Exploring the latest advances in first-line treatment of ES-SCLC: Translating the data to clinical practice

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Agenda

Advances in the first-line treatment of ES-SCLC: Where are we now?

Exploring safety with immunotherapy combinations: How can we mitigate side effects?

Emerging therapies for ES-SCLC: What is on the horizon?

ES-SCLC, extensive stage small cell lung cancer.

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Advances in the first-line treatment of ES-SCLC: Where are we now?

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Approval status in first-line ES-SCLC

PD-L1 inhibitors **durvalumab** and **atezolizumab** are approved by the EMA,[1,2] FDA[3,4] and PMDA[5,6] for the first-line treatment of ES-SCLC in combination with platinum-based chemotherapy

PD-1 inhibitors **pembrolizumab** and **nivolumab** were used in second- or later-line and assessed in clinical trials for first-line treatment of ES-SCLC,[7,8] but they are no longer approved in any line of treatment

EMA, European Medicines Agency; ES-SCLC, extensive stage small cell lung cancer; FDA, US Food and Drug Administration; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI, prescribing information; PMDA, Pharmaceuticals and Medical Devices Agency; SmPC, summary of product characteristics.

1. EMA. Durvalumab SmPC. Available at www.ema.europa.eu/en/medicines (accessed 27 July 2022); 2. EMA. Atezolizumab SmPC. Available at: www.ema.europa.eu/en/medicines (accessed 27 July 2022); 3. FDA. Durvalumab PI. Available at: www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed 27 July 2022); 4. FDA. Atezolizumab PI. Available at: www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed 27 July 2022); 5. PMDA. Durvalumab Review Report. Available at: https://www.pmda.go.jp/files/000243599.pdf (accessed 22 June 2022); 6. PMDA. Atezolizumab Review Report. Available at: https://www.pmda.go.jp/files/000235287.pdf (accessed 22 June 2022); 7. Rudin CM, et al. *J Clin Oncol*. 2020;38:2369–79;
8. Leal T, et al. *J Clin Oncol*. 2020;38(Suppl. 15):9000.

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CASPIAN trial with durvalumab[1,2]

NCT03043872

N=805
Eligible adults with untreated ES-SCLC

R

- **Durvalumab + EP*** n=268
- **EP alone*** n=269
- **Durvalumab + tremelimumab + EP*** n=268

Primary endpoint:
OS

Updated analysis: 25-month follow-up[2]

	Durvalumab + EP	EP alone	Durvalumab + tremelimumab + EP
Median OS, months	12.9	10.5	10.4
	Durvalumab + EP vs EP alone HR 0.75 (95% CI 0.62–0.91)		No OS advantage compared with EP alone

*Investigator's choice of either carboplatin or cisplatin.
CI, confidence interval; EP, etoposide-platinum; ES-SCLC, extensive stage small cell lung cancer; HR, hazard ratio; OS, overall survival; R, randomized.
1. Al-Salama ZT. *Target Oncol*. 2021;16:857–64; 2. Goldman JW, et al. *Lancet Oncol*. 2021;22:51–65.

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IMpower133 trial with atezolizumab

NCT02763579

N=403
Eligible adults with untreated ES-SCLC

Primary endpoints:
OS, PFS

Updated analysis: 23-month follow-up

	Atezolizumab + EC	Placebo + EC	
Median OS, months	12.3	10.3	HR 0.76 (95% CI 0.60–0.95)
Median PFS, months	5.2	4.3	HR 0.77 (95% CI 0.62–0.96)

CI, confidence interval; EC, etoposide carboplatin; ES-SCLC, extensive stage small cell lung cancer; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; R, randomized.

1. Liu SV, et al. *J Clin Oncol*. 2021;39:619–30.

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Exploring safety with immunotherapy combinations: How can we mitigate side effects?

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Overview of potential irAEs

Common toxicities

- **Fatigue**
- **Infusion-related reactions**
- **Gastrointestinal:** nausea, diarrhoea, colitis, hepatitis
- **Skin:** rash, pruritus
- **Musculoskeletal:** arthralgia, myalgia
- **Ophthalmological:** dry eye, uveitis
- **Endocrine:** hypo-/hyperthyroidism
- **Pulmonary:** pneumonitis
- **Renal:** tubulointerstitial nephritis, AKI

Rare (life-threatening) toxicities

- **Skin:** pemphigus, pemphigoid, lichenoid rash, SJS/TEN
- **Endocrine:** hypophysitis
- **Neurological:** myasthenia gravis, Guillain–Barré syndrome
- **Haematological:** thrombocytopenia, haemolytic anaemia
- **Cardiovascular:** myocarditis
- **Musculoskeletal:** myositis

AKI, acute kidney injury; irAE, immune-related adverse event; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

Brahmer JR, et al. *J Immunother Cancer*. 2021;9:e002435.

