Current treatment paradigm and future prospects for extensive-stage small cell lung cancer in the relapsed setting

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The current treatment paradigm of extensive-stage small cell lung cancer

Prof. Taofeek Owonikoko

Emory University School of Medicine, Georgia, USA

This expert interview was recorded on 26 February 2021

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Why is there a need for novel first-line treatment approaches in extensive-stage small cell lung cancer?

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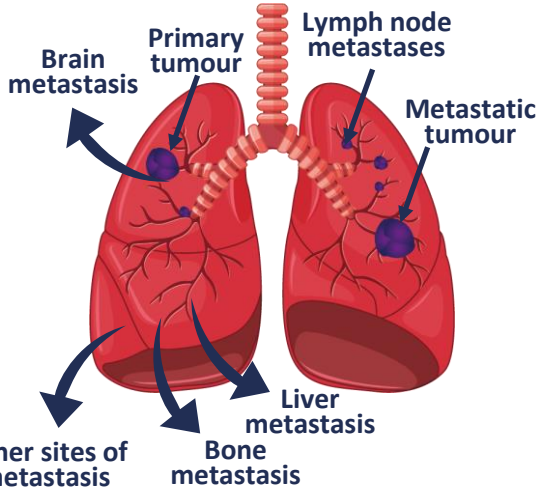
SCLC has been considered ‘a graveyard for drug development’ until quite recently[1]

- ✓ SCLC is a **neuroendocrine tumour** known for its aggressive behaviour and early spread to distant sites[2]
- ✓ SCLC represents **13–15%** of **new lung cancer** cases in the US[3]
- ✓ ES-SCLC is the presence of **metastatic disease outside the hemithorax** at first diagnosis[1]



- **80–85%** of patients with SCLC have ES-SCLC at diagnosis[3]
- Most patients with ES-SCLC will relapse, with a **5-year OS of ~2%**[2]
- Addition of **immunotherapy** to conventional chemotherapy has **OS benefit (HR=1.40)**[4]

2021 NCCN guidelines recommend either:
atezolizumab or durvalumab + platinum chemotherapy + etoposide in first-line treatment for ES-SCLC[5]

ES-SCLC, extensive-stage small cell lung cancer; HR, hazard ratio; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; SCLC, small cell lung cancer.

1.Taniguchi H, et al. *Front Oncol.* 2020;10:741; 2. Tsiouprou I, et al. *Can Resp J*. 2019. doi.org/10.1155/2019/6860432; 3. Saltos A, et al. *Front Oncol.* 2020;10:1074; 4. Zhou T, et al. *JAMA Netw Open*. 2020;3:e2015748; 5. NCCN Guidelines. Small-cell lung cancer. Version 2, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/sclc.pdf (accessed 24 February 2021).

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How has the addition of checkpoint inhibitors impacted the treatment landscape in extensive-stage small cell lung cancer?

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Evolving role of immunotherapy in ES-SCLC treatment

Agent	FDA approval date and indication	
Atezolizumab[1]	**2019:** in combination with etoposide + carboplatin, for the first-line treatment of adult patients with ES-SCLC	Preferred first-line NCCN recommended treatments[6]
Durvalumab[2]	**2020:** in combination with etoposide + either carboplatin or cisplatin, as first-line treatment of adult patients with ES-SCLC	
Nivolumab[3]	**2018 (subsequently withdrawn for use in SCLC, 29 December 2020):**[4] in patients with metastatic SCLC with progression after platinum-based chemotherapy and at least one other line of therapy	Later-line
Pembrolizumab[5]	**2019:** for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy	

Immune checkpoint inhibitors have shown modest yet promising effects when combined with a platinum drug + etoposide for patients with ES-SCLC and no greater toxic effects[7,8]

Update: On 1 March 2020, withdrawal of the metastatic small cell lung cancer indication for pembrolizumab from the US market was announced

ES-SCLC, extensive-stage small cell lung cancer; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network; SCLC, small cell lung cancer.

