3	–
	Non-trilaciclib	1.2	1.7	0.2	–

FCS Florida Cancer Specialists and Research Institute, *iKM* iKnowMed, *SD* standard deviation, *ECOG* Eastern Cooperative Oncology Group, *LOT* line of therapy, *1L* first line, *IO* immuno-oncology, *HAE* hematologic adverse event

[a]The proportion of patients with an ECOG score of 0/1 was estimated among patients with non-missing ECOG scores. ECOG scores were not reported for the iKM network and non-network studies because of > 50% patients in the trilaciclib groups having missing ECOG scores. The proportion of patients with missing ECOG data was 58.4%, 63.2%, and 21.2% in the all trilaciclib, LOT1 trilaciclib initiators, and non-trilaciclib groups in the iKM network studies and 68.6%, 72.2%, and 35.1% in the iKM non-network studies, respectively. The proportion of patients with missing ECOG data was 8.0%, 9.4%, and 16.5% in the all trilaciclib, LOT1 trilaciclib initiators, and non-trilaciclib groups, respectively, in the FCS studies; 0% and 15.3% in the all trilaciclib and non-trilaciclib groups, respectively, in the Integra Connect study

[b]The analysis among LOT1 trilaciclib initiators was conducted on the basis of the iKM network and non-network study populations as well as the FCS study. The two iKM-based studies defined LOT1 trilaciclib initiators as those using trilaciclib before the first cycle in the first-line treatment, while the FCS study defined it as initiation of trilaciclib anytime during the first-line treatment

[c]Data were provided by authors of the corresponding studies

Table 3 Real-world outcomes reported in trilaciclib studies and historical non-trilaciclib studies among patients with ES-SCLC

Outcomes	Study population	iKM network *n* = 31 (all trilaciclib) *n* = 19 (LOT1 trilaciclib initiators[b]) *n* = 1574 (non-trilaciclib)	iKM non-network *n* = 35 (all trilaciclib) *n* = 18 (LOT1 trilaciclib initiators[b]) *n* = 959 (non-trilaciclib)	FCS *n* = 50 (all trilaciclib) *n* = 32 (LOT1 trilaciclib initiators[b]) *n* = 1239 (non-trilaciclib)	Integra Connect *n* = 21 (all trilaciclib) *n* = 3277 (non-trilaciclib)	Pooled[a] *n* = 137 (all trilaciclib) *n* = 69 (LOT1 trilaciclib initiators[b]) *n* = 7049 (non-trilaciclib)
Follow-up duration (months), mean (SD)	All trilaciclib	4.8 (3.0)	4.0 (2.9)	4.1 (3.3)	–	4.3 (3.1)
	LOT1 trilaciclib initiators[b]	–	–	–	–	–
	Non-trilaciclib	8.9 (8.5)	9.5 (9.3)	10.4 (11.3)	–	9.5 (9.7)
Number of chemotherapy cycles, mean (SD)[c]	All trilaciclib	5.0 (4.3)	5.0 (2.1)	–	–	–
	LOT1 trilaciclib initiators[b]	4.1 (2.2)	4.7 (1.6)	–	–	–
	Non-trilaciclib	4.4 (2.8)	5.3 (3.9)	–	–	–
Prevalence of grade ≥ 3 myelosuppressive HAEs, %[d]						
Grade ≥ 3 neutropenia	All trilaciclib	28.6	40.9	26.0	19.0	29.1
	LOT1 trilaciclib initiators[b]	35.3	40.0	18.8	–	28.9
	Non-trilaciclib	35.7	37.3	42.7	44.6	41.6

Table 3 continued

Outcomes	Study population	iKM network *n* = 31 (all trilaciclib) *n* = 19 (LOT1 trilaciclib initiators[b]) *n* = 1574 (non-trilaciclib)	iKM non-network *n* = 35 (all trilaciclib) *n* = 18 (LOT1 trilaciclib initiators[b]) *n* = 959 (non-trilaciclib)	FCS *n* = 50 (all trilaciclib) *n* = 32 (LOT1 trilaciclib initiators[b]) *n* = 1239 (non-trilaciclib)	Integra Connect *n* = 21 (all trilaciclib) *n* = 3277 (non-trilaciclib)	Pooled[a] *n* = 137 (all trilaciclib) *n* = 69 (LOT1 trilaciclib initiators[b]) *n* = 7049 (non-trilaciclib)
Grade ≥ 3 thrombocytopenia	All trilaciclib	7.1	25.0	24.0	4.8	17.6
	LOT1 trilaciclib initiators[b]	0.0	11.8	12.5	–	8.9
	Non-trilaciclib	22.9	37.8	36.1	33.3	32.1
Grade 3 anemia	All trilaciclib	7.1	31.3	18.0	14.3	18.3
	LOT1 trilaciclib initiators[b]	0.0	23.5	9.4	–	10.5
	Non-trilaciclib	28.5	37.8	32.7	34.0	33.0
Grade 3 neutropenia	All trilaciclib	28.6	31.8	24.0	19.0	26.1
	LOT1 trilaciclib initiators[b]	35.3	40.0	18.8	–	28.9
	Non-trilaciclib	27.3	28.4	26.5	29.3	28.3
Grade 3 thrombocytopenia	All trilaciclib	7.1	25.0	20.0	4.8	16.0
	LOT1 trilaciclib initiators[b]	0.0	11.8	9.4	–	7.4
	Non-trilaciclib	19.3	32.8	31.0	30.2	28.3

