

Systematic Literature Review of Second-line Treatments for Small-cell Lung Cancer

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Background

- Lurbinectedin (3.2 mg/m² every 3 weeks; intravenous [IV], 1-hour infusion) received accelerated approval from the US Food and Drug Administration (June 2020) for the treatment of adult patients with metastatic small-cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy¹ based on results of the SCLC cohort from a phase 2 basket trial²
 - A single-arm, phase 2 basket trial of lurbinectedin (ClinicalTrials.gov Identifier: NCT02454972) demonstrated an overall response rate (ORR) of 35.2%, a median duration of response (DoR) of 5.3 months, and a median overall survival (OS) of 9.3 months, as measured by investigator assessment (data cutoff: January 15, 2019)²
- Head-to-head randomised controlled trials (RCTs) comparing the efficacy of lurbinectedin monotherapy with other second-line SCLC therapies are not available

Objective

- We conducted a systematic literature review (SLR) to identify clinical trials of second-line SCLC therapies recommended by the National Comprehensive Cancer Network (NCCN) guidelines and assessed the feasibility of an indirect treatment comparison (ITC) to estimate the relative efficacy and safety of lurbinectedin versus relevant comparators

Methods

SLR

- A comprehensive database search using predefined criteria (summarised in **Table 1**) included:
 - Published data from EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials
 - Grey literature search results from the US National Institutes of Health Clinical Trial Registry, the American Society of Clinical Oncology (ASCO), the American Association for Cancer Research (AACR), and the International Association for the Study of Lung Cancer World Conference on Lung Cancer (IASLC WCLC)
 - The bibliographies of recently published relevant systematic reviews and meta-analyses were also searched
- Searches were executed on January 6, 2021; only studies published in English from 1990 to January 2021 were included
- Two independent reviewers conducted abstract/full-text selection and data extraction

Unanchored Matching-adjusted Indirect Comparison (MAIC) and Network Meta-analysis (NMA)

- An unanchored MAIC was performed to connect the single-arm lurbinectedin study (Trigo 2020) to the connected network of RCTs identified through the SLR
- A fixed-effect NMA using a Bayesian framework was subsequently performed to evaluate the comparative efficacy of lurbinectedin versus relevant competing interventions
 - Although both fixed- and random-effects models were considered for all analyses, fixed-effect models were preferred given that all evidence networks consisted of relatively few trials, which caused the random-effects models to lead to unstable estimates
- Relative effectiveness was assessed with hazard ratios (HRs) and odds ratio (ORs) with 95% credible intervals (CrIs)

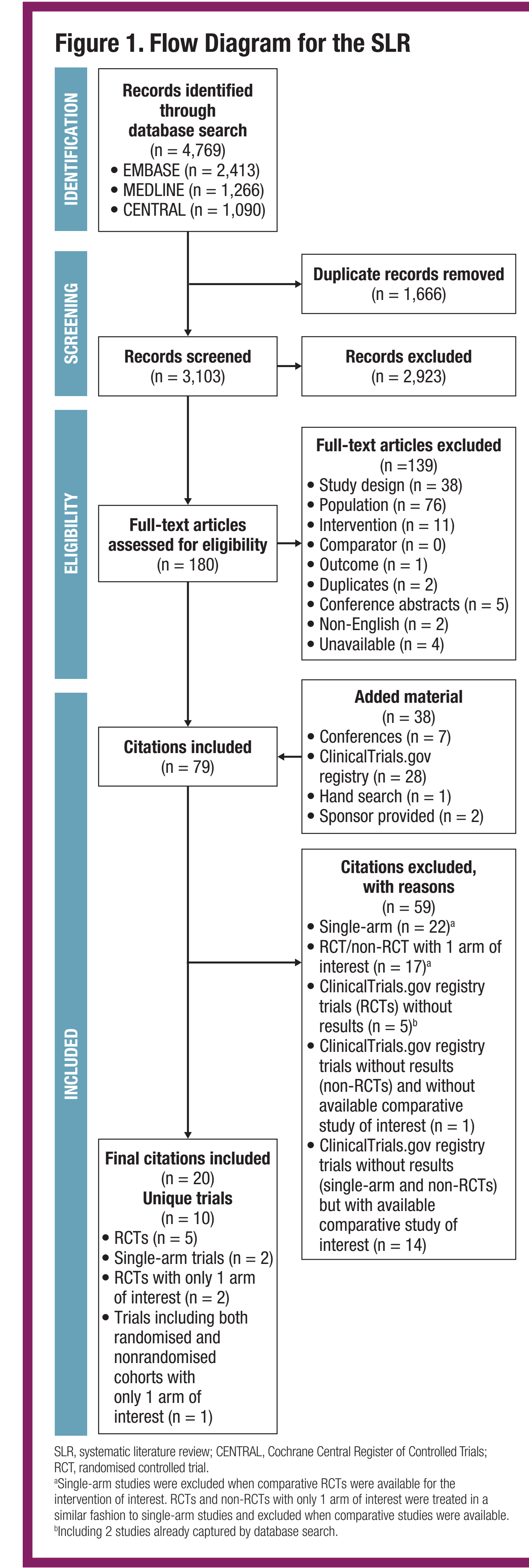
Table 1. Eligibility Criteria for Study Screening