1. Atezolizumab Prescribing Information (PI). Last updated July 2018; 2. Durvalumab PI. Last updated March 2020; 3. Nivolumab PI. Last updated June 2020; 4. The ASCO Post. Nivolumab Indication in Small Cell Lung Cancer Withdrawn in US Market. Available at: ascopost.com/issues/january-25-2021/nivolumab-indication-in-small-cell-lung-cancer-withdrawn-in-us-market/ (accessed 24 February 2021); 5. Pembrolizumab PI. Last updated January 2020; All drug PIs available at www.accessdata.fda.gov/ (all accessed 24 February 2021); 6. NCCN Guidelines. Small-cell lung cancer. Version 2, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/sclc.pdf (accessed 24 February 2021); 7. Taniguchi H, et al. *Front Oncol.* 2020;10:741. 8. Zhou T, et al. *JAMA Netw Open.* 2020;3:e2015748.

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Why is the development of targeted agents a challenge in small cell lung cancer?

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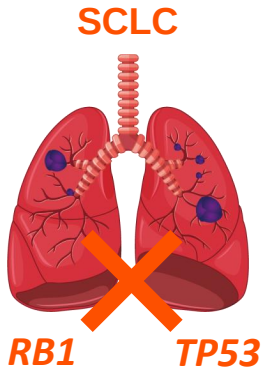
Identifying therapeutic targets has been challenging due to a lack of targetable oncogenic mutations[1]

At a molecular level, SCLC is characterized by functional inactivation of *RB1* and *TP53* tumour suppressor genes[1,2]

SCLC tumours carry a **high mutation load** associated with heavy tobacco exposure[1]



Attempts to target these driver mutations (*RB1* and *TP53*) have failed, because they are primarily **loss-of-function genes**

Recent gene expression profiling of SCLC tumours has enabled the identification of **four molecular subtypes**, defined by differential expression of transcription factors **ASCL1, NEUROD1, and POU2F3, and presence of an inflamed gene signature (including YAP1)**, each with distinct therapeutic vulnerabilities[2,3]

ASCL1, Achaete-Scute family BHLH transcription factor 1; NEUROD1, neurogenic differentiation 1; POU2F3, POU domain class 2 transcription factor 3; SCLC, small cell lung cancer; YAP1, yes-associated protein 1.

1. Taniguchi H, et al. *Front Oncol*. 2020;10:741; 2. Gay CM, et al. *Cancer Cell.* 2021;39:1–15; 3. Rudin C, et al. *Nat Rev Dis Primers.* 2021;7:3.

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What other therapeutic mechanisms can be used to manage extensive-stage small cell lung cancer?

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Novel therapeutic strategies in clinical use or showing promise in SCLC

Novel therapeutic strategy in clinical use[1,2]

Targeted transcription inhibitor[1]

- RNA polymerase II inhibitor

FDA approval (2020)[2]

- Lurbinectedin indicated for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy

Therapeutic strategies showing promise in SCLC[1,3]

Antibody-drug conjugates

- DLL3-targeted antibody-drug conjugate

DNA damage response and cell cycle

- PARP inhibitors targeting central DDR mediators combined with chemotherapy produce synergistic effects[4]

Growth and survival signalling pathways

- Targeting inhibition of mTOR and BCL-2

Epigenetic modifiers

- Epigenetic regulatory proteins

BCL-2, B-cell lymphoma 2; DLL3, delta-like protein 3; DDR, DNA damage response; DNA, deoxyribonucleic acid; ES-SCLC, extensive-stage small cell lung cancer; FDA, US Food and Drug Administration; mTOR; mammalian target of rapamycin; PARP, poly-ADP ribose polymerase; RNA, ribonucleic acid; SCLC, small cell lung cancer.

1. Taniguchi H, et al. *Front Oncol.* 2020;10:741; 2. Lurbinectedin Prescribing Information 2020. Available at: www.accessdata.fda.gov/ (accessed 24 February 2021); 3. Rudin CM, et al. *Nat Rev Dis Primers.* 2021;7:3. Available at: doi.org/10.1038/s41572-020-00235-0 (accessed 24 February 2021); 4. Barayan R, et al. *J Thorac Dis.* 2020;12:6240-6252.

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How will the updated NCCN guidelines impact patient management and outcomes in extensive-stage small cell lung cancer?

