Supplementary Materials: The Evolving Scenario of ES-SCLC Management: From Biology to New Cancer Therapeutics

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Table S1: Summary of Real-world clinical trials in first-line with CT plus ICI in patients with ES-SCLC

	MAURIS	IMFIRST	CLINATEZO	ORIENTAL	LUMINANCE	CANTABRICO
Trial ID	NCT04028050	2019-002784-10*	NCT04920981	NCT04449861	NCT04774380	NCT04712903
Recruitment status	Completed *(ESMO 2023 poster)*	Completed *(ESMO 2023 poster)*	Completed *(ASCO 2023 poster)*	Completed *(ESMO 2023 poster)*	Active, Not recruiting *(April 2024)*	Completed *(ESMO 2023 poster)*
Study phase	IIIB	IIIB	Retrospective (EAP)	IIIB	IIIB	IIIB
Treatment	CBDCA+EP Atezolizumab (4/6 cycles)	CDDP/CBDCA+EP Atezolizumab (4/6 cycles)	CBDCA+EP Atezolizumab (4/6 cycles)	CDDP/CBDCA+EP Durvalumab (4/6 cycles)	CDDP/CBDCA+EP Durvalumab (4/6 cycles)	CDDP/CBDCA+EP Durvalumab (4/6 cycles)
n (pts)	155	155	518	166	152	101
ECOG PS	0-2	0-2	0-2	0-2	0-2	0-2
PCI allowed	Yes	Yes	Yes	Yes	Yes	No
Chest RT allowed	Yes	Yes	Yes	No	No	No
1°endpoint	Incidence G≥3 AE ir-AE	Incidence G≥3 AE ir-AE	Incidence G≥3AE ir AE	Incidence G≥3 AE ir AE	Incidence G≥3 AE ir AE	Incidence G≥3 AE ir-AE

Legend: * EudraCT Number. **Abbreviations:** N (pts) = patient number; ID= identification; PS = Eastern Cooperative Oncology Group (ECOG) Performance Status; PCI = prophylactic cranial irradiation; RT = radiotherapy; CBDA = carboplatin; EP = etoposide; CDDP = cisplatin; G = grade; AEs = adverse events; ir-AEs = immune-related adverse events; ESMO = European Society of Medical Oncology; ASCO = American Society of Clinical Oncology.

Table S2: Summary of studies with Topotecan in relapsed SCLC

TOPOTECAN History Trials	Topotecan IV vs CAV von Pawel et al. (JCO 1999)	Topotecan OS Vs Topotecan IV von Pawel et al. (JCO 2001)	Topotecan OS vs BSC O'Brien et al. (JCO 2006)	Amrubicin vs Topotecan IV von Pawel et al. (JCO 2014)
Study Phase	III	II	III	III
Line of treatment	2	2	2	2
n (pts)	211 (S)	106 (S)	141 (S/R)	637 (S/R)
ORR (%)	24% (T) 18% (CAV) p = .285	23% (OS) 95% CI 11.6-34.5 15% (IV) 95% CI 5.3-24.3	NR (BSC) 7% (T) → >R	31% (A) 17% (T) OR= 2.223; p < .001
mPFS (mos)	3.2 mos (T) 3.0 mos (CAV) p = .552	3.7 mos (OS) 3.2 mos (IV)	NR (BSC) 4 mos (T)	4.1 mos (A) >S 3.5 mos (T) >S HR 0.802; p = .018
mOS (mos)	6.2 mos (T) 6.2 mos (CAV) p = .795	8 mos (OS) 6.2 mos (IV) HR 0.84 (95% CI, 0.53-1.32)	3.5 mos (BSC) 4.0 mos (T)	7.5 mos (A) >S 7.8 mos (T) >S HR 0.880; p = .170
Grade ≥3 toxicity (%)				
Anemia	42% (T), 20% (CAV)	31% (OS), 30% (IV)	NR (BSC), 25% (T)	16% (A), 31% (T)
Thrombocytopenia	58% (T), 15% (CAV)	53% (OS), 49% (IV)	NR (BSC), 38% (T)	21% (A), 54% (T)
Neutropenia	89% (T), 87% (CAV)	57% (OS), 94% (IV)	NR (BSC), 61% (T)	41% (A), 54% (T)
FDA approval	Topotecan IV 1998		Topotecan OS 2007	

Abbreviations: *n (pts)* =patient number; R= resistant; S= sensitive. ORR = overall response rate; mPFS = median Progression Free Survival; mOS = Median Overall Survival; mos= months; T = Topotecan; A = amrubicin; CAV = vincristine, adriamycin, cyclophosphamide; BSC = Best Supportive Care; OS = Oral Administration; IV = Intravenous; HR= Hazard Ratio; OR= Odds Ratio; NR=not reported.

Table S3: Summary of studies with platinum-etoposide rechallenge in patients with relapsed SCLC

Reference	Phase	Schedule	Pt N	ORR	mDoR	MS
Giaccone 1987	II	VAC VAC/CE CDE	13	50%	22 weeks	23.5 months
Genestreti 2015	Retr.	CE	112	45%	5.5 months*	7.9 months
Naito 2018	Retr.	CE	67	52.2%	5.1 months*	10.8 months
Baize 2020	III	CE	86	49%	5.4 months	7.5 months

Legend * we stated mPFS (median progression-free survival) on behalf of mDoR because it was not reported. **Abbreviations:** Pt N=patient number; ORR = overall response rate; mDoR = Median duration of response; MS = Median survival; Retr. = retrospective; VAC = vincristine, adriamycin, cyclophosphamide; CE = cisplatin/etoposide; CDE = cyclophosphamide, doxorubicin and etoposide.