Table 3 continued

Outcomes	Study population	iKM network $n = 31$ (all trilaciclib) $n = 19$ (LOT1 trilaciclib initiators[b]) $n = 1574$ (non-trilaciclib)	iKM non-network $n = 35$ (all trilaciclib) $n = 18$ (LOT1 trilaciclib initiators[b]) $n = 959$ (non-trilaciclib)	FCS $n = 50$ (all trilaciclib) $n = 32$ (LOT1 trilaciclib initiators[b]) $n = 1239$ (non-trilaciclib)	Integra Connect $n = 21$ (all trilaciclib) $n = 3277$ (non-trilaciclib)	Pooled[a] $n = 137$ (all trilaciclib) $n = 69$ (LOT1 trilaciclib initiators[b]) $n = 7049$ (non-trilaciclib)
Grade 4 neutropenia	All trilaciclib	3.6	22.7	4.0	9.5	9.4
	LOT1 trilaciclib initiators[b]	0.0	10.0	0.0	–	2.6
	Non-trilaciclib	16.7	20.3	26.9	29.0	25.1
Grade 4 thrombocytopenia	All trilaciclib	3.6	3.1	6.0	0.0	3.8
	LOT1 trilaciclib initiators[b]	0.0	0.0	3.1	–	1.4
	Non-trilaciclib	10.3	19.3	16.1	14.6	14.5
Grade ≥ 3 myelosuppressive HAEs in ≥ 2 lineages	All trilaciclib	7.1	21.9	18.0	4.8	14.5
	LOT1 trilaciclib initiators[b]	0.0	11.8	6.3	–	6.0
	Non-trilaciclib	33.0	31.3	33.9	23.0	28.0
Grade ≥ 3 neutropenia + anemia	All trilaciclib	0.0	22.7	8.0	4.8	9.4
	LOT1 trilaciclib initiators[b]	0.0	20.0	6.3	–	8.1
	Non-trilaciclib	12.7	17.4	20.6	20.3	18.5

Table 3 continued

Outcomes	Study population	iKM network *n* = 31 (all trilaciclib) *n* = 19 (LOT1 trilaciclib initiators[b]) *n* = 1574 (non-trilaciclib)	iKM non-network *n* = 35 (all trilaciclib) *n* = 18 (LOT1 trilaciclib initiators[b]) *n* = 959 (non-trilaciclib)	FCS *n* = 50 (all trilaciclib) *n* = 32 (LOT1 trilaciclib initiators[b]) *n* = 1239 (non-trilaciclib)	Integra Connect *n* = 21 (all trilaciclib) *n* = 3277 (non-trilaciclib)	Pooled[a] *n* = 137 (all trilaciclib) *n* = 69 (LOT1 trilaciclib initiators[b]) *n* = 7049 (non-trilaciclib)
Grade ≥ 3 neutropenia + thrombocytopenia	All trilaciclib	0.0	22.7	10.0	4.8	10.1
	LOT1 trilaciclib initiators[b]	0.0	10.0	6.3	–	5.5
	Non-trilaciclib	12.4	18.7	22.8	23.0	20.3
Grade ≥ 3 anemia + thrombocytopenia	All trilaciclib	7.1	15.6	16.0	0.0	11.4
	LOT1 trilaciclib initiators[b]	0.0	5.9	6.3	–	4.5
	Non-trilaciclib	11.7	27.9	21.5	19.6	19.1
Cytopenia-related healthcare utilization, %						
G-CSF (during the defined outcome observation period[c])	All trilaciclib	9.7	34.3	60.0	71.4	43.8
	LOT1 trilaciclib initiators[b]	5.3	33.3	56.3	–	36.3
	Non-trilaciclib	71.5	69.6	89.7	83.9	80.2
G-CSF (within 3 days after index date)	All trilaciclib	3.2	8.6	–	47.6	16.1
	LOT1 trilaciclib initiators[b]	0.0	5.6	–	–	2.7
	Non-trilaciclib	43.9	41.3	–	61.1	53.2

