Systematic Review

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Indirect comparison of nivolumab ± ipilimumab (CheckMate 032) versus other treatments for recurrent small-cell lung cancer

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Aim: To estimate the comparative efficacy of nivolumab ± ipilimumab versus alternative treatments for small-cell lung cancer after at least one prior line of chemotherapy. **Materials & methods:** A systematic literature review identified six randomized controlled trials (RCTs) that could be connected in a network. The Kaplan–Meier survival curves from these RCTs were synthesized using network meta-analysis models. Aggregate-level matching was used to connect CheckMate 032 to the RCTs. **Results:** CheckMate 032 was connected to the network by Amrubicin Clinical Trial-1. Nivolumab ± ipilimumab had a more durable tumor response and more favorable long-term survival versus topotecan via intravenous and versus amrubicin. **Conclusion:** Compared with chemotherapies for recurrent small-cell lung cancer, nivolumab ± ipilimumab improves response duration, which may translate to long-term survival benefits.

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Keywords: aggregate-level matching • ipilimumab • network meta-analysis • nivolumab • small-cell lung cancer • survival • topotecan

Small-cell lung cancer (SCLC) is an aggressive malignancy that accounts for 10–15% of all lung cancers [1,2]. First-line (1L) treatment commonly includes platinum-based chemotherapy [3,4], which may be combined with radiotherapy [3–6]. Despite high initial response rates to 1L chemotherapy for select patients, median survival in 1L ranges from 15 to 20 months and from 8 to 13 months for patients with limited disease (LD), defined as stages I–III (T any, N any, M0) using American Joint Committee on Cancer Tumor, Node, Metastasis (TNM) classification, and extensive disease (ED), defined as stage IV (T any, N any, M 1a/b), respectively. Most patients (70%) fall into the latter group at diagnosis [5,7,8], for whom 5-year survival is only 1–2%. Five-year survival for LD patients is only marginally better at 10–20% [1,2,7,9]. ED patients who respond to 1L treatment may be considered for maintenance therapy, but this is not routinely offered because of minimal survival benefit (4% increase in 2-year survival rate) and potential for increased risk of cumulative toxicities [3,10].

For patients who fail to respond to 1L treatment or who subsequently progress, treatment options are limited. Topotecan, a topoisomerase I inhibitor, is currently the only drug approved by the US FDA for second-line (2L) treatment [3,4,9,11], which has been associated with median overall survival (OS) between 6.0 and 7.6 months for oral (p.o.) administration and between 5.8 and 8.0 months for intravenous (iv.) administration in 2L [3,4,9,11–17]. Furthermore, a recent study based on the US SEER database suggested median OS after initiating 2L treatment was less than 6 months for both platinum-refractory (3.7 months; 95% CI: 3.5–4.1) and platinum-sensitive patients (5.3 months; 95% CI: 4.9–5.8) in the Medicare population [18]. Given these suboptimal outcomes, the National Comprehensive Cancer Network (NCCN) still recommends that clinical trials be considered for 2L treatment, and if necessary third-line (3L) treatment, where available [10].

Future Medicine

Nivolumab, a PD-1 checkpoint inhibitor, with or without the CTLA-4 inhibitor ipilimumab (nivolumab ± ipilimumab), has been recommended by the NCCN as an alternative to chemotherapy for 2L treatment of SCLC patients who have failed prior systemic therapy within 6 months in either the primary or adjuvant setting [10]. This recommendation was based on positive results from CheckMate 032 [19–23], a Phase I/II, open-label trial of nivolumab ± ipilimumab for SCLC patients who are platinum-sensitive (relapse ≥90 days) or platinum-resistant (relapse <90 days) after having received at least one platinum-based chemotherapy regimen (or during treatment for platinum-resistant patients). More recently, the FDA granted an accelerated approval for nivolumab as the first and only immuno-oncology treatment option for patients with metastatic SCLC whose cancer has progressed after platinum-based chemotherapy and at least one other line of therapy [24]. CheckMate 032 consisted of a nonrandomized cohort of patients treated with nivolumab alone or in combination with ipilimumab (nivolumab monotherapy 3 mg/kg iv. on day 1 of a 2-week cycle [Q2W]; nivolumab 1 mg/kg + ipilimumab 3 mg/kg iv. on day 1 of each 3-week cycle [Q3W] for a maximum of four cycles, followed by nivolumab 3 mg/kg iv. Q2W). A randomized cohort was added to the trial to evaluate nivolumab ± ipilimumab in this population. At the time of analysis, only the results of the nonrandomized cohort had been published, where the median OS for nivolumab + ipilimumab was 7.8 months (95% CI: 3.6–14.2) [22]. The aim of this study was to use data from the nonrandomized cohort in CheckMate 032 to estimate the comparative efficacy of nivolumab ± ipilimumab versus alternative treatments for SCLC after at least one prior line of chemotherapy.

Methods

Systematic literature review

A systematic literature review (SLR) was performed to identify randomized controlled trials (RCTs) featuring systemic therapies for the treatment of adults with refractory SCLC or disease progression after at least one prior line of chemotherapy or chemoradiotherapy. The RCTs were required to evaluate at least one of the following efficacy outcomes: OS, progression-free survival (PFS) and/or objective response rate (ORR). Relevant studies were identified based on predefined search strategies in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25] from the following databases on 1 June 2018 using the Ovid platform: Medical Literature Analysis and Retrieval System Online, including In-Process/MEDLINE®, Daily/MEDLINE®, Excerpta Medica database and Cochrane Central Register of Controlled Trials (search strategies presented in Supplementary Tables 1–3). The proceedings of the following conferences from 2014 to 2016 were also searched: American Association for Cancer Research Annual Meeting, American Society of Clinical Oncology Annual Meeting, European Society for Median Oncology Congress and the International Association for the Study of Lung Cancer World Conference on Lung Cancer. Finally, manual searches were conducted of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform to identify eligible trials that had not yet been published but had results (Supplementary Tables 4 & 5). Two investigators participated in study selection and data extraction. A third investigator provided arbitration if there were any discrepancies in decisions. For all included trials, relevant patient and study characteristics and outcomes of interest were extracted.

Statistical analyses

In the absence of head-to-head clinical trial evidence for nivolumab ± ipilimumab and other chemotherapies including topotecan, an indirect treatment comparison by means of a network meta-analysis (NMA) of RCTs identified through an SLR provides a valid alternative [26–29]. In order to gauge the appropriateness of proceeding with an NMA [30], a feasibility assessment was first carried out to: determine whether the RCT evidence for the interventions formed one evidence network for the population and each outcome of interest; and assess the distribution of study characteristics, treatment characteristics, outcomes and patient characteristics that may have affected treatment effects across direct comparisons of the evidence networks. The most important potential treatment effect modifiers were identified as lines of previous treatments (1 vs >1), platinum sensitivity (sensitive vs resistant) and race (Asian vs non-Asian), which were included as subgroups of interest.

Given that the preexpansion cohort of CheckMate 032 was not randomized, it could not be connected to the wider network of RCTs. In the absence of a connected network of RCTs, a population-adjusted indirect treatment comparison can be performed using individual patient data (IPD) from an index trial, such as CheckMate 032, to create a connection with one of the trials in the network [31]. As IPD were not available for CheckMate 032 at the time of this analysis, we instead used matching based on aggregate study-level data from the nonrandomized cohort. By examining study design, inclusion and exclusion criteria and patient characteristics of all trials, the trial

which was most similar to CheckMate 032 was selected and the CheckMate 032 arms were then treated as arms of this trial within the NMA. This relied on the same assumption as traditional NMA, as well as an additional assumption that the outcomes in the control arm from the external trial were applicable to CheckMate 032.

NMAs were performed for each outcome of interest where the RCTs identified in the SLR, including the matched trial featuring the previously disconnected arms of CheckMate 032, formed one evidence network and were deemed sufficiently similar for the population of interest. Under the assumption of consistency, the NMA model relates the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of each intervention compared with the control (i.e., topotecan via iv.). Based on these basic parameters, the relative treatment effects between each of the contrasts in the network were obtained. All analyses were performed in a Bayesian framework involving a model with parameters, data and a likelihood function, and prior distributions. Only fixed-effect models were used as there was an insufficient number of trials per comparison to estimate between-study heterogeneity.

The NMA of OS and PFS was performed assuming nonproportional hazards. Fractional polynomial models were used to model the log hazard functions of the interventions in a trial. The difference in the parameters was considered the multidimensional treatment effect, which was pooled and indirectly compared across studies [27,32,33]. For the median duration of response (DOR) and number of patients at risk, a binomial likelihood and cloglog link (with offset for median) were used [34]. For ORRs, the NMA was performed based on the proportion of patients experiencing the event of interest using a regression model with a binomial likelihood and logit link [26]. Noninformative prior distributions were used for all models (assuming a normal distribution for the difference measures with a mean 0, variance 10^4).

The parameters of the different models were estimated using a Markov Chain Monte Carlo method implemented in the OpenBUGS software package [35,36]. A first series of iterations from the OpenBUGS sampler were discarded as 'burn-in', and the inferences were based on additional iterations using two chains. All analyses were performed using R version 3.0.3 (www.r-project.org/) and OpenBUGS version 3.2.3 (OpenBUGS Project Management Group).

The results of the NMA were presented with estimates for treatment effects of each intervention relative to the reference treatment. The posterior distributions of relative treatment effects were summarized by the median and 95% credible intervals (CrIs), which were constructed from the 2.5th and 97.5th percentiles of the posterior distributions. For OS, PFS and DOR, results were presented in terms of hazard ratios (HRs). Results for ORR were presented in terms of odds ratios (ORs).