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Recommendations for systemic treatment of ES-SCLC

1 First line

Preferred: Either atezolizumab or durvalumab + platinum chemotherapy + etoposide

= Maintenance

Continue atezolizumab or durvalumab

2 Second line and later lines

If **relapse ≤6 months** after last dose of first-line treatment

Preferred: Topotecan, lurbinectedin or clinical trial

Other:

- Pembrolizumab
- Paclitaxel
- Docetaxel
- Irinotecan
- Temozolomide
- **Nivolumab (category 3)***
- CAV
- Vinorelbine
- Oral etoposide
- Gemcitabine
- Bendamustine

Note: Nivolumab or pembrolizumab not recommended after primary therapy that included atezolizumab or durvalumab

Update: Nivolumab now category 3 recommendation*
Revised regimen: Nivolumab no longer recommended in combination with ipilimumab

If **relapse >6 months** after completion of first-line treatment

Preferred: Original first-line regimen

Other: Lurbinectedin

Update: Original regimen not recommended for relapsed disease in patients on maintenance atezolizumab or durvalumab at time of relapse

Update: On 1 March 2020, withdrawal of the metastatic small cell lung cancer indication for pembrolizumab from the US market was announced

*Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.
CAV, cyclophosphamide/doxorubicin/vincristine; ES-SCLC, extensive-stage small cell lung cancer; NCCN, National Comprehensive Cancer Network.
NCCN Guidelines. Small-cell lung cancer. Version 2, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/sclc.pdf (accessed 24 February 2021).

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New treatment options in the second-line and beyond for small cell lung cancer

Dr Viola Zhu

University of California Irvine,
California, USA

This expert interview was recorded on 23 February 2021

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What is the evidence base for the accelerated FDA approval of second-line lurbinectedin in extensive-stage small cell lung cancer?

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Approval data for lurbinectedin

Study design[1,2]

- Single-arm, open-label, multi-centre **phase II** basket trial (NCT02454972)
- 3 weekly IV lurbinectedin 3.2 mg/m^2
- **N=105**
- Disease progression after only 1 prior CT-containing therapy
- ECOG PS ≤2
- Measurable disease
- No BM + adequate organ function

Efficacy data[1]

- Median follow-up: 17.1 months
- Primary endpoint **ORR=35.2%**
- Secondary endpoints
  - DOR=5.3 months
  - PFS=3.5 months
  - OS=9.3 months

Safety data[1]

- Most common grade 3–4 AEs were **haematological** in nature
- 10% of patients had serious TRAEs (neutropenia and febrile neutropenia were most common)
- No treatment-related deaths reported

FDA-approved in adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy[3]

NCCN guidelines v2.2021 – January 11 2021**: lurbinectedin as a second-line treatment option for patients with relapsed ES-SCLC[4]**

AE, adverse event; BM, brain metastases; CT, chemotherapy; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small cell lung cancer; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; IV, intravenous; OS, overall survival; PFS, progression-free survival; PS, performance status; SCLC, small cell lung cancer; TRAE, treatment-related adverse event.

1. Trigo J, et al. *Lancet Oncol.* 2020;21:645–54; 2. NCT02454972. Available at: clinicaltrials.gov/ct2/show/NCT02454972 (accessed 24 February 2021); 3. FDA Statement. 16 June 2020. Available at: www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-lurbinectedin-metastatic-small-cell-lung-cancer (accessed 24 February 2021); 4. NCCN Guidelines. Small-cell lung cancer. Version 2, 2021. www.nccn.org/professionals/physician_gls/pdf/sclc.pdf (accessed 24 February 2021).

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What evidence led to the approval of nivolumab in the third-line setting and its subsequent withdrawal from the US market?

Nivolumab approval and withdrawal data

Phase I/II: CheckMate-032[1]

Treatment: Nivolumab monotherapy in SCLC in third-line setting

Primary outcome: ORR=11.9%

Safety: Grade 3/4 TRAEs=11.9%

Phase III: CheckMate-451[2]

Treatment: Nivolumab vs. nivolumab + ipilimumab vs. placebo as maintenance therapy in ES-SCLC after no progression on first-line therapy

Primary outcome: OS not significantly prolonged with nivolumab vs. placebo, HR=0.84; or nivolumab + ipilimumab vs. placebo, HR=0.92

Safety: Consistent with previous reports in SCLC

Phase III: CheckMate-331[3]