Table S4: Results of clinical trials of lurbinectedin-based therapy in relapsed SCLC patients

Reference		Phase	Schedule	Pt N	ORR		mPFS		AEs G> 3 rate
Trigo el al. 2020		II	Lurbinectedin 3.2 mg/sm q21 days	105	35.2%		3.5 mos		NR
R D <90	S D ≥90				12%	45%	2.6 mos	4.6 mos	
Ponce-Aix et al 2021		I-II	Lurbinectedin 2 mg/sm q21 plus irinotecan 75mg/ms 1,8q21 days (+GCSF)	21	62%		6.2 mos		28.6 % G4 neutropenia 9.5% Febrile neutropenia
R D <90	S D ≥90				50%	69%	3.7 mos	8.5 mos	
Aix et al. 2023*		III	lurbinectedin 2 mg/m2 plus doxorubicin 40 mg/m2 q 21 days	307	32%		4 mos		48%
R D <180	S D ≥180				NR	NR	4.5 mos	8.2 mos	
Calles Blanco et al. 2023		II	Lurbinectedin 3.2 mg/sm plus pembrolizumab 200 mg q21 days	28	46.4%		5.3 mos		82.1%
R D <90	S D ≥90				35%	54%	3 mos	10 mos	

Abbreviations: mg = milligrams; sm = square meter; q = every; Pt N = patient number; ORR = overall response rate; mPFS = median progression-free survival; AEs= adverse events; G = grade; R= resistant; S=sensitive; D=days; mos= months; GSCF= Granulocyte colony-stimulating factor; NR= not reported.

Table S5: Ongoing clinical trials of lurbinectedin in ES-SCLC

N. Identifier	Phase	Drug(s)	Disease	Pt N	Principal endpoint(s)	Notes
IMforte NCT05091567	III	Lurbinectedin + atezolizumab vs atezolizumab	M SCLC	450	PFS/OS	Key eligibility criteria: No BM SFs are: ECOG PS 0 vs 1 Liver metastases y vs n LDH ULN > vs < PCI y vs n
NCT02611024	I/II	Lurbinectedin + irinotecan	Relapsed Solid tumors	320	RP2D/ORR	Aix SP 2019: phase I ORR (3/11) 27% The RD is LUR 2.0 mg/m2 on D1 + CPT11 75 mg/m2 D1,8 q21
LAGOON NCT05153239	III	Lurbinectedin +irinotecan vs Lurbinectedin vs irinotecan or topotecan	2L SCLC	705	OS	Key eligibility criteria: CTFI > 30 days SFs are: CTFI < or > 90 days Prior ICI y vs n LDH ULN > vs < BM y vs n Topotecan vs irinotecan
NCT04607954	II	Durvalumab + topotecan or lurbinectedin	Relapsed SCLC (after CT/IO)	70	ORR	Group 1 SCLC sens. D + T Group 2A SCLC sens D+ L Group 2B SCLC refr. D+L
LURBIMUNE NCT05572476	II	Durvalumab + lurbinectedin	Relapsed SCLC	82	ORR	Sensitive SCLC; non comparative ARM B Rechallenge CT
NCT04253145	I/II	Atezolizumab+ lurbinectedin	Relapsed SCLC	184	ORR	After CT or CT/IO
NCT05572476	Ib	Lurbinectedin + RT	Relapsed SCLC	22	DLT/ORR	After CT or CT/IO
NCT05578326	II	Lurbinectedin + trilaciclib	Relapsed SCLC	30	ORR	Trilaciclib is a myelopreservation drug
NCT04802174	I/II	Lurbinectedin + Berzosertib	Relapsed tumor	75	DLT/ORR	High grade NE tumors Berzosertib ATR inh At least one line CT

Abbreviations: Pt N = patient number; RT = radiotherapy; M = maintenance; SCLC = small cell lung cancer; 2L = second line; CT = chemotherapy; IO = immunotherapy; NE = neuroendocrine tumor; BM = brain metastases; PFS = progression-free survival; OS = overall survival; SFs = stratification factors; ECOG PS = Eastern Cooperative Oncology Group performance status; ULN = upper limit normal; PCI = Prophylactic cranial irradiation; ORR = overall response rate; RD = recommended dose; sens. = sensitivity; refr = refractory; ATR = Ataxia telangiectasia and Rad3; inh. = inhibitor