Results

Systematic literature review

Based on the SLR, 18 RCTs [12–17,37–55] and one nonrandomized study [19–23] (CheckMate 032 was included as the reference population) evaluating 15 combination chemotherapies, 23 single-agent chemotherapies and best supportive care were identified (Figure 1 & Supplementary Table 6).

Feasibility assessment

Figure 2 presents the overall network of evidence, which included the disconnected nodes from the nonrandomized cohort of CheckMate 032 and all RCTs from the SLR that could be connected to each other. Three RCTs, which compared topotecan via iv. or p.o. administration to linsitinib, irinotecan to irinotecan + gemcitabine, and cisplatin + amrubicin to cisplatin + doxorubicin + etoposide + vincristine, were not included in the network given that they did not share an intervention in common with the other trials [40,49,51]. Four trials in the network were conducted exclusively in Asia [42–46,55]. Asian versus non-Asian race may be a treatment effect modifier based on evidence of significant OS improvement associated with amrubicin versus topotecan in Japan [44] that was not identified in a similar study conducted in Europe and North America [15]. Additional evidence from an RCT including both Asian and non-Asian patients is required to better understand whether these differences may be explained by distinctions in genetic background, medical care, study design and drug exposure. The Asian trials connected to a pooled node for platinum doublet, which included either cisplatin + etoposide [48,50] or a mix of carboplatin + etoposide (76.7%), carboplatin + irinotecan (13.3%) and cisplatin + irinotecan (10.0%) [46]. Finally, three trials in the network evaluated interventions that failed to demonstrate improved efficacy and therefore have not been recommended or licensed for SCLC [10] (cabazitaxel [37–39], lomustine + cyclophosphamide + etoposide [41],

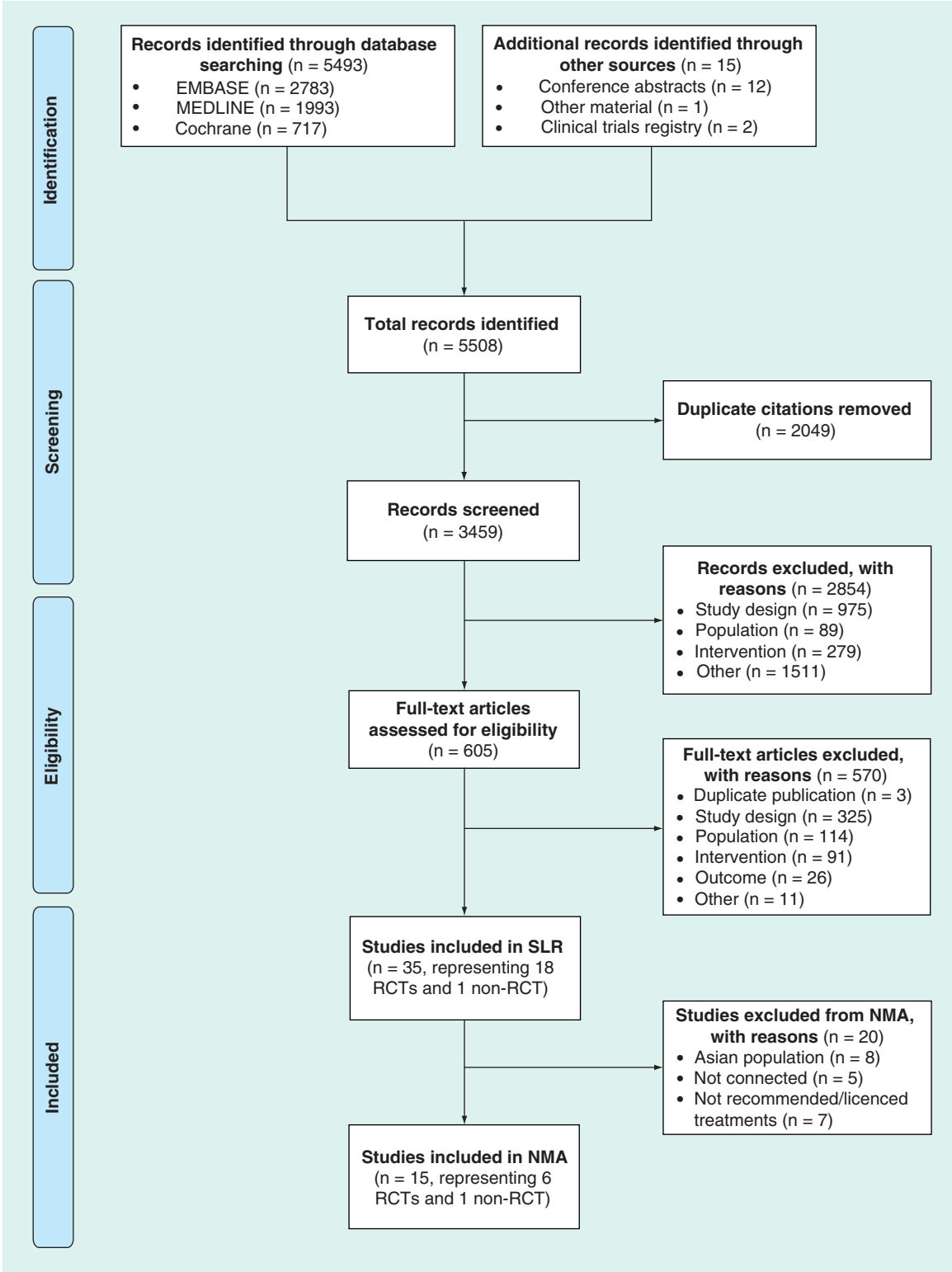

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses study selection flow diagram.
NMA: Network meta-analysis; RCT: Randomized controlled trial; SLR: Systematic literature review.

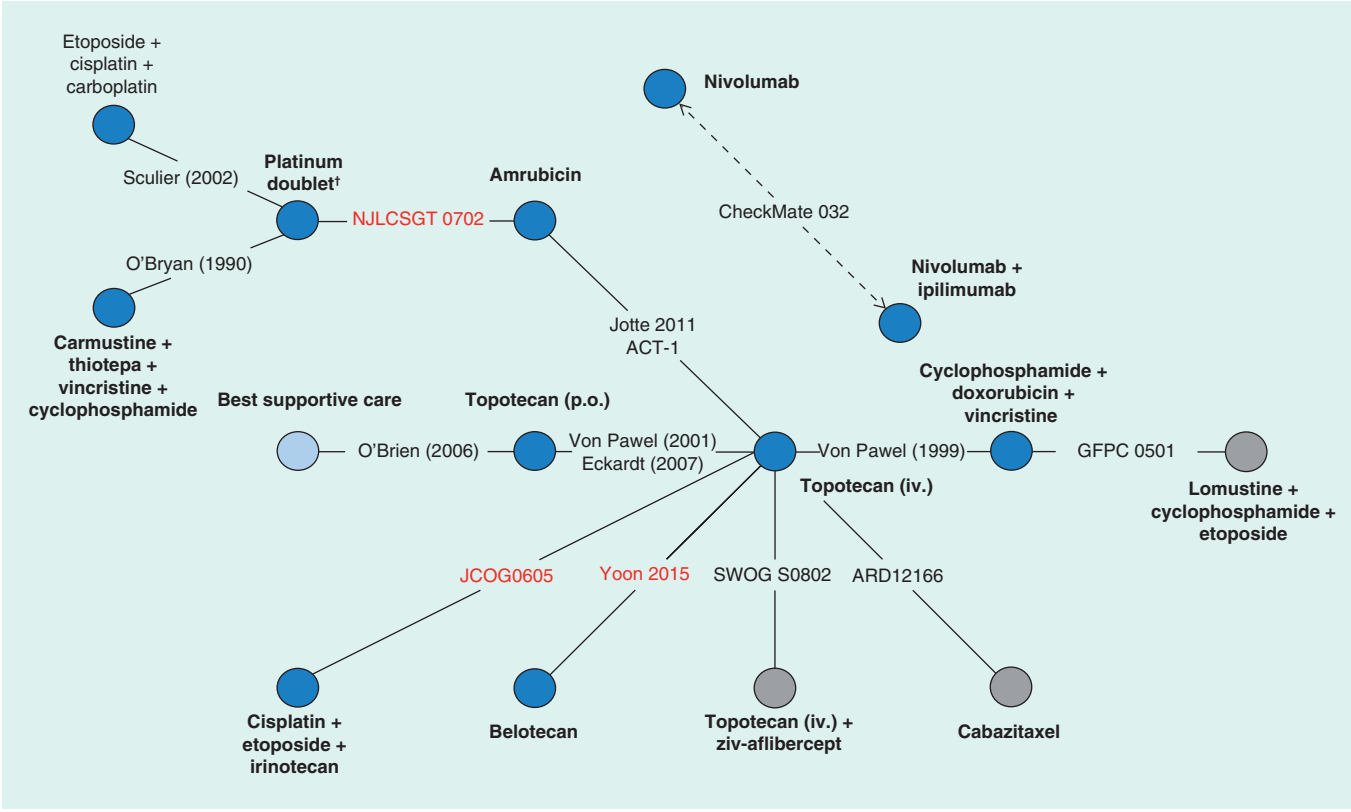

Figure 2. Network of trials included in the feasibility assessment. Solid lines: randomized controlled trials; dotted line: nonrandomized controlled trial; red text: Asian studies; blue treatment nodes: approved or recommended for small-cell lung cancer; gray treatment nodes: not approved or recommended; light blue treatment node: only included in sensitivity analysis (excluded from base case).
†Platinum doublet included: cisplatin + etoposide ([50]., [48]) or a mix of carboplatin + etoposide (76.7%), carboplatin + irinotecan (13.3%) and cisplatin + irinotecan (10.0%; Inoue *et al.*).
GFPC: Groupe Français de Pneumo-Cancérologie; iv.: Intravenous; JCOG: Japan Clinical Oncology Group; NJLCSGT: North Japan Lung Cancer Study Group Trial; p.o.: Oral; SWOG: Southwest Oncology Group.

and topotecan via iv. + ziv-aflibercept [52,53]). These trials did not provide indirect evidence regarding other interventions of interest.