Table 3 continued

Outcomes	Study population	iKM network *n* = 31 (all trilaciclib) *n* = 19 (LOT1 trilaciclib initiators[b]) *n* = 1574 (non-trilaciclib)	iKM non-network *n* = 35 (all trilaciclib) *n* = 18 (LOT1 trilaciclib initiators[b]) *n* = 959 (non-trilaciclib)	FCS *n* = 50 (all trilaciclib) *n* = 32 (LOT1 trilaciclib initiators[b]) *n* = 1239 (non-trilaciclib)	Integra Connect *n* = 21 (all trilaciclib) *n* = 3277 (non-trilaciclib)	Pooled[a] *n* = 137 (all trilaciclib) *n* = 69 (LOT1 trilaciclib initiators[b]) *n* = 7049 (non-trilaciclib)
ESAs (during the defined outcome observation period[e])	All trilaciclib	6.5	28.6	22.0	19.0	19.7
	LOT1 trilaciclib initiators[b]	0.0	11.1	15.6	–	10.1
	Non-trilaciclib	13.4	12.9	24.4	14.5	15.8
RBC transfusion or transfusion eligible (hemoglobin < 8 g/dL)	All trilaciclib	3.2	28.6	18.0	4.8	15.3
	LOT1 trilaciclib initiators[b]	0.0	22.2	9.4	–	10.2
	Non-trilaciclib	21.3	24.2	32.6	10.7	18.8
Platelet transfusion or transfusion eligible (platelets < 10,000/μL)	All trilaciclib	0.0	0.0	2.0	0.0	0.7
	LOT1 trilaciclib initiators[b]	0.0	0.0	0.0	–	0.0
	Non-trilaciclib	1.9	3.2	3.7	2.4	2.6

Table 3 continued

Outcomes	Study population	iKM network $n = 31$ (all trilaciclib) $n = 19$ (LOT1 trilaciclib initiators[b]) $n = 1574$ (non-trilaciclib)	iKM non-network $n = 35$ (all trilaciclib) $n = 18$ (LOT1 trilaciclib initiators[b]) $n = 959$ (non-trilaciclib)	FCS $n = 50$ (all trilaciclib) $n = 32$ (LOT1 trilaciclib initiators[b]) $n = 1239$ (non-trilaciclib)	Integra Connect $n = 21$ (all trilaciclib) $n = 3277$ (non-trilaciclib)	Pooled[a] $n = 137$ (all trilaciclib) $n = 69$ (LOT1 trilaciclib initiators[b]) $n = 7049$ (non-trilaciclib)
IV hydration	All trilaciclib	32.3	37.1	24.0	–	30.2
	LOT1 trilaciclib initiators[b]	15.8	44.4	15.6	–	23.2
	Non-trilaciclib	59.0	49.5	52.1	–	54.3

ANC absolute neutrophil count, ES-SCLC extensive-stage small cell lung cancer, *FCS* Florida Cancer Specialists and Research Institute, *iKM* iKnowMed, *LOT* line of therapy, *SD* standard deviation, *HAE* hematologic adverse event, *G-CSF* granulocyte colony-stimulating factors, *ESAs* erythropoiesis-stimulating agents, *RBC* red blood cell, *IV* intravenous, *EMR* electronic medical record

[a]Pooled analysis was conducted by estimating the weighted average among the study populations reporting a specific outcome using sample size as the weight

[b]The analysis among LOT1 trilaciclib initiators was conducted on the basis of the iKM network and non-network study populations as well as the FCS study. The two iKM-based studies defined LOT1 trilaciclib initiators as those using trilaciclib before the first cycle in the first-line treatment, while the FCS study defined it as initiation of trilaciclib anytime during the first-line treatment

[c]Data were provided by the authors of the corresponding studies

[d]The denominator for each outcome was the number of patients with the relevant lab values. For single lineage outcomes, the denominators were the number of patients with non-missing ANC for the prevalence of neutropenia, the number of patients with non-missing hemoglobin value for the prevalence of anemia, the number of patients with non-missing platelet value for the prevalence of thrombocytopenia. For multilineage outcomes, the denominators were the number of patients with non-missing values for ANC, hemoglobin and platelet counts for the prevalence of grade ≥ 3 myelosuppressive HAEs in ≥ 2 lineages, the number of patients with non-missing values for ANC and hemoglobin count for the prevalence of grade ≥ 3 neutropenia + anemia, the number of patients with non-missing values for ANC and platelet count for the prevalence of grade ≥ 3 neutropenia + thrombocytopenia, and the number of patients with non-missing values for hemoglobin and platelet counts for the prevalence of anemia + thrombocytopenia

[e]The outcome observation period was defined as the time from the index date to 14 days after last trilaciclib administration of index chemotherapy regimen in the iKM-based study, the period during chemotherapy cycles when trilaciclib was used in the FCS study, and the time from the index date to the end of follow-up (i.e., date of death, last EMR activity date, or end of the study period, whichever occurs first) in the Integra Connect study