Table S6: Summary of clinical trials with ICI in relapsed SCLC

	KEYNOTE-028 Ott et al., JCO 2017	KEYNOTE-158 Chung et al., JCO 2018	IFCT-1603 Pujol et al., JTO 2019	CHECKMATE-032 Ready et al., JTO 2019	CHECKMATE-331 Spigel et al., Ann Onc 2021
Drug	Pembrolizumab (only Pdl1+)	Pembrolizumab (any Pdl1)	Atezolizumab vs CT	Nivolumab +/- Ipilimumab	Nivolumab Vs Topot. or Amrub.
Line	2/3	2/3	2	2/3	2
Phase Study	IB (basket)	II (basket)	II	I/II	III
n (pts)	24	107 (42 Pdl1+/50 Pdl1-)	73 (49 A, 24 CT)	147 (N) 96 (N+I)	781 (284 N, 285 CT)
1°endpoint	ORR	ORR	ORR	ORR	OS
ORR (%)	33.3% [95% CI, 16-55]	18.7% (O) [95% CI, 11.8–27.4] 35.7% (Pdl1+) 6% (Pdl1-)	2.3% (A) [95% CI: 0.0–6.8] 10% (CT) 95% CI: 0.0–23.1	11.6% (N) 21.9% (N+I) OR: 2.12 (95% CI 1.06–4.26)	13.7% (N) 16.5% (CT) OR 0.80 (95% CI, 0.50-1.27)
mPFS (mos)	1.9 mos [95% CI, 1.7-5.9]	2.0 mos (O) [95% CI, 1.9-2.1] (2.1 Pdl1+, 1.9 pdl1-)	1.4 mos (A) [95% CI, 1.2-1.5] 4.3 mos (CT) [95% CI, 1.5-5.9]	1.4 mos (N) [95% CI, 1.3–1.4] 1.5 mos (N+I) [95% CI, 1.4–2.2]	1.4 mos (N) 3.8 mos (CT) HR 1.41 (95% CI, 1.18-1.69)
mOS (mos)	9.7 mos [95% CI, 4.1-not reached]	9.1 mos [95% CI, 5.7-14.6] (14.6 Pdl1+, 7.7 Pdl1-)	9.5 mos (A) 8.7 mos (CT) HR 0.84 (95% CI, 0.45-1.58)	5.7 mos (N) [95% CI, 3.8-7.6] 4.7 mos (N+I) [95% CI, 3.1 to 8.3]	7.5 mos (N) 8.4 mos (CT) HR 0.86 (95%CI, 0.72-1.04, p 0.11)
DoR (mos)	19.4 mos >3.6 to >20.0	NR	NR	15.8 mos (N) [95% CI, 7.4– not reached] 10.0 mos (N+I) [95% CI, 6.7–not reached]	8.3 mos (N) [95% CI, 7.0-12.6] 4.5 mos (CT) [95% CI, 4.1-5.8]

Abbreviations: ICI= immune checkpoints inhibitors; n (pts) =patient number; ORR = overall response rate; mPFS = median Progression Free Survival; mOS = Median Overall Survival; DoR = Duration of Response; CT = Chemotherapy; O=0verall population; A = Atezolizumab; N = Nivolumab ; I = Ipilimumab; CI= confidence interval; OR= Odds ratio; HR= Hazard ratio; mos=months. NR= not reported.

Table S7: Survival according to subtypes in IMpower133*

Subtypes	phenotype	EP+ A arm		EP+ placebo arm		HR (95% CI)
		n.	mOS (months)	n.	mOS (months)	
SCLC-A	NE	77	10.9	63	10.6	0.807 (0.547-1.189)
SCLC-N	NE	25	10.6	36	9.4	0.631 (0.353-1.129)
SCLC-P	non-NE	9	9.6	12	6.0	0.595(0.223-1.589)
SCLC-I	non-NE	21	18.2	28	10.4	0.572 (0.284-1.15)
All	/	132	11.6	139	10.1	/

Legend: * Analysis reported in the publication of Gay's at al. **Abbreviations:** N (pts) =patient number; mOS = Median Overall Survival; HR = Hazard Ratio; CI= confidence interval; NE = Neuroendocrine; non-NE= non neuroendocrine. EP= etoposide/carboplatin chemotherapy; A = atezolizumab; SCLC= small cell lung cancer.

Table S8: Summary of clinical trials with chemotherapeutic agents in patients with relapsed SCLC

Reference	Setting	Phase	Schedule	Pt N	ORR	mPFS	MS	Notes
Topoisomerase I inhibitors								
Goto 2016	2L	III	CPT11 + CE vs topotecan	180	84% vs 27%	5.7 mos vs 3.6 mos	18.2 mos vs 12.5 mos	Severe toxicity
Kondo 2018	≥2L	II	CPT11	30	41.3%	4.1 mos	10.4 mos	-
Alamgeer 2018	2L	II	CPT11/Hyaluronic + CBDCA	13	22%	7 mos	3.5 mos	-
Arnold 2020	2L	II	CPT11+ carfilzomib	62	21.6%	3.6	6.9 mos	-
Zhao 2020	2L	II	CPT11+ apatinib	17	40%	-	-	-
Edelman 2020	2L	II/III	Dinutuximab + CPT11 vs CPT11 or topotecan	471	17.1% vs 18.9%	3.5 mos vs 3 mos	6.9 mos vs 7 mos	Negative trial
Spigel 2021 [RESILIENT]	2L	II/III	Liposomal CPT11	30	44%	4 mos	8 mos	Phase III controlled vs topotecan negative
Kang 2021	2L	R II	Belotecan Vs topotecan	164	33% Vs 21%	4.8 mos Vs 3.8 mos	13.2 mos Vs 8.2 mos	Belotecan was favorable for Pts < 65 years
Alkylating agents								
Tanaka 2018	2L	II	Ifosfamide	12	0%	0.9 mos	4.8 mos	Negative trial
Pietanza 2018	2-3L	R II	TMZ + veliparib vs TMZ	104	39% 14%	3.8 mos 2 mos	8.2 mos 7 mos	Plus PARP inhibitor
Goldman 2022	≥2L	II	Low dose TMZ + Talazoparib	28	39.3%	4.5 mos	11.9 mos	Plus PARP inhibitor
Other chemotherapeutic agents								
Zheng 2016	≥2L	II	Amrubicin	95	39%	NR	9.2 mos	-
Yoshioka 2018	≥2L	II	Weekly amrubicin	21	19%	4 mos	10 mos	Lack of efficacy
Moharana 2016	2L	IV	Paclitaxel	NR	9.5%	1.5 mos	12.5 mos	Designed for CT refractory
Scagliotti 2016	2L	R II	TAS-102 vs Topotecan or amrubicin	18	0	1.4 mos vs 2.7	NR	Lack of efficacy
Gelsomino 2020 [NABSTER]	2L	II	Nabpaclitaxel	68 S 47 R 25	14% 8%	1.9 mos 1,8 mos	6.6 mos 3.6 mos	Negative trial
Cheng 2021	2L	IV	Lobaplatin-based CT	431	33%	4 mos	9.2 mos	Real world data in China-