Criteria	Inclusion
Population	Adults ≥18 years of age with 2L SCLC and ≥1 prior platinum-based chemotherapy regimen Subgroups of interest: <ul style="list-style-type: none"> Age: <65 years; ≥65 years Platinum-sensitivity status: sensitive (CTFI ≥90 days); resistant (CTFI <90 days) Performance status: ECOG = 0; ECOG = 1; ECOG = 2 Stage at diagnosis: LS SCLC; ES SCLC
Interventions*	Treatments recommended as subsequent systemic therapy in the NCCN guidelines (v1.2021) ³ : <ul style="list-style-type: none"> Lurbinectedin Topotecan (oral or IV) Platinum rechallenge with carboplatin or cisplatin + etoposide or irinotecan Paclitaxel, docetaxel, irinotecan, nivolumab, pembrolizumab
Comparators	<ul style="list-style-type: none"> Placebo or BSC Any intervention of interest Any treatment that facilitates an indirect comparison
Outcomes	At least 1 of the following efficacy outcomes: <ul style="list-style-type: none"> OS, PFS/TTP, tumor response (ORR, CR, PR, SD, PD, CBR, DCR), and DoR
Study design*	<ul style="list-style-type: none"> Phase 1/2, 2, or 3 RCTs In a stepwise manner, where no RCTs were available, nonrandomised prospective clinical trials or single-arm clinical trials (phase 1/2, 2, or 3) were included⁴

2L, second-line; SCLC, small-cell lung cancer; CTFI, chemotherapy-free interval; ECOG, Eastern Cooperative Oncology Group; LS, limited-stage; ES, extensive-stage; NCCN, National Comprehensive Cancer Network; IV, intravenous; BSC, best supportive care; OS, overall survival; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; RCT, randomised controlled trial; CAU, cyclophosphamide + doxorubicin + vincristine.
*Only monotherapy regimens were included unless otherwise specified. Excluded treatments: nonpharmacologic interventions (eg, surgery, radiotherapy), lurbinectedin combination therapy, nivolumab + ipilimumab, gemtuzumab, bendamustine, etoposide monotherapy, temozolomide, vinorelbine, and GAV. Long-term follow-up and post hoc analyses of relevant studies were included. *Included for an intervention of interest only when comparative studies were unavailable.

Results

- Of 4,769 citations identified, 10 unique relevant trials were included (5 RCTs, 2 single-arm trials, 2 RCTs with 1 arm of interest, and 1 trial with randomised and nonrandomised cohorts with 1 arm of interest; **Figure 1**)



SLR, systematic literature review; CENTRAL, Cochrane Central Register of Controlled Trials; RCT, randomised controlled trial.
*Single-arm studies were excluded when comparative RCTs were available for the intervention of interest. RCTs and non-RCTs with only 1 arm of interest were treated in a similar fashion to single-arm studies and included when comparative studies were available.
^aIncluding 2 studies already captured by database search.

- Baseline patient characteristics were generally consistent across trials (**Table 2**), although there were differences in the proportion of patients with:
 - Limited-stage and extensive-stage SCLC
 - Eastern Cooperative Oncology Group (ECOG) performance status
 - Platinum-sensitive and platinum-resistant disease

Table 2. Summary of Baseline Patient Characteristics of Trials Identified in the SLR