Figure 3 shows the network that was analyzed after excluding the Asian studies (n = 4), trials no longer connected due to exclusion of Asian studies (n = 2) and nonrecommended/licensed treatments (n = 3). O'Brien *et al.* was the only trial in the network that included patients who were incompatible with standard iv. chemotherapy due to co-morbidities or refusal on account of the risk of toxicity [56]. In contrast, all other trials in the network, except for CheckMate 032, featured at least one arm with iv. chemotherapy. Therefore, O'Brien *et al.* was only included in a sensitivity analysis. As CheckMate 032 was not connected to the network and IPD were not available, aggregate-level matching was used to connect CheckMate 032 to the network of RCTs. To identify the most similar trial to CheckMate 032, the trials included in this network [12–17] were compared in terms of study, patient, outcome and treatment characteristics. Amrubicin Clinical Trial-1 (ACT-1) was the most similar trial to CheckMate 032; consequently, the nivolumab and the nivolumab + ipilimumab arms from the nonrandomized cohort of CheckMate 032 were included as additional arms in ACT-1.

All the trials included adults with either LD or ED SCLC, and had disease progression after at least one previous platinum-containing regimen. CheckMate 032, ACT-1 and O'Brien *et al.* included both platinum-sensitive and platinum-resistant or -refractory patients, whereas the other four trials included only patients who were platinum-sensitive [13,14,16,17], with definitions regarding platinum sensitivity ranging from recurrence or progression at least 60 or 90 days after completion of 1L chemotherapy. All trials were conducted entirely in 2L patients, except for CheckMate 032, which also included patients with up to five prior lines of therapy. CheckMate 032 allowed ECOG performance score of 0–1, which was consistent with ACT-1 (amended from 0 to 2), whereas other trials included

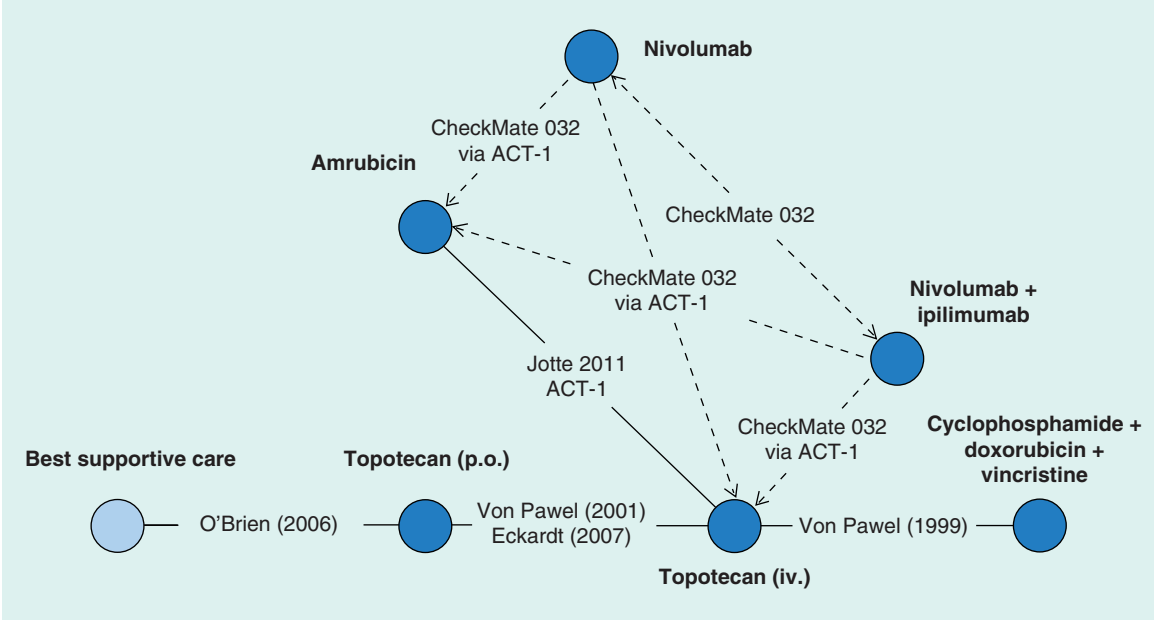

Figure 3. Network of non-Asian randomized controlled trials included in the network meta-analysis with CheckMate 032 connected through Amrubicin Clinical Trial-1. Solid lines: randomized controlled trials; dotted lines: hypothetical nonrandomized controlled trial; blue treatment nodes: approved or recommended for small-cell lung cancer; light blue treatment node: only included in sensitivity analysis (excluded from base case).
ACT-1: Amrubicin Clinical Trial-1; iv.: Intravenous; p.o.: Oral.

patients with ECOG 0–2. All trials allowed patients with asymptomatic CNS metastases. Within interventions, dosing was consistent across the included trials, although ACT-1 was the only trial to place a limit on the maximum number of cycles (six) that could be received. Overall, the inclusion criteria in CheckMate 032 were most similar to ACT-1 in terms of platinum sensitivity and ECOG status.

CheckMate 032 is an ongoing Phase I/II multicenter trial conducted in Europe and North America. ACT-1 was a Phase III multicenter trial conducted in a similar region (also including sites in Australia) published in 2014. Other trials included a mix of older (1999–2011) Phase II or Phase III trials (or phase was not reported) that included centers from North America, except for Von Pawel 2001, which included only centers from Europe, South Africa and Australia. Beyond North America and Europe, other regions included southeast Asia and Australia [14], South Africa [17] and Russia [12]. With the exception of CheckMate 032, where the nonrandomized cohort was included, all trials were randomized and generally low risk of bias (or unclear), except in terms of performance bias, which was high risk given the open-label or single-blinded trial designs (Supplementary Figure 1). Patients characteristics from all the included studies can be found in Table 1.

OS and ORRs were reported in all of the trials. ORR (a complete response [CR] or partial response [PR]) was investigator-assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) in CheckMate 032 (version 1.1) and ACT-1 (version 1.0), whereas three trials assessed ORR by blinded-independent review using the WHO criteria [13,14,17]. Jotte *et al.* did not provide a definition for OS or PFS but did report that RECIST (v1.0) was used to assess response. O'Brien *et al.* did not report how ORR was determined. All of the trials, except O'Brien *et al.*, reported DOR, defined as time from first documented response to disease progression. However, CheckMate 032 defined DOR as time from a best overall response of PR or CR until the date of documented progressive disease or death due to any cause.

Three trials [15,16,19–22] reported PFS, whereas three trials [13,14,17] reported time to progression (TTP). TTP differs from PFS in that any deaths are considered censored values in the TTP analyses, while they are considered events in the PFS analyses. In the context of NMA, there are differences between treatment arms that are modeled. This means that if the mortality rates are equivalent across arms in a trial, then the bias arising from the use of TTP is not expected to be substantial. No significant differences in OS were observed in either of the two trials reporting TTP data, so they were included within the PFS analysis.

Table 1. Summary of patient characteristics in second-line/third-line trials included in the systematic literature review.