Abbreviations: Pt N = patient number; ORR = overall response rate; mPFS = median progression-free survival; MS = median survival; CPT11 = irinotecan; NA not applicable; mos = months; TMZ= temozolomide; 2L = second-line setting; CT = chemotherapy; S = sensitive; R refractory.

Table S9: Summary of studies with ICIs combinations in patients with relapsed SCLC

Reference	Setting	Drug(s)	Phase	Pt N	ORR	mPFS	mOS	Notes
PD-1 inhibitors								
Kim 2019	2L	Pembrolizumab + paclitaxel	II	26	23%	5 mos	9.1 mos	-
Fischer 2019 [BIOLUMA]	2L	Nivolumab + Ipilimumab	II	18	38.8%	-	-	Trial emendated to select highTMB
Lycan 2021	2L	Nivolumab + gemcitabine	II	14	8%	1.8 mos	3.2 mos	Closed due to futility
Akamatsu 2021	≥2L	Pembrolizumab + amrubicin	II	25	52%	4 mos	-	-
Ozuma 2023	2L	Nivolumab + LF eribulin	Ib/II	34	24%	4 mos	NR	mFUP 10.6 mos
Fan 2020 [PASSION]	2L	Camrelizumab + Apatinib	II	59	34%	3.6 mos	8.4 mos	-
Zhang 2021	2L	Penpulimab + Anlotinib	II	20	50%	4.7 mos	-	-
PD-L1 inhibitors								
Thomas 2019	2L	Durvalumab + olaparib	II	20	10.5%	1,8 mos	4,1 mos	
Pakkalas 2020	≥2L	Durvalumab + Tremelimumab +/- SRT	RII	18	0% vs 28.6%	2.1 mos vs 3.3 mos	2.8 mos vs 5.7 mos	
Anti-TIGIT								
Rudin 2023 SKYSCRAPER-02	1L	Tiragolumab +/- CE+ Atezolizumab	III	490	73.5% vs 66.7%	5.4mos vs 5.6 mos	13.1 mos vs 13.1 mos	G3/4 AEs 64.0% vs 63.8%
Anti-LAG3								
Uboha 2019	≥2L	Spartalizumab (antiPDL1) + LAG525 (anti-LAG3)	II	76 (15*)	NR	NR	NR	Solid tumors

Abbreviations: Pt N = patient number; ORR = overall response rate; mPFS = median progression-free survival; mOS = median overall survival; PD-1 = Programmed Cell Death Protein 1; PD-L1 = PD-1 ligand 1; 2L = second-line; R II= randomized phase II trial; LP = liposomal; CE = cisplatin/carboplatin etoposide; SRT = stereotactic radiotherapy; mos = months; TMB = tumor mutational burden; mFUP = median follow-up; LDH = Lactate dehydrogenase; UNL = upper normal limit; mets = metastases; G=grade; AEs=adverse events: NR= not reported.

Table S10: Ongoing clinical trials with immunotherapy in patients with ES-SCLC

Identifier	Phase	Pt N	Drugs	Setting	Principal Aim	Note
ASTRIDE **NCT05468489**	III	200	CE+ atezolizumab vs CE + Serplulimab (anti-PD1)	1L	OS	Recruiting USA
NCT04346914	Ib	20	Socazolimab [ZKAB001] (anti-PDL1) + CT	1L	DLT	Recruiting China

NCT04702880	R II	120	BMS-986012 (antiFucosyl-GM1)$^{\$}$ + CT+ Nivolumab	1L	AEs	Not Recruiting USA, Canada, Europe, Japan, Australia
NCT05309629	II	40	CE+ QL1706 (bispecific antibody anti-PDL1/anti-CTL4)	1L	Safety	Not Recruiting
NCT05844150	II/III	445	PM8002 (bispecific antibody anti-PDL1/anti-VEGF-A) + CT vs atezolizumab + CT	1L	ORR/OS	Recruiting China
KEYMOTE-B99 **NCT04924101**	II	120	pembrolizumab + CP/EP + MK-4830 (anti-ILT4 antibody) + boserolimab (anti-CD27 antibody) or lenvatinib	1L	ORR/6-mos PFS	Active, not recruiting
MOZART **NCT05903092**	II	38	Monalizumab (anti HLA-E) + CT + Durvalumab	1L	1-yr PFS	Recruiting USA
TAXIO **NCT05856695**	II	67	Carbo + taxolo + durvalumab	1L	OS	Etoposide CT free Recruiting France
EDUR-BRA **NCT06008353**	IV	60	Durvalumab + CT	1L	Observational	RWD Recruiting Brazil
DRIVE **NCT05761977**	IV	50	Durvalumab + CT	1L	Observational	RWD Recruiting Greece
ARSENAL **NCT05683977**	IV	250	Durvalumab + CT	1L	TTD	RWD Recruiting France
NCT05191797	I/II	34	Bomedemstat (anti LSD1) + Atezolizumab	M	DLT	Recruiting USA
NCT05901584	II	30	Cadonilimab [AK104] (bispecific antibody anti-PD1/anti-CTL4) +/- 2L CT*	≥2L	PFS	Recruiting China
NCT05505825	I/II	42	AK104 (antiPD1/CTLA4) + Chiauranib (mTKI)	2L	ORR	Recruiting
NCT04085185	Ia/Ib	268	IBI110 (anti-LAG3) +/- sintilimab	2L	safety	Solid tumors (include SCLC)