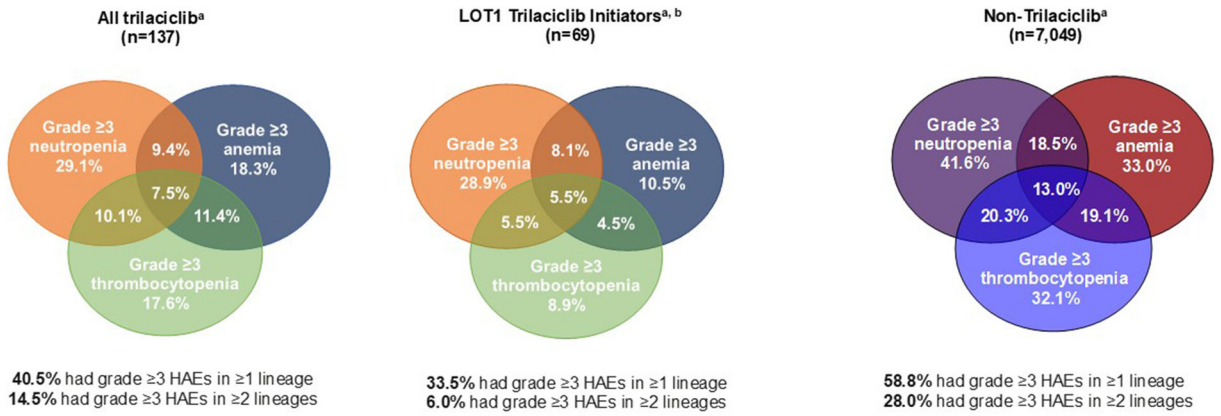

Fig. 2 Real-world prevalence of grade ≥ 3 myelosuppressive HAEs by lineage. *ANC* absolute neutrophil count, *iKM* iKnowMed, *HAE* hematologic adverse event, *FCS* Florida Cancer Specialists and Research Institute, *LOT* line of therapy. [a]Weighted average prevalence was calculated using sample size as weight. The denominator for each outcome was the number of patients with the relevant lab values. The all trilaciclib group had 131 patients, the LOT1 trilaciclib initiators group had 69 patients, and the non-trilaciclib group had 6547 patients with relevant lab values. For single lineage outcomes, the denominators were the number of patients with non-missing ANC for the prevalence of neutropenia, the number of patients with non-missing hemoglobin value for the prevalence of anemia, the number of patients with non-missing platelet value for the prevalence of thrombocytopenia. For multilineage outcomes, the denominators were the number of patients with non-missing values for ANC, hemoglobin and platelet counts for the prevalence of grade ≥ 3 myelosuppressive HAEs in ≥ 3 and ≥ 2 lineages. [b]The analysis among LOT1 trilaciclib initiators was conducted on the basis of the iKM network and non-network study populations as well as the FCS study. The two iKM-based studies defined LOT1 trilaciclib initiators as those using trilaciclib before the first cycle in the first-line treatment, while the FCS study defined it as initiation of trilaciclib anytime during the first-line treatment

with EP with or without an IO agent [34, 35, 37], which was also the most common chemotherapy regimen in the historical non-trilaciclib groups (87–96%).

Baseline myelosuppression rates were generally numerically higher in the trilaciclib cohorts compared to their corresponding historical non-trilaciclib groups (Table 2). Notably, the trilaciclib cohorts had numerically higher rates of neutropenia, anemia, and thrombocytopenia during baseline in the iKM-based and FCS studies [34, 35]. The Integra Connect study did not report such information.

Real-World Outcomes of Trilaciclib

All outcomes were evaluated during the follow-up period as defined in the individual studies (Table 1). The mean follow-up time was similar across the trilaciclib studies, ranging from 4.0 to 4.8 months [34, 35, 37]. Compared to the trilaciclib cohorts, the mean follow-up duration was longer in the historical non-trilaciclib cohorts, ranging from 8.9 to 10.4 months [14, 36–38] (Table 3). However, despite the differences in the follow-up time, the mean number of chemotherapy cycles was comparable between the trilaciclib (5 cycles) and the corresponding non-trilaciclib (4.4–5.3 cycles) cohorts in the iKM-based study, which was the only study that included such information.

Myelosuppressive HAEs

The prevalence of any grade ≥ 3 myelosuppressive HAE among trilaciclib-treated patients ranged from 28.6% in the Integra Connect study [37] to 50.0% in the iKM non-network study [34], with a weighted average of 40.5% (Table 3, Fig. 2). The weighted average prevalence of grade ≥ 3 neutropenia, grade ≥ 3 thrombocytopenia, and grade 3 anemia in the trilaciclib cohorts was 29.1%, 17.6%, and

18.3%, respectively (Table 3, Fig. 2). The weighted average prevalence of grade ≥ 3 myelosuppressive HAEs in at least two lineages was 14.5% (Fig. 2), with the prevalence in individual studies ranging from 4.8% to 21.9%. The weighted average prevalence was similar for different lineage combinations, ranging from 9.4% for grade ≥ 3 neutropenia + grade ≥ 3 anemia to 11.4% for grade ≥ 3 anemia + grade ≥ 3 thrombocytopenia (Table 3, Fig. 2). The prevalence of grade ≥ 3 myelosuppressive HAEs in all three lineages ranged from 0% in the iKM network study [34] and the Integra Connect study [37] to 18.2% in the iKM non-network study [34], with a weighted average of 7.5% (Fig. 2).