Treatment: Nivolumab monotherapy vs. chemotherapy in relapsed SCLC after first-line therapy

Primary outcome: OS not significantly improved in nivolumab vs. chemotherapy, OS=7.5 vs. 8.4 months, HR=0.86

Safety: No new safety signals seen

August 2018: FDA accelerated approval for use in patients with metastatic SCLC with progression after platinum-based chemotherapy and ≥ 1 other line of therapy[4]

December 2020: Confirmatory studies failed to meet OS endpoint leading to withdrawal of indication in SCLC from the US market[5]

ES-SCLC, extensive-stage small cell lung cancer; FDA, US Food and Drug Administration; HR, hazard ratio; ORR, overall response rate; OS, overall survival; SCLC, small cell lung cancer; TRAE, treatment-related adverse event.

1. Ready N, et al. *J Thorac Oncol.* 2019;14:237–44; 2. Owonikoko TK, et al. *Ann Oncol.* 2019;30:ii77–ii80; 3. Spigel DR, et al. *Ann Oncol.* 2021;S0923–7534(21)00099-5; 4. Nivolumab prescribing information. Revised January 2021. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s090lbl.pdf (accessed 24 February 2021); 5. The ASCO Post. Nivolumab Indication in Small Cell Lung Cancer Withdrawn in US Market. Available at: ascopost.com/issues/january-25-2021/nivolumab-indication-in-small-cell-lung-cancer-withdrawn-in-us-market/ (accessed 24 February 2021).

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What are the key data that led to the accelerated approval of pembrolizumab in the third-line setting?

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Approval data for pembrolizumab

Study design[1,2]

- **Pooled analysis**:
  - Phase Ib KEYNOTE-028 (cohort 1)
  - Phase II KEYNOTE-158 (cohort G) multi-cohort studies (basket trial including patients with MSI-H cancers)
- **Treatment**: KEYNOTE-028: 2 weekly pembrolizumab 10 mg/kg, and KEYNOTE-158: 3 weekly pembrolizumab 200 mg, for up to 2 years
- **n=83** with ES-SCLC
- ≥2 prior treatment lines

Efficacy

Data leading to FDA approval in 2019[2]

- Primary endpoint: **ORR=19%**
- Secondary endpoint: DOR ≥18 months in **56%** of responders

Updated data (published 2020)[1]

- Primary endpoint: **ORR=19.3%**
- Secondary endpoint: DOR ≥18 months in **61%** of responders

New data in first-line setting[3]

Phase III KEYNOTE-604 study

- **First-line pembrolizumab + etoposide and platinum chemotherapy significantly improved PFS vs. placebo + etoposide and platinum therapy in ES-SCLC**
- HR=0.80
- 12-month PFS=13.6% vs. 3.1%, respectively

2019 FDA approval for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and ≥ 1 other prior line of therapy[2]

Update: On 1 March 2020, withdrawal of the metastatic small cell lung cancer indication for pembrolizumab from the US market was announced

DOR, duration of response; ES-SCLC, extensive-stage small cell lung cancer; FDA, US Food and Drug Administration; HR, hazard ratio; MSI-H, microsatellite instability-high; ORR, overall response rate; PFS, progression-free survival; SCLC, small cell lung cancer.

1. Chung HC, et al. *J Thorac Oncol.* 2020;15:618–27; 2. FDA. 18 June 2019. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-metastatic-small-cell-lung-cancer#:~:text=On June 17%2C 2019%2C (accessed 24 February 2021); 3. Rudin C, et al. *J Clin Oncol.* 2020;38:2369–79.

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What adverse events may be experienced with immune checkpoint inhibitors and lurbinectedin?