						Recruiting
NCT06016270	I/II	130	nelmastobart [hSTC810] (anti-BTN1A1)$^{\$}$ + PTX	2L	ORR/PFS	Recruiting USA/Korea
NCT05199272	I/II	141	23ME-00610 (anti-CD200R1)$^{\$}$	≥2L	DLT	Solid tumors (include SCLC), Recruiting USA Canada

Legend: *Platinum based chemotherapy; $^{\$}$Humanized monoclonal antibody; GM1: ganglioside; **Abbreviation:** CE=carboplatin/etoposide; CT=chemotherapy; 1L= first line; 2L= second line; DLT=dose limiting toxity; ORR=overall response rate; OS= overall survival; PFS= progression free survival; VEGF-A= vascular endothelial growth factor A; HLA-E =human leucocyte antigen-E; LSD1 = Lysine-specific demethylase 1; SCLC=small cell lung cancer; RWD= real world data; PTX= paclitaxel.

Table S11: Summary of clinical trials with apatinib (anti-VEGFR2) in patients with SCLC

Reference	Phase	Drug	Pt N	ORR	mPFS	MS
Xu 2019	II	Apatinib	40	17.5%	3 mos	5.8 mos
Liu 2019	II	Apatinib	22	13.6%	5.4 mos	10 mos
Hua 2019	IV	Apatinib	52	19.4%	6.18 mos	-
Phase II trials of combo						
Zhao 2020	II	Apatinib +CPT11	17	40%	-	-
Fan 2020 PASSION	II	Apatinib+ Camrelizumab (anti-PD1)	59	34%	3.6 mos	8.4 mos
He 2021	II	Apatinib+ Vepesid	53	21%	3 mos	5 mos
Ma 2021	II	Apatinib + CPT11 or TXT	31	25%	7.4 mos	12.5 mos

Abbreviations: Pt N: patients number; mPFS: median progression-free survival; ORR: Overall Response Rate; MOS: Months;CPT11: Irinotecan; TXT: Docetaxel

Table S12: Summary of clinical trials multi-tyrosine kinase (mTKI) in patients with ES-SCLC

Reference	Phase	setting	Drug	Target(s)	Pt N	ORR	mPFS	M=S
Cheng 2021 [ALTER 1202]	R II	≥2L	Anlotinib vs placebo	VEGFR PDGFR FGFR c-kit	120	4.9% vs 2.6%	4.1 mos vs 0.7 mos	7.3 mos vs 4.9 mos
Wang 2021 [SALTER]	II	≥2L	Anlotinib + S1		52	43.8%	4.8 mos	6.3 mos
Zhang 2021	II	≥2L	Anlotinib + penpulimab (anti-PD1)		20	50%	4.7 mos	-
Zhang 2023	II	≥2L	Anlotinib+ TXT or CPT11		36	58%	4.4 mos	7.9 mos
Cheng 2023	III	1L	Anlotinib+ Benmelstobart (anti-PD-L1) + CP/EP vs CP/EP + placebo		493	81% vs 66%	6.9 mos vs 4.2 mos	19.32 mos vs 11.89 mos
Koinis 2017	II	≥2L	Pazopanib	VEGFR PDGFR cKIT	58	13.8%	2.5 mos	6 mos
Sun 2018 KCSG-LU12-07	R Ph II	≥2L	Pazopanib		95	NA vs NA	3.7 mos vs 1.8	10.6 mos vs 12.9 mos
Shi 2021	II	≥2L	Chiauranib	Aurora B VEGFR c-KIT CSF1-R	28	17.9%	3.6 mos	8.4 mos

Abbreviations: Pt N: patients number; mPFS: median progression-free survival; mOS: median overall survival; CP: carboplatin; EP:etoposide; NR: not reported; S1: oral dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine; VEGFR: Vascular Endothelial Growth Factor Receptor; FGFR: Fibroblast Growth Factor Receptor; PDGFR: Platelet Derived Growth Factor Receptor; c-KIT: Proto-oncogene receptor Tyrosine Kinase; NA: Not Available; mos: months; TXT: Docetaxel; CPT11: Irinotecan; CSF1-R: colony stimulating factor receptor

Table S13: Summary of ongoing clinical trials with antiangiogenics and combinations in patients with ES-SCLC

Identifier	Phase	Setting	Pt N	Drugs	Principal Aim	Note
BELIEVE NCT05588388	II	1L	39	CT+Atezolizumab + Bevacizumab	6-moPFS rate	Pts with liver mets Not yet recruiting USA
CeLEBrATE	II	1L	53	CT+ Atezolizumab + Bevacizumab	1year-OS rate	Active, recruiting
NCT05668767	II	1L	20	CT+ Durvalumab + Surufatinib$^{\$}$	PFS	Recruiting China
NCT05882630	I/II	1L	39	CT+ Serplulimab (antiPD1) +Surufatinib$^{\$}$	PFS	Recruiting China
NCT04660097	II	1L	120	CT+ Durvalumab + Anlotinib	OS	Recruiting China
PEERS NCT05384015	II	1L	85	CT+ Pembrolizumab + Lenvatinib	AEs/PFS	Recruiting Spain
NCT04683198	II	1L	68	CT+ Camrelizumab (antiPD1) +Apatinib	PFS	Recruiting (last updated 24 Dec 2020) China