In general, the historical non-trilaciclib cohorts [14, 36–38] had numerically higher prevalence of myelosuppressive HAEs compared to the corresponding trilaciclib cohorts. This was observed in the weighted average prevalence of any grade ≥ 3 myelosuppressive HAE, grade ≥ 3 neutropenia, grade ≥ 3 thrombocytopenia, and grade 3 anemia, as well as multilineage grade ≥ 3 myelosuppressive HAEs, which were all higher in the non-trilaciclib cohorts compared to the trilaciclib cohorts (Table 3, Fig. 2). This trend was consistent across different severity levels of

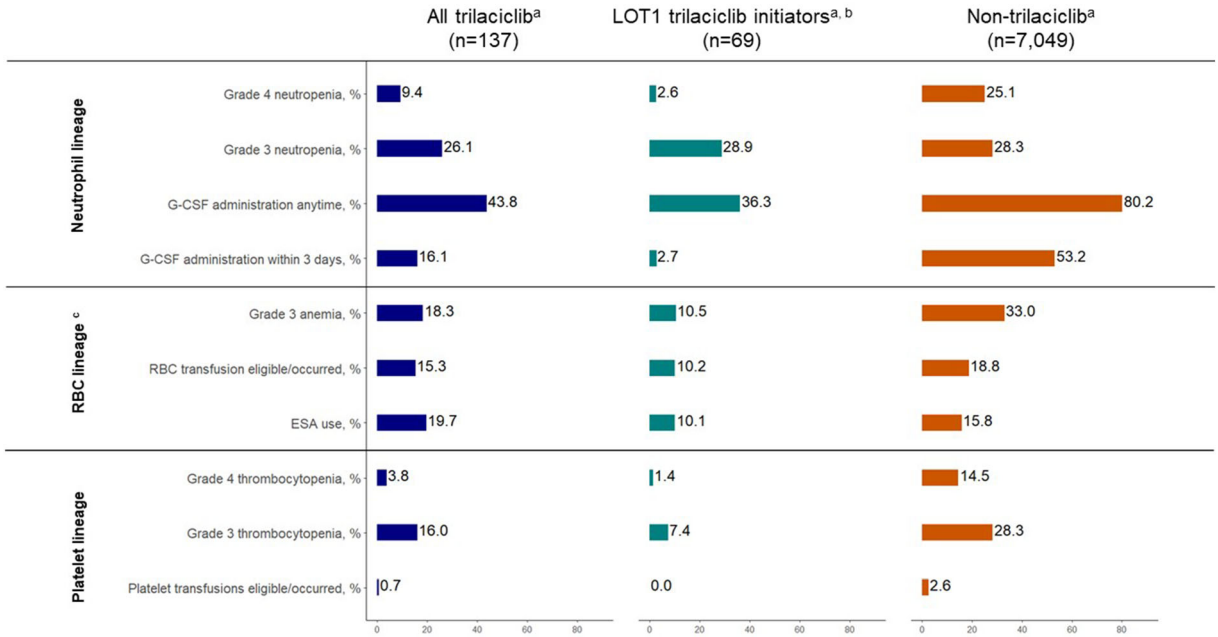

Fig. 3 Real-world outcomes associated with trilaciclib and non-trilaciclib studies. *ESAs* erythropoiesis-stimulating agents, *G-CSF* granulocyte colony-stimulating factors, *iKM* iKnowMed, *LOT* line of therapy, *RBC* red blood cell, *FCS* Florida Cancer Specialists and Research Institute. [a]Weighted average prevalence was calculated using sample size as weight. The denominator for grade 3 or higher cytopenia outcome was the number of patients with the relevant lab values. The all trilaciclib group had 131 patients, the LOT1 trilaciclib initiators group had 69 patients, and the non-trilaciclib group had 6547 patients with relevant lab values. The denominator for G-CSF administration, ESA and transfusion was the number of patients in the corresponding cohort [b]The analysis among LOT1 trilaciclib initiators was conducted on the basis of the iKM network and non-network study populations as well as the FCS study. The two iKM-based studies defined LOT1 trilaciclib initiators as those using trilaciclib before the first cycle in the first-line treatment, while the FCS study defined it as initiation of trilaciclib anytime during the first-line treatment. [c]For RBC and platelet transfusions, the iKM-based and FCS studies estimated the percentages using the number of patients eligible for transfusion based on their lab values, whereas the Integra Connect study used the number of patients receiving transfusions

myelosuppressive HAEs, with more pronounced differences observed in grade 4 myelosuppressive HAEs (Table 3, Fig. 3). For instance, while the weighted average prevalence of grade 3 neutropenia was similar between the non-trilaciclib and trilaciclib cohorts (28.3% vs. 26.1%, respectively), the prevalence of grade 4 neutropenia was numerically higher in the non-trilaciclib cohorts (25.1% vs. 9.4%). Similarly, the weighted average prevalence of grade 3 thrombocytopenia was nearly doubled in the non-trilaciclib cohorts compared to the trilaciclib cohorts (28.0% versus 16.8%), while the prevalence of grade 4 thrombocytopenia was more than three times higher in the non-trilaciclib cohorts than in the trilaciclib cohorts (14.5% versus 3.8%).