Trial ID	Treatment	Analysis population	Line of therapy	N	ECOG PS, n (%)			Disease stage, n (%)		Response to 1L, n (%)	
					0	1	2	LS	ES	Resistant	Sensitive
RCTs											
Baize 2020 ⁵ (N = 164)	Topotecan (oral)	ITT, CTFI ≥90 d	2L	81	26 (32.1)	48 (59.3)	7 (8.6)	30 (37.0)	51 (63.0)	0 (0)	81 (100)
	Carboplatin + etoposide	ITT, CTFI ≥90 d	2L	81	28 (34.6)	49 (59.3)	5 (6.2)	29 (35.8)	52 (64.2)	0 (0)	81 (100)
O'Brien 2006 ⁶ (N = 141)	BSC	ITT	2L	70	6 (8.6)	41 (58.6)	23 (32.9)	27 (38.6)	43 (61.4)	35 (50.0)	35 (50.0)
	Topotecan (oral) + BSC	ITT	2L	71	8 (11.3)	44 (62.0)	19 (26.8)	23 (32.4)	48 (67.6)	41 (57.7)	30 (42.3)
Eckardt 2007 ⁷ (N = 309)	Topotecan (oral)	ITT, CTFI ≥90 d ^a	2L	153	48 (31.4)	85 (55.6)	20 (13.1)	51 (33.3)	102 (67.7)	15 ^b (9.8)	134 ^c (87.6)
	Topotecan (IV)	ITT, CTFI ≥90 d ^a	2L	151	35 (23.2)	98 (64.9)	18 (11.9)	45 (29.8)	106 (70.2)	13 ^b (8.6)	137 ^c (90.7)
von Pawel 2001 ⁸ (N = 106)	Topotecan (oral)	ITT, CTFI ≥90 d ^a	2L	52	10 ^a (19.2)	34 ^a (65.4)	8 ^a (15.4)	14 ^a (26.9)	37 ^a (71.2)	1 (1.9)	51 (98.1)
	Topotecan (IV)	ITT, CTFI ≥90 d ^a	2L	54	18 ^a (33.3)	21 ^a (38.9)	15 ^a (27.8)	14 ^a (25.9)	39 ^a (72.2)	1 (1.9)	53 (98.1)
United Therapeutics 2017 ⁹ (N = 483)	Irinotecan	ITT	2L	190	40 (21.1)	150 (78.9)	0 (0)	–	–	–	–
	Topotecan (IV)	ITT	2L	94	19 (20.2)	75 (79.8)	0 (0)	–	–	–	–
RCTs with only 1 arm of interest											
Owonikoko 2020 ¹⁰ (N = 178)	Paclitaxel + placebo	ITT	2L	89	18 (20.2)	71 (79.8)	0 (0)	8 ^a (9.0)	62 ^a (69.7)	33 ^{a*} (37.1)	35 ^{a*} (39.3)
CheckMate 331 ¹¹ (N = 569)	Nivolumab	ITT	2L	284	75 (26.4)	209 (73.6)	0 (0)	74 (26.1)	210 (73.9)	121 (42.6)	163 (57.4)
Non-RCTs/RCTs with only 1 arm of interest											
CheckMate 032	Nivolumab	Overall	2L+	98 ^a	–	–	–	–	–	30 ^{a*} (30.6)	55 ^{a*} (56.1)
CheckMate 032	Nivolumab	ITT	2L+	147 ^a	49 (33.3)	98 (66.7)	–	–	–	73 ^{a*} (49.7)	73 ^{a*} (49.7)
Single-arm trials											
Trigo 2020 ² (N = 105) ^b	Lurbinectedin	Treated population	2L	105	38 (36.2)	59 (56.2)	8 (7.6)	32 (30.5)	73 (69.5)	45 (42.9)	60 (57.1)
Smyth 1994 ¹² (N = 34)	Docetaxel	Overall	1L+	34	8 ^a (23.5)	22 ^a (64.7)	4 ^a (11.8)	0 (0)	34 (100)	–	–

ECOG PS, Eastern Cooperative Oncology Group performance status; 1L, first-line; LS, limited-stage; ES, extensive-stage; RCT, randomised controlled trial; ITT, intent-to-treat; CTFI, chemotherapy-free interval; d, days; 2L, second-line; BSC, best supportive care; IV, intravenous; WHO, World Health Organization.
Note: Highlighting indicates similarity (green), some differences (yellow), and major differences (red) in characteristics based on visual assessment.
^aApproximately 10% of patients in both treatment groups had a CTFI <90 days at study entry. Missing patient data was reported. ^bApproximately 2% of patients in both treatment groups had a CTFI <90 days at study entry. ^cWHO performance status. ^dPlatinum refractory. 16/89 (18%). Mixed population, baseline characteristics for the 2L population not provided. ^eThree patients in the nivolumab 3 mg/kg group did not receive 1L platinum therapy and did not meet eligibility criteria, although they were treated and included in the analysis. ^fThe study enrolled 110 patients; however, 5 patients did not receive treatment.