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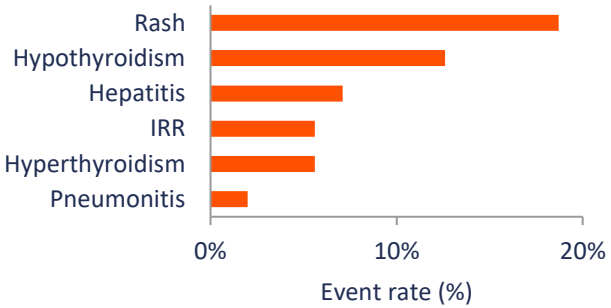
irAEs with immunotherapies in ES-SCLC

Atezolizumab + EC[1]

irAEs occurred in 40% of patients who received atezolizumab + CT

Most common irAEs

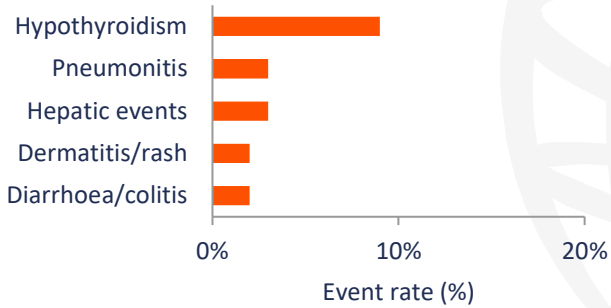


- Grade ≥3 irAEs included: rash (2%), IRRs (2%), hepatitis (1.5%), colitis (1%), pneumonitis (<1%), pancreatitis (<1%), rhabdomyolysis (<1%), nephritis (<1%), Guillain–Barré syndrome (<1%)

Durvalumab + EP[2,3]

irAEs occurred in 20% of patients who received durvalumab + CT

Most common irAEs



- Grade ≥3 irAEs included: hepatic events (2%), type 1 diabetes mellitus (2%), pneumonitis (1%), diarrhoea/colitis (<1%) and pancreatic events (<1%)

CT, chemotherapy; EC, etoposide-carboplatin; EP, etoposide-platinum ;ES-SCLC, extensive stage small cell lung cancer; irAE; immune-related adverse event; IRR, infusion-related reactions.

1. Horn L, et al. *N Engl J Med*. 2018;379:2220-29; 2. Paz-Ares L, et al. *Lancet*. 2019;394:1929-39; 3. Hou W, et al. *Front Oncol*. 2021;11:604227.

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Emerging therapies for ES-SCLC: What is on the horizon?

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Phase III clinical trials with ICIs in the first-line setting

Trial	Regimen	Status	Est. completion	Initial results
SKYSCRAPER-02[1] (NCT04256421)	Atezolizumab (anti-PD-L1) + EC + tiragolumab (anti-TIGIT)	Active, not recruiting	December 2022	• Median follow up: 13.9 months • No PFS/OS benefit with the addition of tiragolumab • Study ongoing until final OS analysis
ASTRUM-005[2] (NCT04063163)	Serplulimab (anti-PD-1) + EC	Recruiting	December 2022	• mOS: serplulimab 15.4 months vs placebo 10.9 months; HR 0.63, 95% CI 0.49–0.82; P<0.001 • mPFS: serplulimab 5.8 months vs placebo 4.3 months; HR 0.47, 95% CI 0.38–0.59; P<0.001
CAPSTONE-1[3] (NCT03711305)	Adebrelimab (anti-PD-L1) + EC	Active, not recruiting	October 2022	• Median follow up: 13.5 months • mOS: adebrelimab 15.3 months vs placebo 12.8 months; HR 0.72, 95% CI 0.58–0.90; P=0.0017

CI, confidence interval; EC, etoposide-carboplatin; HR, hazard ratio; ICI, immune checkpoint inhibitor; mOS, median overall survival; mPFS, median progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain.

1. Rudin CM, et al. *J Clin Oncol*. 2022;40:LBA8507; 2. Cheng Y, et al. *J Clin Oncol*. 2022;40:8505-8505; 3. Wang J, et al. *Lancet Oncol*. 2022;23:739-47.

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Lack of biomarkers to predict response to ICIs

- There are currently no predictive biomarkers for response to ICI in ES-SCLC which have been validated for use in clinical practice[1]
- The clinical utility of PD-L1 expression and TMB is still under investigation[1]

PD-L1

- In both CASPIAN and IMPower-133, response to ICIs was independent of PD-L1 expression[2,3]

TMB

- In both CASPIAN and IMPower-133, TMB was not predictive of treatment outcomes[3,4]

ES-SCLC, small cell lung cancer; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; ES-SCLC, small cell lung cancer; TMB, tumour mutational burden.

1. Ortega-Franco A, et al. *ESMO Open*. 2021;6:100003; 2. Paz-Ares L, et al. *Ann Oncol*. 2019;30(Suppl. 5):v928–9; 3. Liu SV, et al. *J Clin Oncol*. 2021;39:619–30;
4. Goldman JW, et al. *Ann Oncol*. 2020;31(Suppl. 4):S1212–3

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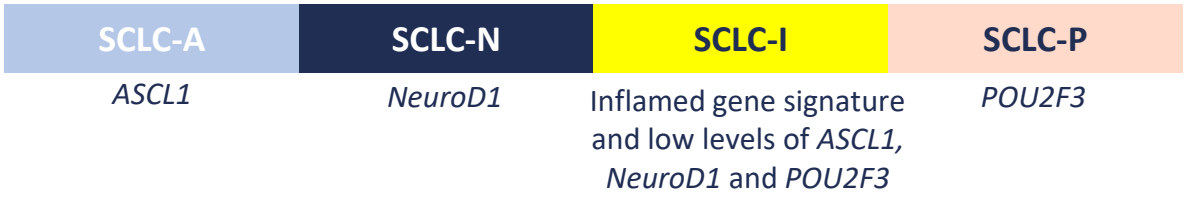
SCLC subtype classification

2019: Rudin et al proposed a consensus nomenclature for the molecular subtypes of SCLC[1]

2021: Gay et al proposed a revised classification, replacing SCLC-Y with SCLC-I[2]



SCLC, small cell lung cancer.

1. Rudin CM, et al. *Nat Rev Cancer*. 2019;19:289–97; 2. Gay CM, et al. *Cancer Cell*. 2021;39:346–60.e7.

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