The subgroup analyses revealed that LOT1 trilaciclib initiators generally had numerically lower prevalence of grade $\geq$ 3 myelosuppressive HAEs compared to the overall trilaciclib cohorts [39, 40] (Table 3, Figs. 2 and 3). Specifically, among LOT1 trilaciclib initiators, the weighted average prevalence of grade $\geq$ 3 neutropenia, grade $\geq$ 3 thrombocytopenia, and grade 3 anemia was 28.9%, 8.9%, and 10.5%, respectively, all of which were numerically lower than the overall trilaciclib cohorts. The weighted average prevalence of grade $\geq$ 3 myelosuppressive HAEs was 33.5% and 6.0% in at least one lineage and at least two lineages, respectively. The weighted average prevalence grade $\geq$ 3 myelosuppressive HAEs in two lineages was consistent across different lineage combinations (Table 3). The weighted average prevalence of grade $\geq$ 3 myelosuppressive HAEs in all three lineages was 5.5% (Fig. 2).

Cytopenia-Related Healthcare Utilization

Cytopenia-related healthcare utilization mirrored the prevalence of grade $\geq$ 3 myelosuppressive HAEs, with generally higher utilization observed as the prevalence increased (Table 3).

In the trilaciclib cohorts, rate of G-CSF use during the defined outcome observation period ranged from 9.7% in the iKM network study [34] to 71.4% in the Integra Connect study [37], with a weighted average of 43.8%. Rate of G-CSF use within 3 days after the index date (i.e., a proxy for prophylactic G-CSF use) ranged from 3.2% in the iKM network study [34] to 47.6% in the Integra Connect study [37], with a weighted average of 16.1%. Rate of ESA use during the defined outcome observation period ranged from 6.5% in the iKM network study [34] to 28.6% in the iKM non-network study [34], with a weighted average of 19.7%. Between 3.2% and 28.6% of trilaciclib-treated patients received RBC transfusion or were RBC transfusion-eligible, averaging 15.3% in the trilaciclib cohorts. Platelet transfusion or transfusion eligible was rare in the identified trilaciclib studies—only the FCS study reported a 2.0% platelet transfusion eligible rate [35], which resulted in a weighted average of 0.7% in the trilaciclib cohorts. IV hydration occurred in 30.2% of trilaciclib-treated patients based on the weighted average of the three trilaciclib cohorts with the available outcomes (i.e., the iKM network and non-network studies and the FCS study [34, 35]).

The historical non-trilaciclib cohorts [14, 36–38] had numerically higher cytopenia-related healthcare utilization in all types compared to the corresponding trilaciclib cohorts, except ESA use, which had similar rates between the trilaciclib and non-trilaciclib cohorts (Table 3). The difference was most pronounced in G-CSF use, with the weighted average rate of 80.2% during the defined outcome observation period and 53.2% within three days after the index date in the historical non-trilaciclib cohorts, compared to the corresponding rates of 43.8% and 16.1% in the trilaciclib cohorts. The weighted average rates of RBC transfusion/transfusion eligible, platelet transfusion/transfusion eligible and IV hydration were 18.8%, 2.6%, and 54.3%, respectively, in the historical non-trilaciclib cohorts, all of which were higher than the trilaciclib cohorts.

The subgroup analyses showed consistently lower cytopenia-related healthcare utilization in the LOT1 trilaciclib initiators compared to the overall trilaciclib users (Table 3). Specifically, the weighted average rates of G-CSF use during the defined outcome observation period and within three days after the index date were 36.3% and 2.7% respectively, much lower than the overall trilaciclib users. The weighted average rate of ESA use during the defined outcome

observation period among LOT1 trilaciclib initiators was also numerically lower than the overall trilaciclib users (10.1% vs. 19.7%). Furthermore, 10.2% LOT1 trilaciclib initiators were RBC transfusion eligible, while none was platelet transfusion eligible. In addition, the weighted average rate of IV hydration was 23.2%, slightly lower than the overall trilaciclib users.

Other Outcomes

Dose reduction and treatment delay were evaluated in the iKM-based trilaciclib and non-trilaciclib studies [14, 34, 40]. Such outcomes were not available in the FCS or Integra Connect studies due to data limitations. When weighted between the iKM network and non-network cohorts, the average rate of dose reduction was 11.3% among the trilaciclib cohorts, numerically lower than 42.3% in the historical non-trilaciclib cohorts. LOT1 trilaciclib initiators had an even lower dose reduction rate of 5.4%. A similar trend was observed in treatment delay, with the weighted average rate of treatment delay of 31–60 days being 8.2%, 5.4% and 18.0% for trilaciclib patients, LOT1 trilaciclib initiators and historical non-trilaciclib, respectively.

Hospitalization was evaluated only in the Integra Connect study [37]. Although the sample size was limited, the findings suggest lower hospitalization rate and shorter length of stay (LOS) in the trilaciclib cohort. Only one patient in the trilaciclib cohort had a hospitalization within 21 days following the index date, resulting in a hospitalization rate of 4.8%, and no patients experienced hospitalization between 8 and 16 days following the index date. The corresponding hospitalization rates in the historical non-trilaciclib cohort were 18.8% and 7.4%, respectively. The mean LOS was 1 day in the trilaciclib cohort vs. 34 days (median 4 days) in the historical non-trilaciclib cohort for the hospitalizations that occurred within 21 days following the index date.