Trial	Treatment	N	ECOG 0	ECOG 1	ECOG 2	LD	ED	Sensitive	Resistant	Patient trial inclusion	Ref.
ACT-1; Phase III	Topotecan, iv.	213	72 (33.8%)	137 (64.3%)	4 (1.9%)	26 (12.2%)	187 (87.8%)	117 (54.9%)	96 (45.1%)	Progression after 1L platinum-based chemo (sensitive [≥90 days] and refractory)	[15]
	Amrubicin	424	126 (29.7%)	289 (68.2%)	9 (2.1%)	53 (12.5%)	371 (87.8%)	225 (53.1%)	199 (46.9%)		
ARD12166; Phase II†††	Cabazitaxel	90	31 (34.4%)	59 (56.6%)	0 (0%)	0 (0%)	90 (100%)	45 (50.0%)	45 (50.0%)	Progressed after 1L chemo (sensitive [≥90 days] and refractory [<90 days])	[37–39]
	Topotecan	89	17 (19.1%)	71 (79.8%)	1 (1.1%)	0 (0%)	89 (100%)	46 (51.7%)	43 (48.3%)		
CheckMate 032; Phase I/II	Nivolumab	98	73/245 (39.8%)†	171/245 (69.8%)†	0 (0%)	(24.0%)‡	(76.0%)‡	55 (56.1%)	30 (30.6%)	Progression after ≥1L platinum-based therapy	[19–23]
	Nivolumab + ipilimumab	61	49/156 (31.4%)†	106/156 (67.9%)†	0 (0%)			25 (41.0%)	23 (37.7%)		
Chiappori *et al.* (2016); Phase II†††	Topotecan, iv. or p.o.	15	12 (80.0%)		3 (20.0%)	0 (0%)	15 (100%)	7 (46.7%)	8 (53.3%)	Progression after 1L platinum-based chemo (sensitive [<90 days] and resistant [>90 days])	[40]
	Linsitinib	29	24 (82.8%)		5 (17.2%)	0 (0%)	29 (100%)	13 (44.8%)	16 (55.2%)		
Eckardt *et al.* (2007); Phase III	Topotecan, p.o.	153	48 (31.4%)	85 (55.6%)	20 (13.1%)	51 (33.3%)	102 (67.7%)	153 (100%)	0 (0%)	Recurrence after ≥90 days after CR or PR to 1L therapy	[14]
	Topotecan, iv.	151	35 (23.2%)	98 (64.9%)	18 (11.9%)	45 (29.8%)	106 (70.2%)	151 (100%)	0 (0%)		
GFPC 0501; Phase II†††	CEL	65	22 (33.8%)	34 (52.3%)	9 (13.8%)	34 (52.3%)	31 (47.7%)	65 (100%)	0 (0%)	Progression after 1L chemo (<3 months)	[41]
	CAV	66	23 (24.8%)	33 (50.0%)	10 (15.2%)	27 (40.9%)	39 (59.1%)	66 (100%)	0 (0%)		
JCOG0605; Phase III†††	CEI	90	52 (57.8%)	36 (40%)	2 (2.2%)	20 (22.2%)	70 (77.8%)	90 (100%)	0 (0%)	Relapse or progression ≥90 days after 1L platinum-based chemo or CRT	[42,43]
	Topotecan, iv.	90	40 (44.4%)	47 (52.2%)	3 (3.3%)	25 (27.8%)	65 (72.2%)	90 (100%)	0 (0%)		
Jotte *et al.* (2011); Phase II	Amrubicin	50	20 (40.0%)	24 (48.0%)	6 (12.0%)	0 (0%)	50 (100%)	50 (100%)	0 (0%)	Recurrence/ progression ≥90 days after completion of 1L chemo	[16]
	Topotecan, iv.	26	10 (38.5%)	14 (53.8%)	2 (7.7%)	0 (0%)	26 (100%)	26 (100%)	0 (0%)		
NJLCSGT 0402; Phase II†††	Amrubicin	29	15 (55.6%)	10 (37.0%)	2 (7.4%)	15 (55.6%)	12 (44.4%)	17 (58.6%)	12 (41.4%)	Progression after 1L platinum-based chemo (sensitive [≥90 days] and refractory)	[44]
	Topotecan, iv.	30	17 (56.7%)	11 (36.7%)	2 (6.7%)	18 (60.0%)	12 (40.0%)	19 (63.3%)	11 (36.7%)		

†Baseline characteristics for the randomized cohort and the nonrandomized cohort of CheckMate 032 were pooled.
‡These estimates are derived from a clinical study report for CheckMate 032 on all cohorts;
§O'Brien was only included in the sensitivity analysis;
¶Patients reported to have a treatment-free interval of more than 90 days are considered platinum-sensitive while those with a treatment-free interval of ≤90 days are considered platinum-resistant.
#Karnofsky performance status of 0–1.
††Karnofsky performance status of 2–3.
‡‡Karnofsky performance status of 60–70.
§§Karnofsky performance status of 80–100.
¶¶Stages I–III.
##Stage IV.
†††Studies not included in the network meta-analysis.
1L: First line; BSC: Best supportive care; CAV: Cyclophosphamide + doxorubicin + vincristine; CCE: Carboplatin + cisplatin + etoposide; CEI: Cisplatin, + etoposide + irinotecan; CEL: Cyclophosphamide + etoposide + lomustine; CODE: Cisplatin + doxorubicin + etoposide + vincristine; CR: Complete response; CRT: Chemoradiotherapy; CTVC: Carmustine + thiotepa + vincristine + cyclophosphamide; ECOG: Eastern Cooperative Oncology Group; ED: Extensive disease; iv.: Intravenous; LD: Limited disease; NR: Not reported; PR: Partial response; p.o.: Oral; SD: Stable disease.

Table 1. Summary of patient characteristics in second-line/third-line trials included in the systematic literature review (cont.).

Trial	Treatment	N	ECOG 0	ECOG 1	ECOG 2	LD	ED	Sensitive	Resistant	Patient trial inclusion	Ref.
NJLCSGT 0702; Phase II†††	Amrubicin	27	6 (8.6%)	41 (58.6%)	23 (32.9%)	27 (38.6%)	43 (61.4%)	27 (100%)	0 (0%)	Relapse or progression >90 days after 1L platinum-based chemo	[45,46]
	Platinum doublet	30	8 (11.3%)	44 (62%)	19 (26.8%)	23 (32.4%)	48 (67.6%)	30 (100%)	0 (0%)		
O'Brien *et al.* (2006)§; Phase III	BSC	70	6 (8.6%)	41 (58.6%)	23 (32.9%)	27 (38.6%)	43 (61.4%)	35 (50.0%)¶	35 (50.0%)¶	Following 1L chemo and unsuitable for chemo iv.	[12]
	Topotecan, p.o.	71	8 (11.3%)	44 (62.0%)	19 (26.8%)	23 (32.4%)	48 (67.6%)	30 (42.3%)¶	41 (57.7%)¶		
O'Bryan *et al.* (1990); Phase NR†††	CTVC	45	24 (53.3%)#		21 (46.7%)§	38 (84.4%)	7(15.6%)	–	–	Failed or relapse after 1L systemic therapy	[48]
	Cisplatin + etoposide	84	33 (39.5%)#		51 (60.7%)§	66 (78.6%)	18 (21.4%)	–	–		
Pallis *et al.* (2009); Phase II†††	Gemcitabine + irinotecan	38	12 (31.6%)	20 (52.6%)	6 (15.8%)	–	–	20 (52.6%)	18 (47.4%)	Following ≥1L chemo (ED patients), or CRT (LD patients)	[49]
	Irinotecan	31	10 (32.3%)	19 (61.3%)	2 (6.5%)	–	–	10 (32.3%)	18 (58.1%)		
Sculier *et al.* (2002); Phase II†††	Cisplatin + etoposide	31	14 (45.2%)‡‡	17 (54.8%)§§	–	2 (6.5%)¶¶	29 (93.5%)##	–	–	Failed during, or relapsed after 1L chemo	[50]
	CCE	34	11 (32.4%)‡‡	23 (67.6%)§§	–	2 (5.9%)¶¶	32 (94.1%)##	–	–		
Sekine *et al.* (2015); Phase II†††	CODE	39	–	–	–	39 (100%)	–	–	–	Responded (CR, PR or SD) to 1L CRT	[51]
	Amrubicin + cisplatin	36	–	–	–	36 (100%)	–	–	–		
SWOG S0802; Phase II†††	Topotecan, iv. + Ziv-Aflibercept	97	26 (26.8%)	71 (73.2%)	0 (0%)	31 (32.0%)	66 (68.0%)	42 (43.3%)	55 (56.7%)	Progression after 1L platinum-based chemo (sensitive [>90 days for ED or ≥180 days for LD] and refractory [≤90 days for ED or <180 days for LD])	[52,53]
	Topotecan, iv.	92	36 (39.1%)	56 (60.6%)	0 (0%)	27 (29.3%)	65 (70.7%)	41 (44.6%)	51 (55.4%)		
Von Pawel *et al.* (1999); Phase NR	Topotecan, iv.	107	18 (16.8%)	64 (59.8%)	25 (23.4%)	18 (16.8%)	89 (83.2%)	107 (100%)	0 (0%)	Progression ≥60 days after completion of 1L chemo	[17]
	CAV	104	20 (19.2%)	64 (61.5%)	20 (19.2%)	16 (15.4%)	88 (84.6%)	104 (100%)	0 (0%)		
Von Pawel *et al.* (2001); Phase II	Topotecan, p.o.	52	10 (19.2%)	34 (65.4%)	8 (15.4%)	14 (26.9%)	37 (71.2%)	52 (100%)	0 (0%)	Recurrence after ≥90 days after CR or PR of 1L chemo	[13]
	Topotecan, iv.	54	18 (33.3%)	21 (38.9%)	15 (27.8%)	14 (25.8%)	39 (72.2%)	54 (100%)	0 (0%)		
Yoon *et al.* (2015); Phase II†††	Belotecan	61	–	–	–	–	–	–	–	Progression <6 months after 1L platinum-based chemo or CRT	[55]
	Topotecan, iv.	55	–	–	–	–	–	–	–		

†Baseline characteristics for the randomized cohort and the nonrandomized cohort of CheckMate 032 were pooled.
‡These estimates are derived from a clinical study report for CheckMate 032 on all cohorts;
§O'Brien was only included in the sensitivity analysis;
¶Patients reported to have a treatment-free interval of more than 90 days are considered platinum-sensitive while those with a treatment-free interval of ≤90 days are considered platinum-resistant.
#Karnofsky performance status of 0–1.
††Karnofsky performance status of 2–3.
‡‡Karnofsky performance status of 60–70.
§§Karnofsky performance status of 80–100.
¶¶Stages I–III.
##Stage IV.
†††Studies not included in the network meta-analysis.
1L: First line; BSC: Best supportive care; CAV: Cyclophosphamide + doxorubicin + vincristine; CCE: Carboplatin + cisplatin + etoposide; CEI: Cisplatin, + etoposide + irinotecan; CEL: Cyclophosphamide + etoposide + lomustine; CODE: Cisplatin + doxorubicin + etoposide + vincristine; CR: Complete response; CRT: Chemoradiotherapy; CTVC: Carmustine + thiotepa + vincristine + cyclophosphamide; ECOG: Eastern Cooperative Oncology Group; ED: Extensive disease; iv.: Intravenous; LD: Limited disease; NR: Not reported; PR: Partial response; p.o.: Oral; SD: Stable disease.