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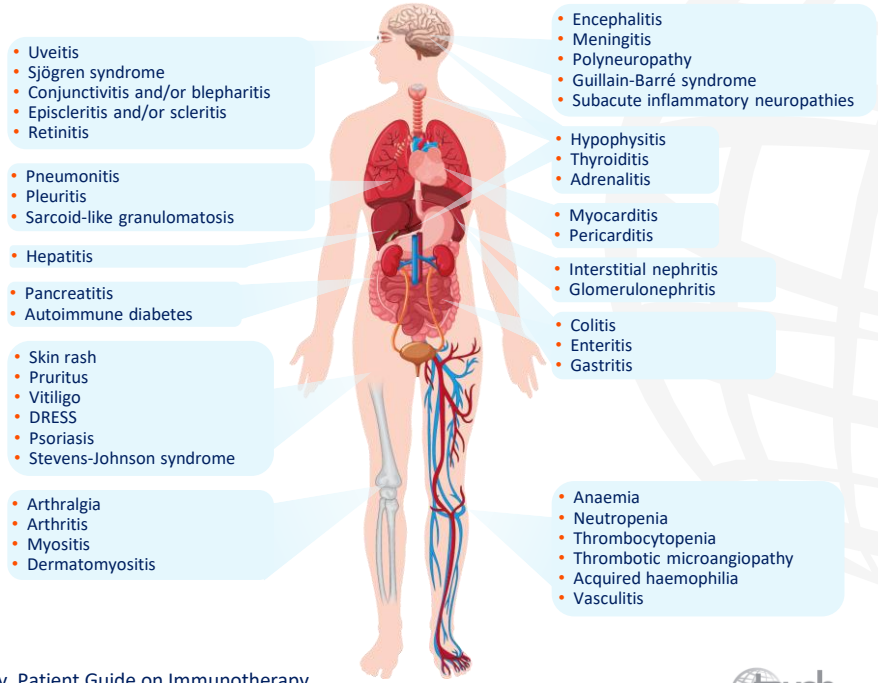
Immune-related adverse events can affect almost any organ with varying frequency and severity

- AEs with immune checkpoint inhibitors are often distinctly different from classical chemotherapy-related toxicities[1]
- May present as rash, diarrhoea, abdominal pain, cough, fatigue, vision changes[2]
- Toxicities with fatal outcomes tend to occur early and evolve rapidly[1]
- Estimated incidence of fatal AEs with immune checkpoint inhibitors: **0.3–1.3%**[1]



AE, adverse event; DRESS, drug reaction with eosinophilia and systemic symptoms.

1. Martins F, et al. *Nat Rev Clin Oncol.* 2019 ;16:563–80; 2. European Society of Medical Oncology. Patient Guide on Immunotherapy side-effects. Available at: www.esmo.org/for-patients/patient-guides/immunotherapy-side-effects (accessed 24 February 2021).

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Myelosuppression is a common adverse event with lurbinectedin

In the ongoing clinical trial of lurbinectedin in second-line SCLC patients:[1,2]

The most common grade 3–4 AEs were **haematological** in nature[1]

Preliminary myelosuppression[2]

- Neutropenia=45.8%
- Febrile neutropenia=3.8%
- Thrombocytopenia=6.6%

15.2% of patients received secondary prophylaxis or therapeutic G-CSF[2]

The most common non-haematological AEs were fatigue (grade 3=4.8%), nausea and vomiting (all grade 1/2)[2]

AE, adverse event; G-CSF, granulocyte colony-stimulating factor; SCLC small cell lung cancer.

1. Trigo J, et al. *Lancet Oncol.* 2020;21:645–54; 2. Paz-Ares J, et al. *J Clin Oncol.* 2019;37:Abstr 8506.

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How are adverse events that are associated with immune checkpoint inhibitors and lurbinectedin best managed in clinical practice?

Management of immune-related adverse reactions depends on the organ system affected

- **Adverse events may be graded using CTCAE definitions[1]***
- **There should be a high level of suspicion that new symptoms are treatment related[2]**

Grade 1	• **Continue therapy with close monitoring for grade 1 toxicities** (except for some neurologic, haematologic and cardiac toxicities)
Grade 2	• **Suspend therapy** for most grade 2 toxicities • **Corticosteroids** may be administered
Grade 3	• **Suspend therapy** • Initiate **high-dose corticosteroids**
Grade 4	• **Permanent discontinuation** of immune checkpoint therapy is generally recommended

Recommendations based on 2018 ASCO Practice Guideline[2]

*Further information on adverse event grading may be found in the Prescribing Information (package insert) for each therapy.
ASCO, American Society of Clinical Oncology; CTCAE, Common Terminology Criteria for Adverse Events.