Conclusions

- Results from the SLR confirmed that it was feasible to evaluate the comparative efficacy of lurbinectedin versus key comparators of interest, as required assumptions were not prohibitive
- Given the inclusion of a disconnected single-arm trial, an unanchored MAIC was used to compare lurbinectedin with other treatments
- Restricting the ITC to patients with platinum-sensitive disease receiving second-line therapy for SCLC reduced heterogeneity
- In the base case fixed-effect NMA, lurbinectedin showed a robust survival benefit for the second-line treatment of patients with platinum-sensitive SCLC compared with topotecan and platinum rechallenge
 - Lurbinectedin had a significantly greater OS versus oral topotecan, IV topotecan, and carboplatin plus etoposide, and a significantly greater ORR versus oral topotecan

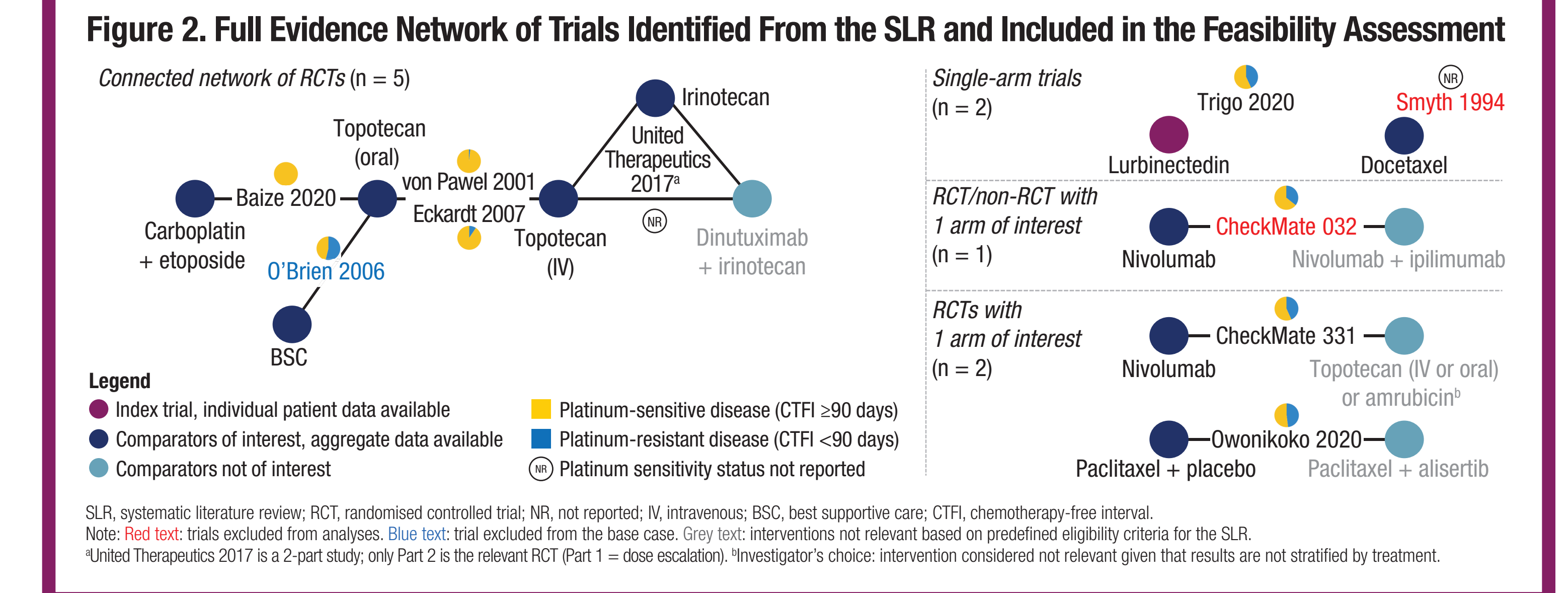
- Data extraction of patient characteristics and outcomes from the SLR does not reflect statistical comparison (**Table 3**)
- For ORR, tumour assessment was based on investigator assessment in 4 trials, independent review committee in 3 trials, both in 1 trial, and unknown assessors in 2 trials
- Among patients with platinum-sensitive disease (CTFI ≥90 days):
 - ORR ranged from 3.0% (O'Brien 2006) to 25.3% (Baize 2020) for oral or IV topotecan, 45.0% (Trigo 2020) for lurbinectedin, and 49.4% (Baize 2020) for platinum rechallenge with carboplatin plus etoposide
 - Median OS ranged from 5.8 months (von Pawel 2001) to 8.1 months (Eckardt 2007) for oral or IV topotecan, 7.5 months (Baize 2020) for platinum rechallenge with carboplatin plus etoposide, 7.6 months (CheckMate 331) for nivolumab, and 11.9 months (Trigo 2020) for lurbinectedin