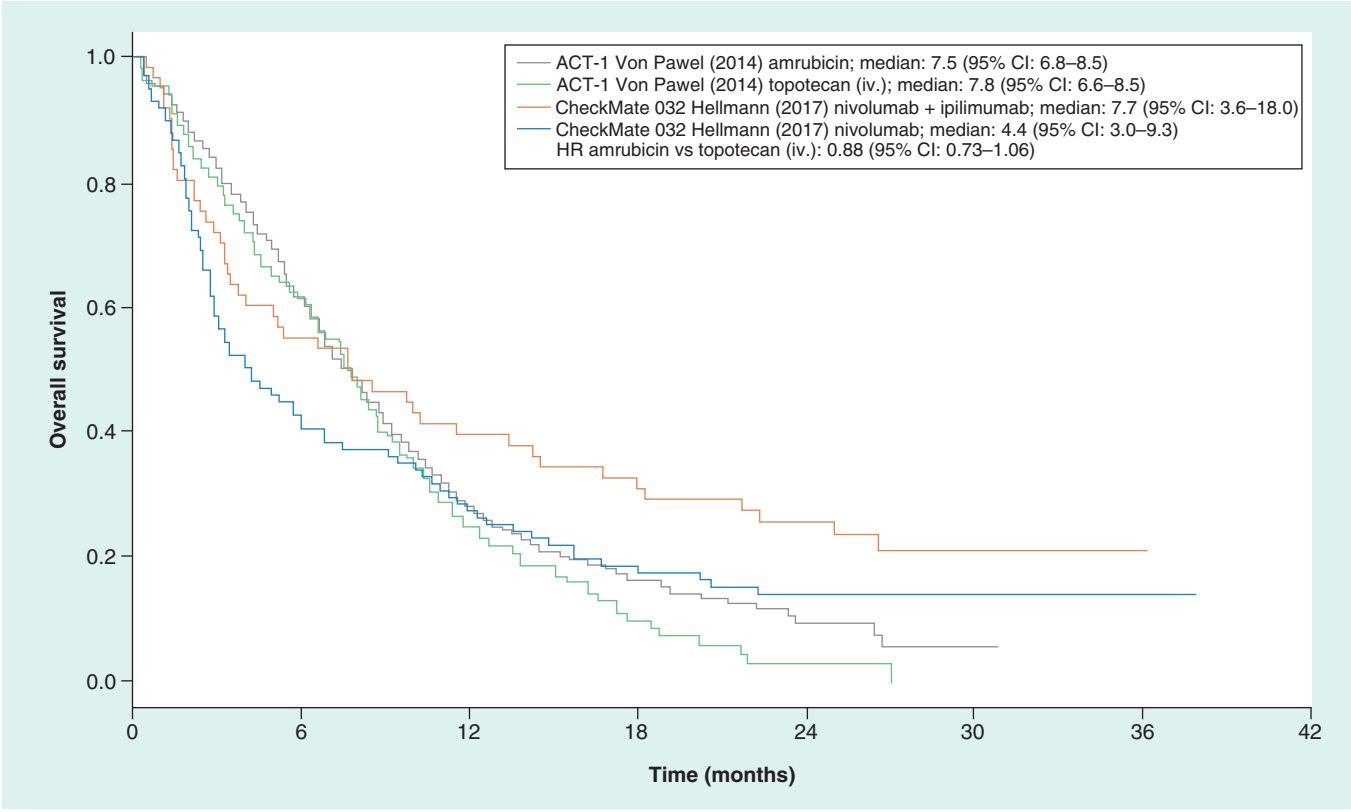

Figure 4. Kaplan–Meier curve of overall survival for CheckMate 032 and Amrubicin Clinical Trial-1.
HR: Hazard ratio; iv.: Intravenous.

Network meta-analysis

Overall survival & progression-free survival

Digitized (DigitizeIt; www.digitizeit.de/) OS Kaplan–Meier curves from ACT-1 are presented in Figure 4, including CheckMate 032 nivolumab ± ipilimumab overlaid with ACT-1 as if patients were randomized to this trial. OS for nivolumab appears to plateau at 24 months (n = 14 patients at risk). Figure 5 presents the time-varying HRs for each intervention versus topotecan via iv. for OS and PFS, including the 95% CrI. The HRs for OS trended in favor of topotecan via iv. versus nivolumab ± ipilimumab in the early time periods (3–6 months), after which the direction of the effect switched in favor of the latter. This advantage steadily increased up to around 30 months at which time the differences between the treatments became relatively constant. Of the remaining chemotherapies, oral totopecan performed best relative to topotecan via iv., suggesting some potential benefit with the p.o. form, while amrubicin appeared to offer very similar efficacy. Including the O'Brien *et al.*'s study as part of the sensitivity analysis did not lead to any substantive changes in the direction or magnitude of the observed relative effects, and showed HRs that trended in favor of nivolumab ± ipilimumab versus best supportive care. For PFS, a similar trend to that seen for OS was observed but in this case the differences in favor of nivolumab ± ipilimumab versus topotecan via iv. became relatively constant at around 18 months.

To facilitate the interpretation of the above results, estimates of the expected survival proportions over time assuming topotecan via iv. as the reference curve are presented in Figure 6, including the proportion of patients alive at 1 and 2 years. In terms of OS, relative to topotecan via iv. or amrubicin, the survival improvement was observed as early as month 6 for nivolumab + ipilimumab and at month 12 for nivolumab. Relative to the chemotherapies, long-term OS results were favorable for both the nivolumab regimens, and improvement in PFS for nivolumab was observed between months 12 and 36 and between 6 and 18 months for nivolumab + ipilimumab. Results were generally consistent when CheckMate 032 was connected to the network using different RCTs that included topotecan via iv. [13–16].

ORR & duration of response

Observed ORRs ranged from 10.2% for nivolumab [19–23] to 44.0% for amrubicin [16], whereas the median DOR ranged from 3.2 months for topotecan via iv. [13] to 17.9 months for nivolumab [19–23]. The estimated ORs resulting from the NMA suggest that nivolumab ± ipilimumab did not improve ORR versus any of the chemotherapies, though point estimates did trend in favor of nivolumab + ipilimumab in all comparisons with the exception of amrubicin. However, nivolumab monotherapy and nivolumab + ipilimumab significantly improved the DOR compared with all chemotherapies, except for nivolumab monotherapy versus CAV, which was not statistically significant. Of note, nivolumab ± ipilimumab significantly improved the DOR compared with the current standard of care topotecan via iv. (Figure 7).

Discussion

The overall prognosis for patients with SCLC remains poor, with little improvement in OS since the late seventies, especially for patients with ED [57]. This is despite high initial response rates to 1L treatment with chemotherapy or chemoradiotherapy. The results of this SLR showed that a limited number of RCTs have been conducted in 2L patients, and just two of the identified trials (CheckMate 032 and Pallis *et al.*) included 3L^{+} patients. After excluding trials conducted in Asian populations, the network of RCTs comprised of evidence on amrubicin, CAV,