1. National Cancer Institute. CTCAE. v5.0. 2017. Available at: ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf#search=%22grade%201%22 (accessed 24 February 2021);
2. Brahmer J, et al. *J Clin Oncol.* 2018;36:1714–68.

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Monitoring and management of adverse reactions with lurbinectedin

Myelosuppression

- **Monitor blood counts** prior to each administration
- **Initiate** treatment only **if baseline neutrophil count is ≥1,500 cells/mm^3** and **platelet count is ≥100,000/mm^3**
- Withhold, reduce the dose, or permanently discontinue based on severity

Hepatotoxicity

- **Monitor liver function tests** prior to initiating and periodically during treatment, and as clinically indicated
- Withhold, reduce the dose, or permanently discontinue based on severity

Lurbinectedin Prescribing Information 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/213702s000lbl.pdf (accessed 24 February 2021).

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Future prospects in the treatment of small cell lung cancer in the relapsed setting

Prof. Giuseppe Giaccone

Weill Cornell Medical Center,
New York, USA

This expert interview was recorded on 23 February 2021

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How can molecular classification of small cell lung cancer facilitate the development of new therapeutic approaches?

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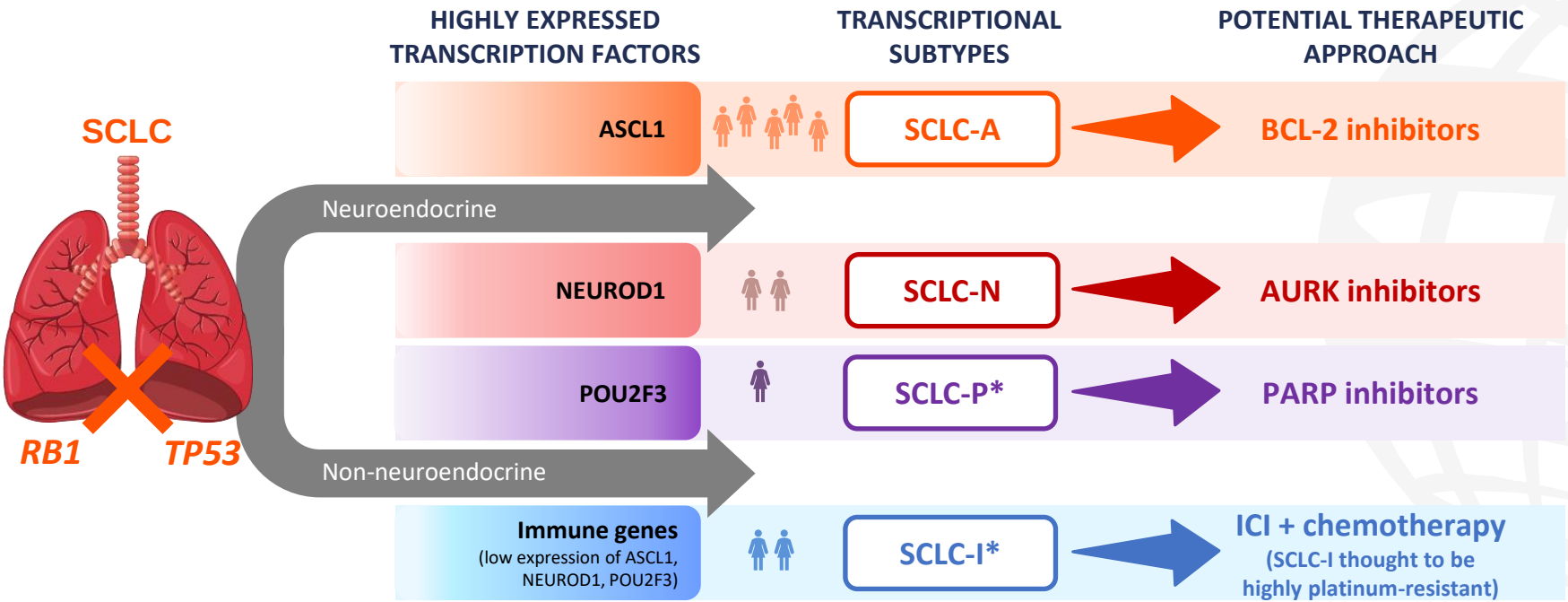
Emerging molecular classification for SCLC[1,2]



*Subtypes can be further divided based on EMT.