Table 3. Select Efficacy Outcomes by Treatment in Patients With SCLC Receiving 2L Therapy in Trials Identified in the SLR

Trial ID	Treatment	Analysis population	N	CTFI ≥90 d, n (%)	ORR, %		Median OS, mos (95% CI)	
					Overall	CTFI ≥90 d	Overall	CTFI ≥90 d
RCTs								
Baize 2020 ⁵ (N = 164)	Topotecan (oral)	ITT, CTFI ≥90 d	81	81 (100.0)	25.3 ^{a,b}	–	7.4 (6.0, 8.7)	–
	Carboplatin + etoposide	ITT, CTFI ≥90 d	81	81 (100.0)	49.4 ^{a,b}	–	7.5 (5.4, 9.5)	–
O'Brien 2006 ⁶ (N = 141)	BSC	ITT	70	35 (50.0)	–	–	3.2 ^c (2.6, 4.3)	–
	Topotecan (oral) + BSC	ITT	71	30 (42.3)	7.0 ^a	3.0 ^a	6.0 ^c (4.2, 7.3)	–
Eckardt 2007 ⁷ (N = 309)	Topotecan (oral)	ITT, CTFI ≥90 d ^a	153	134 (87.6) ^a	18.3 ^d	–	7.6 ^e (6.7, 9.8)	–
	Topotecan (IV)	ITT, CTFI ≥90 d ^a	151	137 (90.7) ^a	21.9 ^d	–	8.1 ^e (7.1, 8.6)	–
von Pawel 2001 ⁸ (N = 106)	Topotecan (oral)	ITT, CTFI ≥90 d ^a	52	51 (98.1)	23.1 ^f	–	7.4 ^g (range: 0.1, 15.9)	–
	Topotecan (IV)	ITT, CTFI ≥90 d ^a	54	53 (98.1)	14.8 ^g	–	5.8 ^g (range: 0.1, 15.0)	–
United Therapeutics 2017 ⁹ (N = 483)	Irinotecan	ITT	190	–	18.9	–	7.0 (5.6, 8.9)	–
	Topotecan (IV)	ITT	94	–	20.2	–	7.4 (6.1, 9.3)	–
RCTs with only 1 arm of interest								
Owonikoko 2020 ¹⁰ (N = 178)	Paclitaxel + placebo	ITT, CTFI <180 d ^a	89	35 (39.3) ^a	18.0 ^f	–	5.42	–
CheckMate 331 ¹¹ (N = 569)	Nivolumab	ITT	284	163 (57.4)	13.7 ^h	–	7.5 (5.6, 9.2)	7.6 (5.6, 11.2)
Non-RCTs/RCTs with only 1 arm of interest								
CheckMate 032	Nivolumab	Subgroup, 2L	40	–	10.0 ^a	–	–	–
CheckMate 032	Nivolumab	Subgroup, 2L	–	–	–	–	6.0 (3.8, 9.4)	–
Single-arm trials								
Trigo 2020 ² (N = 105) ^b	Lurbinectedin	Treated population	105	60 (57.1)	35.2 ^a	45.0 ^a	9.3 (6.3, 11.8)	11.9 (9.7, 16.2)
Smyth 1994 ¹² (N = 34)	Docetaxel	2L	22 ^a	–	18.0	–	–	–