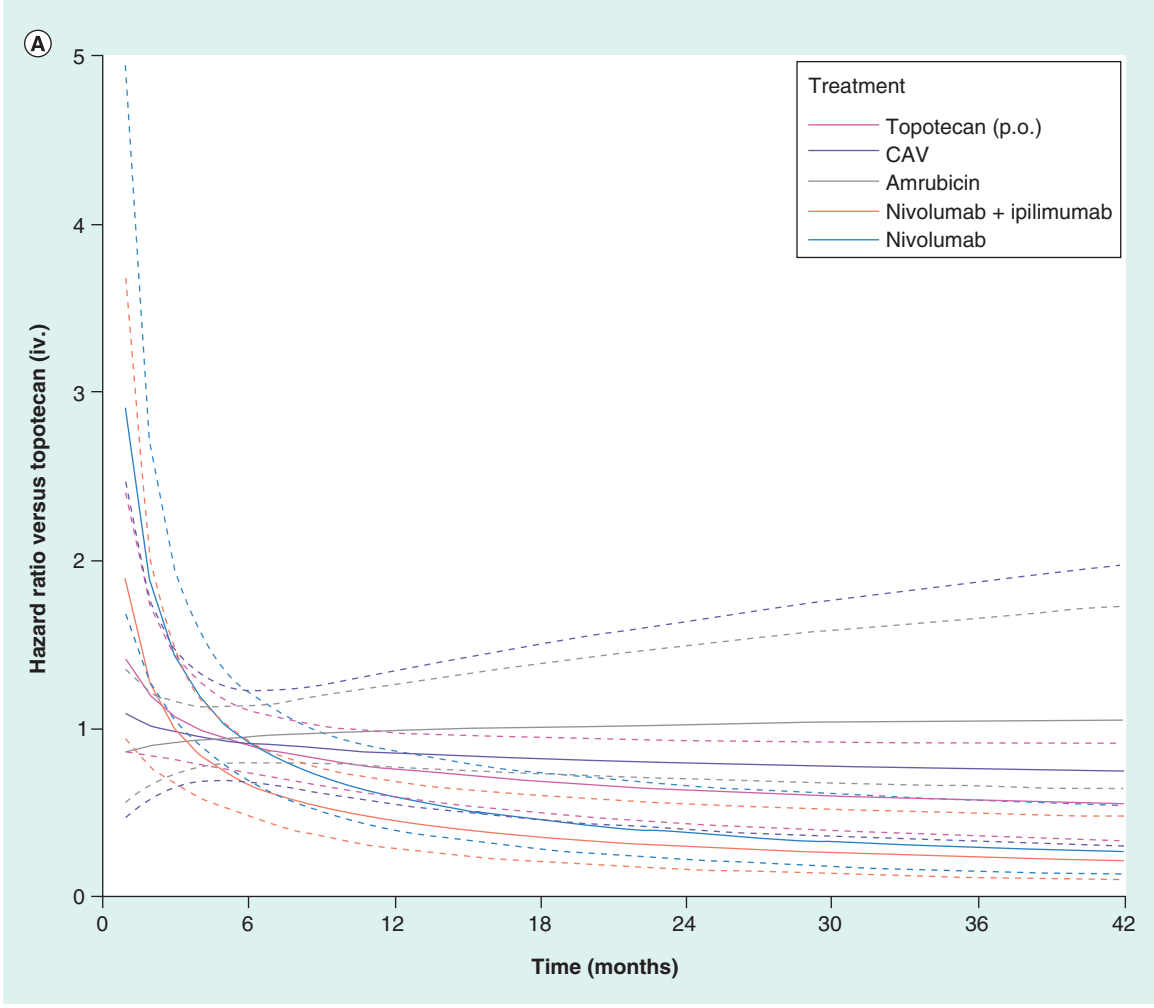

Figure 5. Results from network meta-analysis. Estimated hazard ratios of each intervention versus intravenous topotecan for overall survival **(A)** and progression-free survival **(B)**. Models according to second-order fractional polynomial model for overall survival (p1 = 0 and p2 = 1) and progression-free survival (p1 = 0 and p2 = -1).
CAV: Cyclophosphamide + doxorubicin + vincristine; iv.: Intravenous; p.o.: Oral.

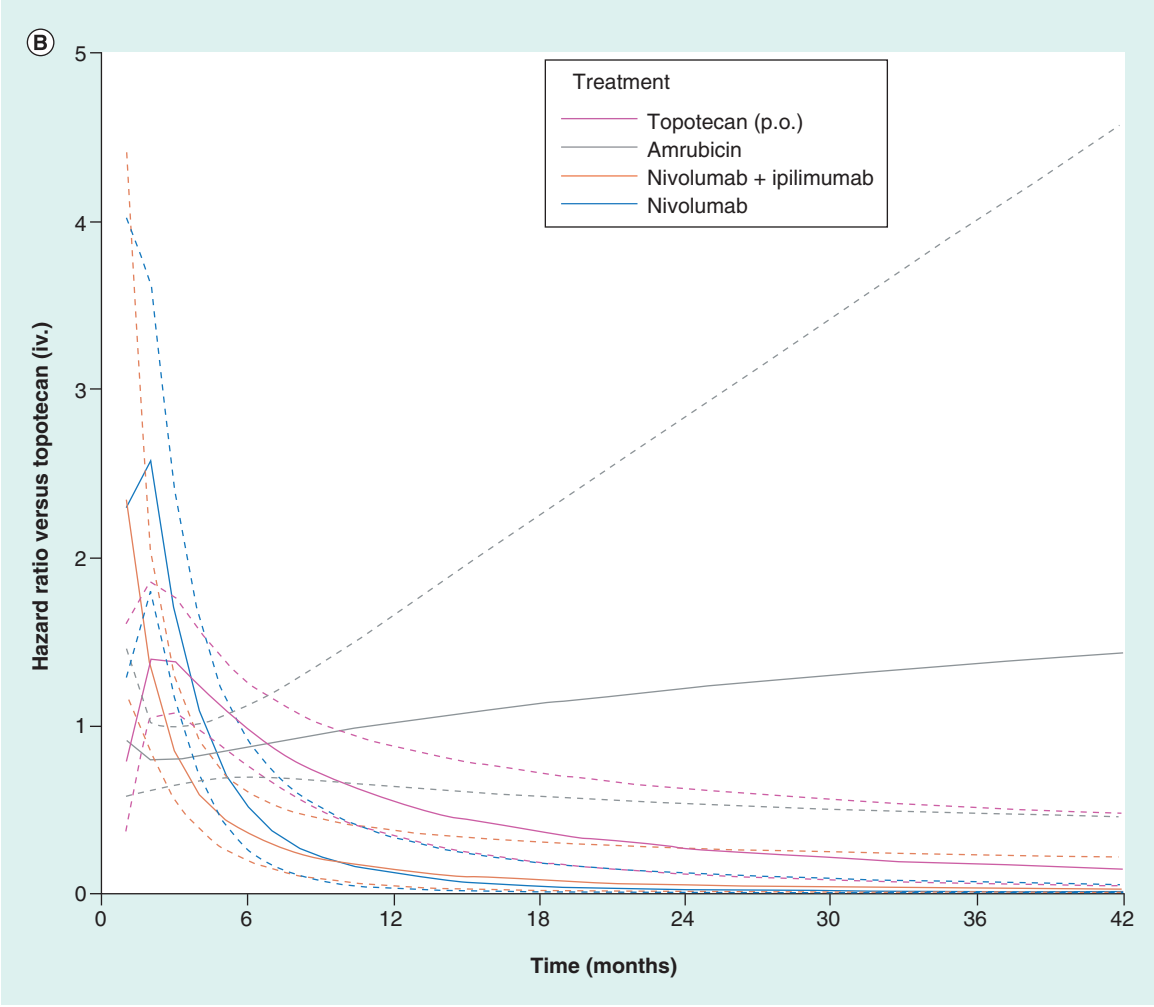

Figure 5. Results from network meta-analysis (cont.). Estimated hazard ratios of each intervention versus intravenous topotecan for overall survival **(A)** and progression-free survival **(B)**. Models according to second-order fractional polynomial model for overall survival (p1 = 0 and p2 = 1) and progression-free survival (p1 = 0 and p2 = -1). CAV: Cyclophosphamide + doxorubicin + vincristine; iv.: Intravenous; p.o.: Oral.

oral topotecan and topotecan via iv. It is noteworthy that the network did not include a trial of rechallenge with a platinum-based regimen, as this has been identified as a key comparator of interest. The median OS among the trials in the network ranged from 5.7 to 9.2 months. The results of this analysis confirm that outcomes among this population are poor despite chemotherapy, and there are no differences between agents in terms of survival. This aligns with observational data from the USA, where median OS after 2L therapy, most often with topotecan, was less than 6 months for both platinum-refractory and sensitive patients [18].

The findings underscore the need for new treatments for this population and provide justification for the recent FDA accelerated approval of nivolumab for SCLC and the recommendation of nivolumab ± ipilimumab by the NCCN based on evidence from CheckMate 032. Despite the significant limitations regarding the methodology for aggregate-level matching, initial results suggest that nivolumab ± ipilimumab had a much longer DOR than existing therapies. These benefits may translate to improvements in longer-term OS and PFS, which will be important to evaluate based on longer follow-up. The analysis of survival outcomes further supports this hypothesis, given outcomes were more favorable for nivolumab at later time points. Note that time-varying HRs were used since nivolumab + ipilimumab curves crossed the observed chemotherapy survival curves in several cases, meaning that the proportional hazards assumption was not valid. These results align with expectations given the differences in the mechanism of action for nivolumab, a novel immunotherapy, compared with traditional chemotherapies.

It is important to emphasize that in the absence of randomization, it is not possible to disentangle the treatment effects from the study effects; therefore, relying on single-arm evidence may introduce a significant risk of bias when used as the foundation for estimating relative treatment effects. For example, ACT-1 included only 2L patients, whereas CheckMate 032 included patients with more than one prior line of therapy. Therefore, comparative efficacy estimates for nivolumab may be conservative given the more advanced population included in CheckMate 032. A population-adjusted indirect treatment comparison using IPD from CheckMate 032 would better account for between-study differences in patient characteristics. However, even with IPD, there is a risk of bias due to unmeasured or unknown study-level differences. Furthermore, some between-study differences within the connected network of RCTs may have introduced bias. For example, platinum sensitivity may act as a treatment effect modifier. However, given the limited number of studies it was not feasible to adjust for differences across studies.