DISCUSSION

Trilaciclib is the first treatment in its class approved by the FDA for decreasing the incidence of CIM in adult patients with ES-SCLC who received platinum/etoposide-containing or topotecan-containing chemotherapies. It proactively protects HSPCs and thus impacts all lineages. As ES-SCLC mainly affects elderly patients who are at an increased risk of CIM and reduced dose intensity [15], trilaciclib may potentially improve the treatment outcomes of chemotherapy in this population. To date, most of the evidence on trilaciclib effectiveness was based on clinical trials. However, real-world outcomes constitute an important part of treatment decision-making because clinical trial results may not be reflected in real-world practice wherein trilaciclib-treated patients are more heterogenous and have some distinctive features compared to the clinical trial population. For example, they appeared to be older (49–81% were age 65 or older in real-world studies, compared to 46% in the pooled results from the three clinical trials) and have fewer male patients (44–52% in real-world studies, compared to 72% in pooled results from the three clinical trials) [26]. On the basis of the available data, real-world trilaciclib-treated patients appeared to have poorer performance status based on the ECOG score of 0/1 (82.6–85.7% in real-world studies vs. overall 87.8% among the clinical trials). Furthermore, trilaciclib was initiated before cycle 1 of chemotherapy in the clinical trials, whereas trilaciclib can be initiated after cycle 1 of chemotherapy in the real world as a result of various reasons. Therefore, it is important to confirm the clinical trial findings in real-world settings. To our knowledge, the current study is the first one to comprehensively review the literature and synthesize the real-world outcomes of trilaciclib in ES-SCLC.

The real-world evidence on trilaciclib is limited, primarily as a result of its recent approval. However, the existing evidence supports the real-world effectiveness of trilaciclib in ES-SCLC. The synthesized evidence showed that trilaciclib-treated patients had numerically lower prevalence of grade $\geq$ 3 myelosuppressive HAE in at least one lineage, grade $\geq$ 3 myelosuppressive HAE in each lineage (i.e., neutropenia, anemia, and thrombocytopenia), and multilineage grade $\geq$ 3 myelosuppressive HAEs in reference to the outcomes of non-trilaciclib-treated patients from the same databases (i.e.,

historical comparisons). In particular, the differences were more prominent in grade 4 compared to grade 3 myelosuppressive HAEs, suggesting that trilaciclib may not only reduce the prevalence of grade ≥ 3 myelosuppressive HAEs but also the severity of myelosuppressive HAEs. Of note, numerical differences in baseline characteristics between the trilaciclib and non-trilaciclib cohorts may impact the outcomes. However, most of the differences were small or biased against the trilaciclib cohort (e.g., a higher percentage of baseline myelosuppressive HAE rates). Although the follow-up time was generally shorter in the trilaciclib cohorts, the duration of chemotherapy exposure was comparable between the trilaciclib and non-trilaciclib cohorts on the basis of the data from the iKM-based study. Given that myelosuppressive HAEs are related to the duration of chemotherapy exposure, we do not expect the difference in the follow-up time would bias the results. Overall, the outcomes are generally consistent across individual studies though there were some variations in prevalence rates between studies. Such variations may be related to the criteria with which trilaciclib patients were selected, certain baseline differences, and some unobserved factors. For example, the iKM non-network and the FCS trilaciclib studies had higher rates of grade ≥ 3 myelosuppressive HAEs at baseline than the iKM network trilaciclib study, and some rates were much higher than the corresponding historical non-trilaciclib cohorts [34, 35].

Mirroring the myelosuppressive HAE outcomes, real-world studies also showed generally lower cytopenia-related healthcare utilization in trilaciclib-treated patients than the corresponding historical non-trilaciclib cohorts [34, 35]. The reduced utilization was more prominent in G-CSF, particularly its use within 3 days after the index date, which was used as a proxy of prophylactic G-CSF use. Evidence on other outcomes is extremely limited in the real world. Two studies evaluated dose reduction and treatment delay and the results suggest the potential impact of trilaciclib on reducing these outcomes [14, 34]. Only one study reported hospitalization [37], which indicated that trilaciclib may be associated with lower hospitalization rate and shorter LOS.

In addition, results for the subgroup of LOT1 trilaciclib initiators generally showed numerically lower prevalence of grade ≥ 3 myelosuppressive HAEs, cytopenia-related healthcare utilization, and rates of dose reduction and treatment delay than the overall trilaciclib cohorts [39, 40]. The differences are more pronounced in grade 4 myelosuppressive HAEs, G-CSF use within 3 days after the index date, and ESA use. Moreover, none of the LOT1 trilaciclib initiators were considered platelet transfusion eligible. These findings suggest potentially greater benefits if trilaciclib is administered before the initiation of the first-line therapy.