NCT05116007	Ib	1L	35	AK112 (BiAb anti-PD1/antiVEGF)+ CT	AEs, ORR	Active, not recruiting
NCT05896059	II	M	21	Tislelizumab (anti-PD1) +Anlotinib	1-yr PFS	Recruiting China
NCT05509699	II	M	60	ICI*+Surufatinib$	PFS	Recruiting China
NCT05505825	I/II	2L	42	AK104 (BiAb antiPDL1/CTLA4) + Chiauranib	ORR	Recruiting China/Australia
NCT05296603	II	2L	83	IBI-322 (BiAb antiPDL1/CD47) + Lenvatinib	ORR	Recruiting China

Legend: *anti-PD (L)-1 inhibitor; $ small molecule, multi-tyrosine kinase inhibitor against VEGFR/FGF1R/CSF1-R. **Abbreviation**: CT=platinum plus etoposide chemotherapy. BiAb= bispecific antibody; PFS= progression free survival, OS= overall survival; AEs= adverse events; ORR= overall response rate.

Table S14: Summary of clinical trials of PARP inhibitors in patients with ES-SCLC

Reference	Setting	Phase	Schedule	Pt N	ORR	mPFS	MS
Pietanza 2018	2L	R II	TMZ + Veliparib vs TMZ+placebo	104	39% vs 14%	3.8 mos vs 2.0 mos	8.2 mos vs 7.0 mos
Owonikoko 2019	1L	R II	C/E+Veliparib Vs C/E+placebo	128	71.9% vs 65.6	6.2 mos vs 5.5 mos	10.3 mos vs 8.09 mos
Thomas 2019	2L	II	Olaparib + Durvalumab	20	10.5%	1,8 mos	4,1 mos
Kim 2020	2L	II	Olaparib + Cediranib (VEGFR-I)	25	28%	4.1 mos	5.5 mos
Park 2021 SUKSES-B	2L	II	Olaparib	15	6.7%	1.25 mos	8.56 mos
Park 2021 SUKSES-N2	2L	II	Olaparib+ Ceralasertib (ATR-I)	26	3.8%	2.75 mos	7.18 mos
Fan 2021	2L	Ib	Fluzoparib + Adebrelimab (PD-L1)	23	4.3%	1.4 mos	6.7 mos
Huang 2023 TRIDENT	M	II	Olaparib + durvalumab	60	NA	5.8 mos	NR
Karim 2023 SWOG S1929	M	R II	Atezolizumab + talazoparib vs Atezolizumab	106	16% vs 12%	4.2 mos vs 2.8 mos	9.4 mos vs 8.5 mos

Ongoing clinical trials						
ID	**Setting**	**Phase**	**Therapy**	**N. Pt**	**Principal Endpoint**	**Notes/status**
THOR NCT05623319	1L	II	Olaparib+ Pembrolizumab	60	mPFS	Recruiting Italy
NCT06217757	1L	I/II	Olaparib + sugemalimab + CT + low dose RT	45	RD	SLFN-11 Positive ES-SCLC Not yet recruiting China
PRIO trial NCT04728230	1L	I/II	Olaparib + durvalimab + CT	63	DLT	Recruiting USA
NCT03830918	M	Ib/II	Niraparib + atezolizumab + TMZ	74	RD/PFS	Recruiting USA
RAISE NCT05718323	M	II	Niraparib + AntiPD-L1	44	PFS	*Pts with SLFN11+* Not yet Recruiting Europe
NCT04782089	M	Ib	Camrelizumab Fluzoparib	20	PFS	Not yer recruiting Last update 4 Mar 2021
NCT04170946	M	Ib	Talozoparib + low dose RT	24	MTD	Recruiting Canada
NCT05975944	2L	I/II	Olaparib + selinexor (anti-JAK)	49	MTD/ORR	Recruiting China
TRIO-US L-07 NCT03672773	2L	II	Talazoparib + low dose TMZ	28	ORR	Recruiting USA
NCT05728619	≥2L	I/II	HTMC0435 + TMZ	64	DLT	Recruiting China

Abbreviations: Pt N = patient number; ORR = overall response rate; mPFS = median progression-free survival; MS = median survival; 2L = second-line setting; M= maintenance; TMZ = temozolomide; VEGFR-I = Vascular Endothelial Growth Factor-inhibitor; ATR= Ataxia-telangiectasia and Rad3 related; Atezo = atezolizumab; mos = months; P=cisplatin; E=etoposide.

Table S15: Clinical trials of targeted agents in patients with ES-SCLC

Reference	Ph	Setting	Drug	Target	Pt N	ORR	mPFS	mOS	Notes
Chiappori 2016	R II	2L	Linsitinib vs topotecan	IGF1R	29 15	0% 13%	1.2 mos 3 mos	3.4 mos 5.3 mos	*Lack of efficacy*
Awad 2017	II	2L	BI2536	PLK1/BRD4	23	0	1.4 mos	7.8 mos	Trial was designed for CT-sensitive SCLC. *Lack of efficacy*
Gregorc 2018	II	≥2L	NGRhTNF + doxorubicin	TNF/CD13R	28	25%	3.2 mos	5.6 mos	Better results were documented in CT sensitive pts. *No further studies*
Morgensztern 2019	II	≥2L	RRx-001 -> CE	Myc	26	27%	7.5 mos	8.6 mos	
REPLATINUM Chiappori 2020	II	2L	RRx-001-> CE CE rechallange	Myc	6 11	NR	7.1 mos 3.5 mos	8.2 mos 6.3 mos	Suspended during the pandemic