ASCL1, Achaete-Scute family BHLH transcription factor 1; AURK, aurora kinase; BCL-2, B-cell lymphoma 2; EMT, epithelial-mesenchymal transition; ICI, immune checkpoint inhibitor; NEUROD1, neurogenic differentiation 1; PARP, poly-ADP ribose polymerase; POU2F3, POU domain class 2 transcription factor 3; SCLC, small cell lung cancer.

1. Gay CM, et al. *Cancer Cell*. 2021;39:1–15; 2. Rudin C, et al. *Nat Rev Dis Primers*. 2021;7:3.

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What therapeutic targets and treatment strategies are being explored in small cell lung cancer?

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Therapeutic targets of interest in SCLC[1,2]

Anti-tumour immunity

- PD-1–PD-L1, CTLA4
- TIGIT, CD47
- Antibody-conjugate
- Bispecific T-cell engager (DLL3)

DNA damage and repair

- PARP
- CHK1

Cell-cycle

- WEE1
- AURK A/B

Growth and signalling pathways

- PI3K–mTOR
- BCL-2

Epigenetic regulators

- EZH2
- LSD1

Transcription

- CDK7
- RNA polymerase

AURK, aurora kinase; BCL-2, B-cell lymphoma 2; CD47, cluster of differentiation 47; CHK1, human checkpoint kinase 1; CTLA4, cytotoxic T lymphocyte-associated antigen 4; DLL3, delta-like ligand 3; DNA, deoxyribonucleic acid; EZH2, enhancer of zeste 2; LSD1, lysine-specific demethylase 1A; PARP, poly-ADP ribose polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PI3K–mTOR, phosphatidylinositol-3-kinase–mammalian target of rapamycin; PKA, protein kinase A; RNA, ribonucleic acid; SCLC, small cell lung cancer; TIGIT, T cell inhibitory receptor.

1. Rudin CM, et al. *Nat Rev Dis Primers.* 2021;7:3; 2. Taniguchi H, et al. *Front Oncol.* 2020;10:741.

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Clinical trials investigating targeted approaches

Examples of several ongoing trials

Anti-tumour immunity

- SKYSCRAPER-02 phase III, atezolizumab + carboplatin + etoposide ± tiragolumab in first-line ES-SCLC (NCT04256421)[1]

DNA damage and repair

- PARP inhibitors show promising activity in early-stage trials[2,3]

Cell-cycle

- WEE1 inhibitors have shown activity in SCLC cell lines[3]

Growth and signalling pathways

- Phase I/II study of navitoclax + vistusertib in relapsed SCLC and other solid tumours (NCT03366103)[4]

Epigenetic regulators

- Phase I/II trial of EZH2 inhibition with chemotherapy in recurrent SCLC (NCT03879798)[5]

Transcription

- ATLANTIS phase III trial of lurbinectedin + doxorubicin (NCT02566993)[6]

DNA, deoxyribonucleic acid; ES-SCLC, extensive-stage small cell lung cancer; EZH2, enhancer of zeste homolog 2; PARP, poly-ADP ribose polymerase; SCLC, small cell lung cancer.

1. ClinicalTrials.gov Identifier: NCT04256421. Available at: clinicaltrials.gov; 2. Rudin CM, *et al. Nat Rev Dis Primers* 2021;7:3; 3. Taniguchi H, et al. *Front Oncol. 2020;*10:741; 4. ClinicalTrials.gov Identifier NCT03366103. Available at: clinicaltrials.gov; 5. ClinicalTrials.gov Identifier NCT03879798. Available at: clinicaltrials.gov; 6. ClinicalTrials.gov Identifier NCT02566993. Available at: clinicaltrials.gov (all accessed 24 February 2021).

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What emerging targets show promise in relapsed small cell lung cancer?