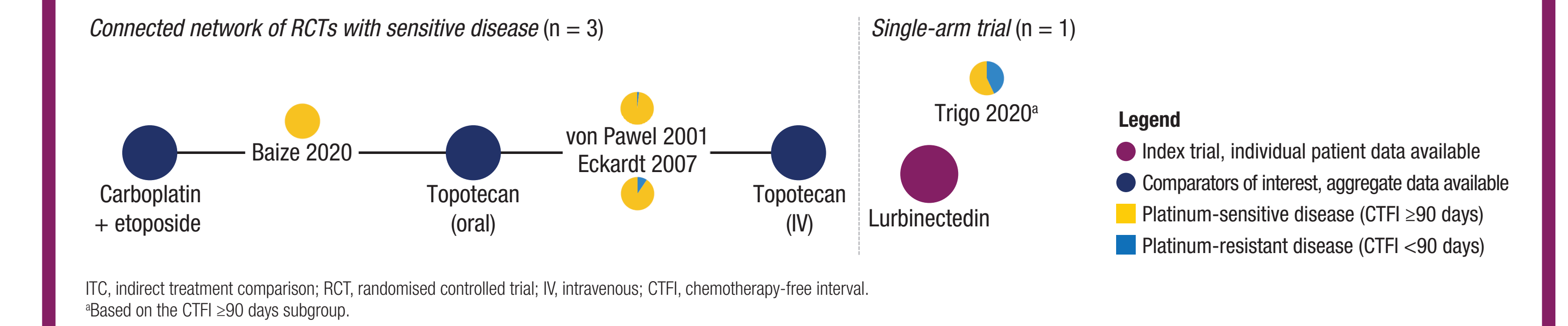
SCLC, small-cell lung cancer; 2L, second-line; SLR, systematic literature review; CTFI, chemotherapy-free interval; d, days; ORR, overall response rate; OS, overall survival; mos, months; CI, confidence interval; RCT, randomised controlled trial; ITT, intent-to-treat; BSC, best supportive care; IV, intravenous; IA, investigator assessment; IRC, independent review committee; 1L, first-line.
^aNon-evaluable patients were excluded from analysis (n = 6 in topotecan arm; n = 2 in carboplatin + etoposide arm). ^bMedian OS was reported in weeks. ^cApproximately 10% of patients in both treatment groups had a CTFI <90 days at study entry. ^dMissing patient data was reported. ^eIRC assessed. ^fApproximately 2% of patients in both treatment groups had a CTFI <90 days at study entry. ^gProtocol Amendment 2 (January 2015) corrected the stratification definition for time to response to follow standard guidance by counting from the date of the last dose of front-line chemotherapy as opposed to counting from the initial response to 1L platinum-based chemotherapy as originally set out in the protocol. Data shown in the table are for analysis done after protocol amendment. ^h13% and 19.3% of patients had missing data in the nivolumab and investigator's choice arms, respectively. ⁱ3% of patients had missing data. ^jThe study enrolled 110 patients; however, 5 patients did not receive treatment. ^kA total of 28 patients were evaluable; of these, 22 were 2L patients.

- Of the 10 trials included in the feasibility assessment, 5 RCTs formed a connected network (Baize 2020, O'Brien 2006, von Pawel 2001, Eckardt 2007, United Therapeutics 2017) while 5 trials were disconnected (Trigo 2020, Smyth 1994, CheckMate 032, CheckMate 331, Owonikoko 2020; **Figure 2**)



- Six of the 10 trials included in the feasibility assessment were excluded from the ITC due to various reasons (eg, lack of data availability, differences in patient characteristics, and being disconnected from the network of RCTs)
- Given the differences in the disease sensitivity status of patients across trials, the base case ITC analyses were restricted to the platinum-sensitive population
- Three RCTs (Baize 2020, von Pawel 2001, Eckardt 2007) had sufficiently similar platinum-sensitive populations and were assessed to identify which should be used to connect Trigo 2020 to the network for the base case ITC analyses (**Figure 3**)

Figure 3. Network of Trials Included in the Base Case ITC for Patients With Platinum-sensitive Disease



- Based on the similarity of patient characteristics, Baize 2020 was selected as the external RCT to connect Trigo 2020 to the base case network in patients with platinum-sensitive disease (**Figure 4**)
 - In the base case fixed-effect NMA, lurbinectedin demonstrated a significantly greater OS compared to oral topotecan (HR: 0.43; 95% CrI: 0.27, 0.67), IV topotecan (HR: 0.43; 95% CrI: 0.26, 0.70), and carboplatin plus etoposide (HR: 0.42; 95% CrI: 0.30, 0.58)
 - Odds ratio estimates from the base case fixed-effect NMA also found lurbinectedin to be associated with a significantly greater ORR than oral topotecan (OR: 2.58; 95% CrI: 1.12, 5.94); however, statistically significant differences were not observed for lurbinectedin versus IV topotecan (OR: 2.36; CrI: 0.89, 6.23) and versus carboplatin plus etoposide (OR: 0.85; 95% CrI: 0.40, 1.83)

Figure 4. Evidence Network for Base Case ITC Analysis in Patients With Platinum-sensitive Disease for ORR and OS