Owonikoko 2020	R II	2L	Alisertib (+ /- PTX)	AuroraKA	89 89	22% 18%	3.3 mos 2.1 mos	6.1 mos 5.4 mos	Among pts with CDK6, RBL1/2 alterations mPFS 3.6 vs 1.8 mos MS 7.2 vs 4.4 mos
Udagawa 2020	II	≥2L	gedatolisib	mTOR	12	0%	0.9 mos	5.8 mos	Selected pts whose SCLC harbouring mTOR pathway alterations
SUKSES Park 2020	II	≥2L	-adavosertib - vistusertib -AZD2811NP	WEE1 mTOR AuroraKB	7 4 15	0% 0% 0%	1.3 mos 1.2 mos 1.2 mos	7.8 mos 11 mos 5.3 mos	
Carneiro 2023	Ib	≥2L	Mirzo-C (+/- PTX)	BCL-Xl	12	0%	NR	NR	*Lack of efficacy*
Ongoing clinical trials									
Identifier	**Phase**	**Setting**	**Drug (s)**	**Target**	**Pt N**	**Principal endpoint**	**Notes**		
NCT04560972	Ib	1L	CT +IO + LB100	Protein Phosphatase 2A	21	ORR	Recruiting USA		
NCT05745350	II	1L	Pembrolizumab + CT + Plinabulin	tubulin polymerization	45	12moPFS	Active, not yet recruiting		
NCT06030258	I/II	1L	CT+ Tislelizumab +IN1001	FAK	120	RD/PFS	Recruiting China		
PUMA-ALI-4201 NCT06095505	II	2L	Alisertib	Aurora Kinase A	60	ORR	Recruiting USA		
NCT04010357	II	2L	Abemaciclib	CDK4/6	29	ORR	Recruiting Last updated 2 Oct 2023 USA		
NCT05353439	I	2L	Tazemetostat + topotecan + pembrolizumab	EZH2	60	MTD	Recruiting USA		
NCT04699838	II	1L	CT+IO Durva + cerelasertib (ATR inhibitor)	ATR	30	PFS	Recruiting		
NCT05731518	I/II	2L	SC0245 (ATR inhibitor) + CPT11	ATR	67	RD/PFS	Recruiting		

Abbreviations: Ph = phase; Pt N = patient number; ORR = overall response rate; mPFS = median progression-free survival; MS = median survival; R II= randomized phase II trial; 2L = second-line; Alisertib = aurora kinase A inhibitor; PTX = paclitaxel; NGRhTNF = Asparagine–glycine–arginine–human tumour necrosis factor; BI2536 = PLK1, polo-like kinase 1, inhibitor; Linsitinib = IGF1R, insulin-like growth factor 1 receptor, inhibitor; ATR = ataxia telangiectasia and Rad3-related protein; Mirzo-C = Mirzotamab clezutoclax, a BCL-XL, B-cell lymphoma-extra large gene, inhibitor; gedatolisib = mTOR, mechanistic target of rapamycin, inhibitor; adavosertib = WEE-1 inhibitor, a G2 checkpoint cell cycle regulator; vistusertib = mTOR, inhibitor; AZD2811NP = an Aurora kinase B inhibitor; RRx-001= M2-M1 tumor associated macrophage repolarization and reversal of chemoresistance; CE = carboplatin/cisplatin etoposide; mos = months; CDK6 = cyclin-dependent kinase 6 gene; RBL1/2 = retinoblastoma-like 1/2 genes; CT = chemotherapy; RD=recommended dose; FAK=focal adhesion kinase; EZH2= Enhancer of Zeste Homologue2; ORR=overall response rate; RD=recommended dose; MTD= maximum tolerated dose; PFS= progression free survival.

Table S16: Ongoing clinical trials with ADC in ES-SCLC.

ID	Phase	Setting	N. Pts	Drug	Target	Primary Endpoint	Secondary Endpoints	Status and notes
NCT06227546	II	≥2L	17	Vobramitamab duocarmazine (MGC018)	B7-H3	ORR	PFS, OS	Active, recruiting
NCT06052423 ARTEMIS-007	II	1L	50	HS-20093	B7-H3	ORR	AEs, DCR, PFS, OS	Withdrawn
NCT04152499	I–II	≥2L	430*	SKB264	TROP2	MTD, ORR	DLTs, DOR, PFS, OS	Active, recruiting
NCT04826341	I–II	≥2L	85[&]	Sacituzumab govitecan + berzosertib	TROP2 + ATR inhibitor	MTD, ORR	PFS, OS, DOR	Recruiting. Patients resistant to PARPi
NCT03221400	I–IIa	≥2L	340*	PEN-866	HSP90	DLT, ORR	DCR, PFS, OS, DOR	Recruiting
NCT02187848	I	≥2L	254*	Tusamitamab Ravtansine (SAR408701)	CEACAM5	MDT, ORR	PK, RP2D	Active, not recruiting

Legend: *Solid tumors (including SCLC). [&]included small cell lung cancer and extrapulmonary small cell neuroendocrine cancer. **Abbreviation:** ORR= overall response rate; PFS= progression free survival; OS= overall survival; AEs=adverse events; DCR=disease control rate; MDT= maximum dose tolerated; DLT=dose limiting toxicity; PARPi= Poly(ADP-ribose) polymerase inhibitors; HSP90=Heat shock protein 90; TRO2=trophoblast cell surface glycoprotein antigen 2; B7-H3=B7 homolog 3 protein; ATR=Ataxia telangiectasia mutated and Rad3 Related; CECAM5=Carcinoembryonic antigen-related cell adhesion molecule 5.