Despite the differences in certain patient characteristics between trilaciclib real-world studies and clinical trials, results from both types of studies suggest that trilaciclib is associated with lower grade ≥ 3 myelosuppressive HAE rates and lower cytopenia-related resource utilization. The weighted average prevalence of any grade ≥ 3 myelosuppressive HAE, grade ≥ 3 neutropenia, grade ≥ 3 anemia and grade ≥ 3 thrombocytopenia in the trilaciclib cohorts was 40.5%, 29.1%, 18.3%, and 17.6%, respectively, similar to the corresponding rates in the pooled analysis of clinical trials, i.e., 44.3%, 32.0%, 16.4%, and 18.0%, respectively [28]. The weighted average prevalences of grade ≥ 3 neutropenia + grade ≥ 3 thrombocytopenia and grade ≥ 3 myelosuppressive HAEs in all three lineages in real-world studies were also within the ranges reported from individual trials [28]. Rates of cytopenia-related healthcare utilization are not directly comparable between the trilaciclib real-world studies and clinical trials because of variations in treatment protocols and outcomes definitions. For example, the rates of RBC and platelet transfusions were based on the observed outcomes in clinical trials but proxies in some real-world studies. Despite the differences, both real-world studies and clinical trials reported lower rates of G-CSF use and RBC transfusion in trilaciclib-treated patients [27]. The findings are less consistent in ESA use and platelet transfusion. The clinical trials found a significantly lower rate of ESA use

in the trilaciclib arm but a similar rate of platelet transfusion between trilaciclib and placebo. In contrast, real-world studies showed a similar rate of ESA use but a lower rate of platelet transfusion/transfusion eligible between the trilaciclib cohort and the historical non-trilaciclib group in the pooled analysis. Regarding dose reduction, treatment delay and HCRU, real-world evidence is limited. However, the existing evidence suggests lower rates of dose reduction and treatment delay, a lower rate of hospitalization, and shorter LOS in trilaciclib-treated patients compared to the historical non-trilaciclib cohorts, similar to the findings in the clinical trials [23–26].

The current real-world evidence on trilaciclib should be interpreted in the context of the limitations of existing studies, with the most important ones being lack of comparative effectiveness studies and small sample size. Of all three identified real-world trilaciclib studies, two were single-arm studies with only trilaciclib-treated patients [34, 35]. Even though the Integra Connect study reported outcomes of both trilaciclib- and non-trilaciclib-treated patients [37], it did not perform a formal comparison between the two groups possibly because of the small sample size of trilaciclib-treated patients (n = 21). Small sample size is a common limitation in all trilaciclib studies, which is not surprising as a result of the recent approval of trilaciclib. These limitations pointed out important gaps in the real-world evidence on trilaciclib, which can be potentially addressed by future studies. Comparative effectiveness studies with a comparable non-trilaciclib cohort and adjustment for confounding factors will provide more robust evidence on the real-world effectiveness of trilaciclib and should be included in the agenda for future studies. In addition, it is also recommended to increase the sample size in future studies and further evaluate the outcomes in subgroups. Moreover, with a larger sample size and longer follow-up time, future real-world studies may include additional outcomes, such as progression-free survival and overall survival as well as safety outcomes.

The current literature review provides timely real-world evidence on trilaciclib to support treatment decision-making. To comprehensively synthesize the existing evidence, great effort was devoted to identifying the studies that are not in the public domain. In addition, to facilitate the interpretation of the results for trilaciclib-treated patients, comparable non-trilaciclib cohorts were also identified and summarized in the current review. The findings support the benefits of trilaciclib that have been demonstrated in the clinical trials. The effect of trilaciclib on reducing grade $\geq$ 3 myelosuppressive HAEs as well as dose reduction and treatment delay may potentially translate into better clinical outcomes and QoL among patients with ES-SCLC. Trilaciclib may be particularly beneficial to patients who suffer from myelosuppressive HAEs in all three lineages. Moreover, potential reduction in cytopenia-related healthcare utilization and hospitalizations may alleviate overall burden of ES-SCLC on healthcare systems. The impact of trilaciclib on ES-SCLC management may be even greater in the context of the COVID-19 pandemic. Patients with cancer are at higher risk than those without cancer of being infected with COVID-19 and suffering from serious complications [41]. In addition, COVID-19 has exacerbated constraints in healthcare resources [41]. Reduction in blood donation due to social isolation and fear of COVID-19 infection has led to limited blood supplies for patients with severe myelosuppressive HAEs who need transfusion. Concerns over hospitalization may direct physicians to use "safer" cancer treatments that are less effective. Trilaciclib may reduce patients' susceptibility to viral infection and alleviate the concerns over limited resources by reducing the need for blood transfusions and hospitalization related to CIM in patients with ES-SCLC.

CONCLUSIONS

The existing evidence suggests that trilaciclib may reduce single and multilineage grade $\geq$ 3 myelosuppressive HAEs and cytopenia-related healthcare utilization among patients with ES-SCLC in the real world. These benefits may be more prominent in LOT1 trilaciclib initiators who receive trilaciclib before or during first-line chemotherapy. Trilaciclib is a promising new treatment for CIM prevention in patients

with ES-SCLC. Future studies with larger sample sizes are recommended to comprehensively evaluate the real-world effectiveness of trilaciclib and confirm the findings of the current study.

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