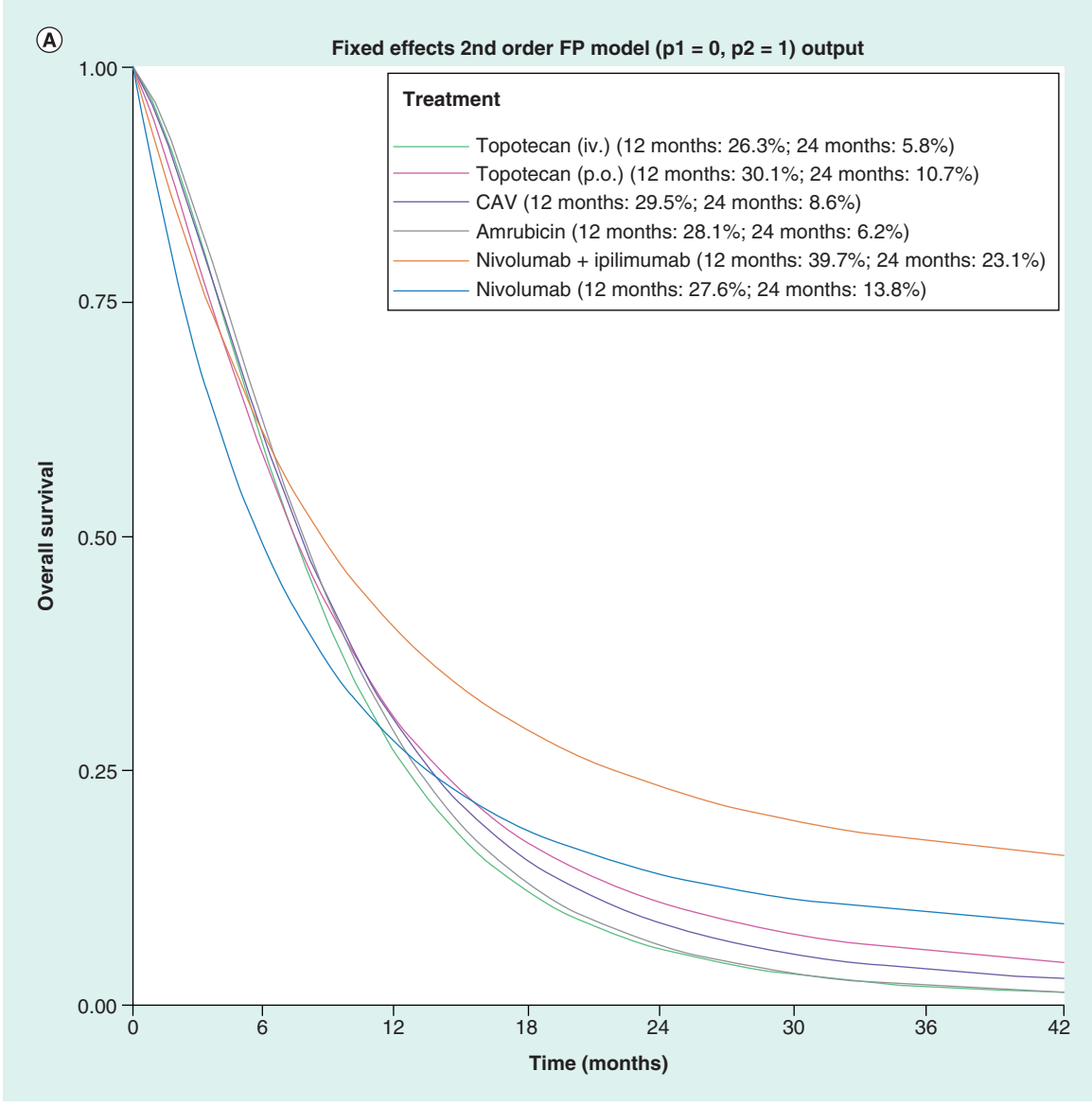

Figure 6. Results from network meta-analysis. Estimated survival proportions over time for overall survival **(A)** and progression-free survival **(B)** assuming intravenous topotecan as the reference curve. Models according to second-order fractional polynomial model for overall survival (p1 = 0 and p2 = 1) and progression-free survival (p1 = 0 and p2 = -1).
CAV: Cyclophosphamide + doxorubicin + vincristine; iv.: Intravenous; p.o.: Oral.

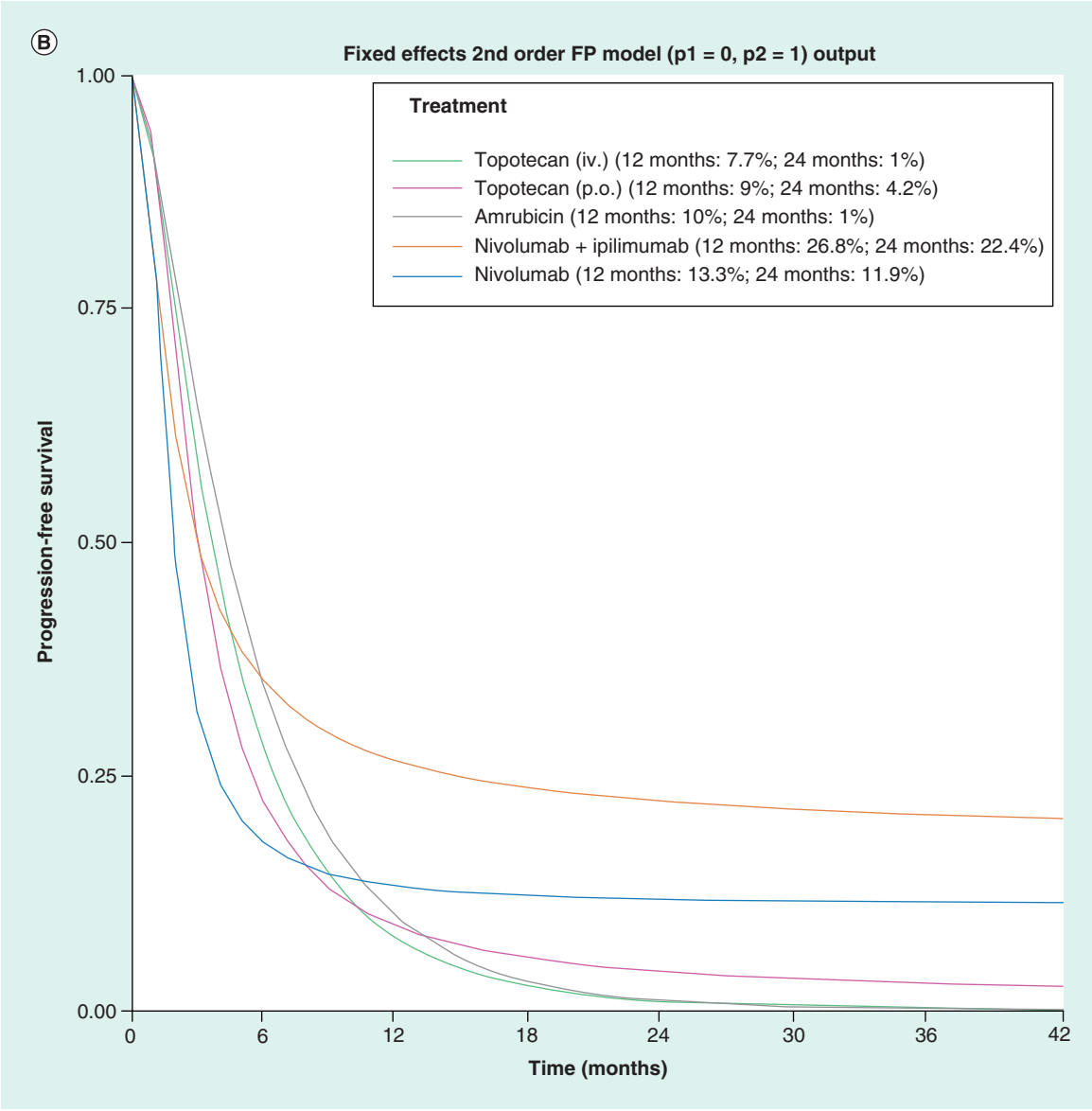

Figure 6. Results from network meta-analysis (cont.). Estimated survival proportions over time for overall survival **(A)** and progression-free survival **(B)** assuming intravenous topotecan as the reference curve. Models according to second-order fractional polynomial model for overall survival (p1 = 0 and p2 = 1) and progression-free survival (p1 = 0 and p2 = -1).
CAV: Cyclophosphamide + doxorubicin + vincristine; iv.: Intravenous; p.o.: Oral.

Given the high-unmet need in SCLC, results from this study can help inform decision-makers of the potential benefit from nivolumab + ipilimumab until results from other trials become available. There are currently several ongoing trials investigating immunotherapies in SCLC. CheckMate 331 is a randomized, open-label, Phase III trial comparing nivolumab monotherapy versus topotecan/amrubicin in patients with progression during or after platinum-based 1L chemotherapy or chemoradiation. Although this trial failed to meet its primary end point of OS [58], an investigation of potential patient subgroups that may benefit from nivolumab, such as those with elevated PD-L1 expression or high tumor mutation burden (TMB), is ongoing.