Table S17: Other ongoing trials in ES-SCLC [cancergov.trials]

Identifier	Phase	Pt N	Drugs	Setting	Principal Aim	Note
Translational research						
MOSAIC NCT05933863	R	200	ICI	1L	mPFS	immune microenvironment differences between subtypes to uncover ICI resistance mechanisms. Recruiting China
Lung Cancer Registry NCT04654364	IV	500	NA	NA	Observation	NSCLC/SCLC Recruiting Last updated 26 Aug 2022 Austria
NCT05945745	IV	500	NA	SCLC	Observation	Molecular analysis and treatment options Recruiting Shanghai
NCT05066945	IV	40	NA	1L	ctDNA	Recruiting China
Vaccine						
NCT04397003	II	27	Personalized vaccine + durvalumab	M	Safety	Recruiting USA
VENEZO-LUNG NCT04487756	Ib/II	20	Atezo + DC vaccine	M	PFS-rate 6mo	Recruiting Spain
Acclaim3 NCT05703971	Ib/II	62	quaratusugene ozeplasmid + atezo	M	MTD/PFS	Recruiting
NCT05205421	I	20	Oncolytic Virus Injection (RT-01)	≥2L	AEs/ORR	Recruiting Last updated 5 Aug 2022 China
Miscellaneous						
NCT05874401	IV	302	Topotecan +/- trilaciclib	2L	OS	Myelo-preservative Recruiting Europe
NCT05299255	II	40	Utiledone	3L	ORR	Epothilone similar to taxanes Recruiting China
FASTimmune NCT05703997	II	20	5-day diet restriction + atezo	M	6MO PFS rate	Not yet recruiting Italy
NCT04919382	II	56	Atezo + TMZ	2/3L	ORR	Recruiting Last updated 19 Dec 2023 USA
RT/radiodrug						
NCT05595460	Ib	31	RYZ101+ CT+IO	1L	RP2D	Radio-drug Recruiting USA
NCT05142696	Ib	39	[177Lu]Lu-DOTA-TATE+ CT + IO	1L	DLT	Recruiting USA/France/ Germany/Spain
DARES NCT05068232	II	49	Ablative RT + durvalumab	1L	PFS	Recruiting USA
NCT06217757	I/II	45	Olaparib + sugemalimab + CT + low dose RT	1L	RD	SLFN-11 Positive ES-SCLC Not yet recruiting China
NCT06223711	II	43	Chest RT + CT+ IO + SRT	1L	PFS	Oligometastatic up to 5 lesions

						Recruiting Germany
TRIPLEX **NCT05223647**	III	302	CT/IO+ chest RT Vs CT/IO	1L	1-yr OS	Recruiting Northern Europe
NCT06187740	Ib	28	RT + IO	M	DLT	Recruiting Shanghai
CHESTRT **NCT05796089**	II	35	CHEST RT + CT + IO	1L	Safety	recruiting Australia
NCT05765825	II	61	Low dose chest RT + CT +IO	1L	PFS	Recruiting China
NCT05403723	Ib	50	CT + IO -> Chest RT for pts SD/PD	1L	AEs	Recruiting USA
TESSERACT **NCT06110572**	I/II		CT/IO+ total body low dose RT	1L	AEs	Recruiting USA
NCT06236997	II	48	Adebrelimab (SHR1316) + CT +RT	1L	6mo PFSrate	Oligometastatic Not yet recruiting China
PRIO trial **NCT04728230**	I/II	63	Olaparib + durva + CT	1L	DLT	Recruiting USA
NCT05484583	II	58	Durva+CT + chest RT + SRT	M	OS	Oligometastatic Not yet recruiting China
NCT06177925	II	62	Adebrelimab (SHR1316) + CT +RT	1L	PFS	Oligometastatic Recruiting China
NCT05544149	II	42	Chest RT after CT +IO	M	Local Recurrence free	Recruiting China
RAPTOR trial **NCT04402788**	II/III	138	Atezo +RT	M	PFS/OS	Recruiting USA
NCT05552846	II	104	Consolidative RT after CTIO	M	1-yr PFS rate	Recruiting China
NCT04923776	II	18	RT on liver mets+ CT +IO	1L	PFS rate	Pts with liver mets Recruiting USA
NCT06243003	I/II	56	WBRT Hyppocampal sparing + SRT	1L	DLT/1yr IC PFS	BM+ Recruiting China
PRIMALung **NCT04790253**	III	600	PCI Vs MRI surveillance	LD or ES	OS	After standard Tx Recruiting worldwide
MAVERICK **SWOG S1827** **NCT04155034**	III	668	PCI Vs MRI surveillance	LD or ES	OS	Recruiting USA

Abbreviations: Ph = phase; Pt N = patient number; ORR = overall response rate; mPFS = median progression-free survival; mOS = median overall survival; R II= randomized phase II trial; L = line; CT = chemotherapy, RT = radiotherapy , IO = immunotherapy , MRI = magnetic resonance imaging, PCI = prophylactic cranial irradiation, MTD = maximum tolerated dose, DLT = dose limiting toxicity; ctDNA = circulating tumor DNA ; AE = adverse events ; TTD = therapeutic target database. Last accessed to clinicaltrial.gov on March 10, 2024.