A treatment approach using immunotherapy in the 1L and 1L maintenance settings, rather than only in the 2L setting, is a promising option to increase the proportion of patients showing a clinical response. In the 1L setting, IMpower133 is a randomized, double-blind, Phase III trial of carboplatin and etoposide with either atezolizumab or placebo in SCLC ED patients who had not previously received treatment [59]. Interim results show that the

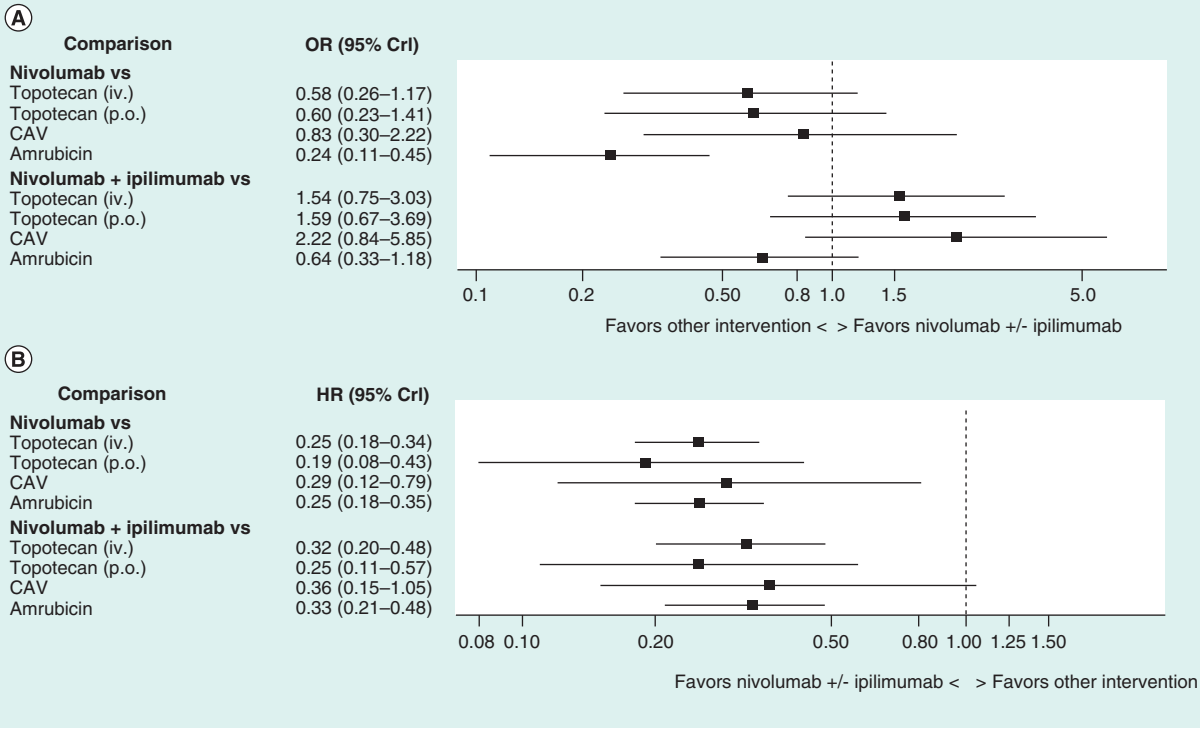

Figure 7. Results from network meta-analysis. Forest plot of odds ratios of objective response **(A)** and hazard ratios of duration of response **(B)** for nivolumab ± ipilimumab versus other interventions.
CAV: Cyclophosphamide + doxorubicin + vincristine; HR: Hazard ratio; iv.: Intravenous; OR: Odds ratio; p.o.: Oral.

addition of atezolizumab to chemotherapy results in significantly longer OS and PFS compared with chemotherapy alone [59]. Other Phase III randomized trials in SCLC ED patients in the 1L setting that do not yet have results available include KEYNOTE-604, a double-blind trial of cisplatin/carboplatin and etoposide in combination with pembrolizumab or placebo, and CASPIAN, an open-label trial of cisplatin/carboplatin and etoposide in combination with durvalumab with or without tremelimumab. In the 1L maintenance setting, CheckMate 451 is a randomized, double-blind, Phase III trial of nivolumab ± ipilimumab versus placebo for ED patients who have either an ongoing CR, PR or SD after completion of four cycles of platinum-based 1L chemotherapy [60]. However, this trial failed to meet its primary end point, though as with CheckMate 331 subgroup analyses are ongoing.

Evidence from these ongoing trials may provide insight into the optimal approach to target therapies. Although PD-L1 expression is a useful biomarker in non-small-cell lung cancer, tumor PD-L1 expression is uncommon in SCLC and has not shown correlation with efficacy parameters [19], so an alternative biomarker may be required. The majority of SCLC patients are current or former smokers, and these patients tend to have a high TMB. An exploratory analysis of CheckMate 032, as well as other studies in non-small-cell lung cancer, urothelial carcinoma and melanoma, have shown an association between high TMB and improved clinical outcomes in patients receiving immunotherapies, suggesting that TMB may be a relevant biomarker in SCLC [23,61–64]. The addition of a CTLA-4 inhibitor, such as ipilimumab, to immunotherapy may further improve the response in SCLC patients with high TMB due to the synergistic effect of these treatments [23,65]. However, an exploratory analysis in IMpower133 of survival according to TMB, using a blood-based assay to measure TMB, did not identify an association [59]. Therefore, further research into the best biomarkers and treatment combinations is required to increase the proportion of SCLC patients who benefit from treatment.

Conclusion

In conclusion, based on data from the nonrandomized cohort in CheckMate 032 to estimate the comparative efficacy of nivolumab ± ipilimumab versus alternative treatments for SCLC after at least one prior line of chemotherapy, results of the indirect comparison suggest nivolumab ± ipilimumab improved response duration and was associated

with favorable OS estimates compared with existing chemotherapies. Therefore, nivolumab ± ipilimumab may provide an immuno-oncology treatment option for SCLC patients who have received prior treatment.

Future perspective

It is anticipated that in 5–10 years the role of immuno-oncology for SCLC patients will be established, based on anticipated results from ongoing trials. Moreover, it is expected that additional data from these trials may help to identify additional biomarkers to select for SCLC patients who may benefit from targeted molecular therapies. These trials may also help to elucidate the role of TMB, which may help to better target the optimal treatments for this difficult to treat population. Ultimately, patients who respond to immuno-oncology treatments may experience sustained benefits in terms of improved survival compared with chemotherapy alone.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2018-0130

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Executive summary

Background

- The majority of patients with small-cell lung cancer (SCLC) are sensitive to first-line chemotherapy; however, for patients with disease progression/recurrence, topotecan is the only approved therapy in the second-line (2L) setting, with no approved third-line (3L) therapies.
- National Comprehensive Cancer Network guidelines now recommend nivolumab ± ipilimumab for SCLC patients who have failed prior systemic therapy within 6 months in either the primary or adjuvant setting based on results from a nonrandomized cohort from CheckMate 032, Phase I/II trial. Pembrolizumab was recently added to the National Comprehensive Cancer Network guidelines following results of the KEYNOTE-158 trial and is also recommended for SCLC patients who relapse within 6 months.
- More recently, the US FDA granted an accelerated approval for nivolumab as the first and only immuno-oncology treatment option for patients with metastatic SCLC whose cancer has progressed after platinum-based chemotherapy and at least one other line of therapy.
- A standard approach to obtain relative treatment effects between the competing interventions not directly compared is based on a network meta-analysis (NMA) of randomized controlled trials (RCTs) as identified through a systematic literature review.
- Given that the preexpansion cohort of CheckMate 032 was not randomized, we used matching based on aggregate study-level data to evaluate the comparative efficacy of nivolumab ± ipilimumab versus alternative treatments for SCLC after at least one prior line of chemotherapy (2L/3L).

Methods

Systematic literature review

- A systematic literature review was performed (June 2018) including searches of EMBASE, MEDLINE and Cochrane Central Registry of Controlled Trials, published ≥1990, along with relevant conferences.
- The quality of individual trials was assessed using the Risk of Bias instrument endorsed by the Cochrane Collaboration.

Network meta-analysis

- Relative treatment effects regarding overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and duration of response (DOR) were estimated for the alternative interventions in 2L/3L treatment of advanced SCLC based on the available RCTs using NMA models.
- To facilitate a comparison of nivolumab ± ipilimumab based on study-level results from the nonrandomized cohort of CheckMate 032 with the other interventions, we linked CheckMate 032 to the RCT that best-matched in terms of study design, inclusion criteria and patient characteristics ('aggregate-level matching').
- ACT-1 (amrubicin versus topotecan via intravenous [iv.] administration) was identified as the best matching trial. Therefore, in the base case, CheckMate 032 arms were treated as arms of ACT-1 within the analysis, which assumed that the outcomes in the control arm of ACT-1 were applicable to CheckMate 032.
- For survival, fractional polynomial models were used to model the log hazard functions of the interventions in a trial. The differences in the parameters were considered the multidimensional treatment effect, which were pooled and indirectly compared across studies. For the median DOR and number of patients at risk, a binomial likelihood and cloglog link (with offset for median) were used. For ORRs, the NMA was performed based on the proportion of patients experiencing the event of interest using a regression model with a binomial likelihood and logit link.

Results

Systematic literature review

- A total of 19 individual clinical trials were identified through the database, conference and hand searches for the NMA: 18 RCTs and one non-RCT (CheckMate 032 was included as the reference population) of 2L/3L treatments (from 35 citations).

Network meta-analysis

- In terms of OS, relative to topotecan via iv. or amrubicin, the survival improvement was observed as early as month 6 for nivolumab ± ipilimumab and month 12 for nivolumab. Relative to other chemotherapies, long-term OS results favored nivolumab ± ipilimumab.
- Relative to other chemotherapies, the improvement in PFS for nivolumab was observed between months 12 and 36 and for nivolumab + ipilimumab between 6 and 18 months.
- Though no meaningful differences were observed between treatments in terms of ORR, nivolumab as monotherapy and nivolumab + ipilimumab significantly improved the duration of response compared with all chemotherapies, especially compared with the current standard of care, topotecan via iv.

Conclusion

- SCLC patients who have received at least one prior line of chemotherapy have poor outcomes despite additional treatment with chemotherapy in the second-line context, and survival is similar with different agents. These results align with observational data from the USA, where median OS after 2L therapy, most often with topotecan, was less than 6 months for both platinum-refractory and sensitive patients.
- Results suggest nivolumab ± ipilimumab responders had a much longer DOR compared with existing therapies. These benefits may translate to improvements in longer-term OS and PFS, which will be important to evaluate based on longer follow-up.

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