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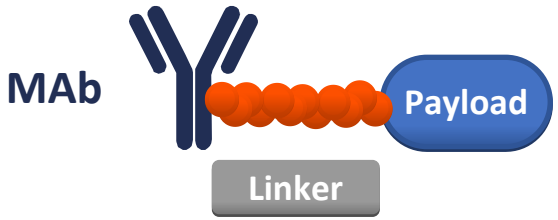
Targeting DLL3: Antibody-drug conjugates

DLL3 is a surface marker expressed on about 80% of SCLC cells[1]

Antibody-drug conjugates[1]
composed of a MAb targeting a specific tumour protein linked to a cytotoxic payload or drug



- Phase III trial (NCT03033511) of rovalpituzumab tesirine (RovaT) as a second-line maintenance therapy in ES-SCLC[2]
- Halted December 2020

DLL3, delta-like ligand 3; ES-SCLC, extensive-stage small cell lung cancer; MAb, monoclonal antibody; SCLC, small cell lung cancer.

1. Deneka A, et al. *Cancers.* 2019;11:1297;doi:10.3390/cancers11091297; 2. ClinicalTrials.gov Identifier: NCT03033511. Available at: clinicaltrials.gov (accessed 24 February 2021).

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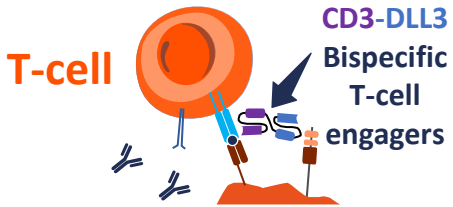
Targeting DLL3: Bispecific T-cell engagers

DLL3 is a surface marker expressed on about 80% of SCLC cells[1]

Bispecific T-cell engagers[1,2]
transiently connect DLL3+ SCLC tumour cells
to CD3+ T-cells and induce T-cell-mediated cell lysis
and concomitant T-cell proliferation



- Phase I trial (NCT03319940) of **AMG 757** monotherapy, in combination with anti-PD-1 and with CRS mitigation strategies in patients with SCLC[3]

CD3, cluster of differentiation 3; CRS, cytokine release syndrome; DLL3, delta-like ligand 3; ES-SCLC, extensive stage small cell lung cancer; PD-1, programmed cell death protein 1; SCLC, small cell lung cancer.

1. Deneka A, et al. *Cancers.* 2019;11:1297;doi:10.3390/cancers11091297; 2. Taniguchi H, et al. *Front Oncol.* 2020;10:741; 3. ClinicalTrials.gov Identifier:NCT03319940. Available at: clinicaltrials.gov (accessed 24 February 2021).

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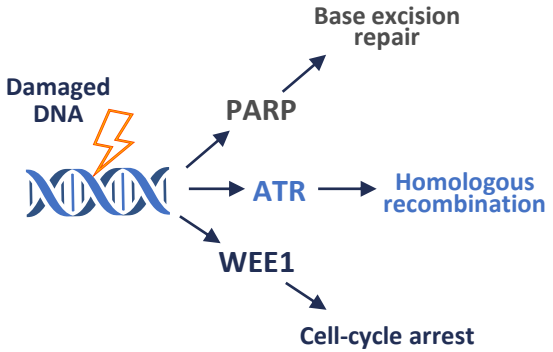
Targeting DDR in SCLC

DDR pathway proteins (PARP1/CHK1) are vulnerable targets in SCLC[1]

PARP inhibitors
trap PARP enzymes on the damaged DNA[1]



Efficacy of PARP in SCLC
- PARP inhibitors ± chemotherapy have shown modest efficacy in SCLC[2]
- Phase II trial of DDR/PARP + immune checkpoint inhibition did not meet pre-set bar for efficacy[3]

Future directions
- PARP inhibitors in combination with novel therapies (WEE1 inhibitor, ATR inhibitor) in SCLC[4]

Future clinical trial designs with selection for specific molecular subtypes
- Synergy observed between inhibition of PARP or CHK1 and PD-1 blockade in immunocompetent SCLC-A mouse models[5]

ATR, ataxia telangiectasia; CHK1, human checkpoint kinase 1; DDR, DNA damage repair; PARP, poly-ADP ribose polymerase; PD-1, programmed cell death protein 1; SCLC, small cell lung cancer.

1. Taniguchi H, et al. *Front Oncol.* 2020;10:741; 2. Barayan R, et al. *J Thorac Dis.* 2020;12:6240–52; 3. Thomas A, et al. *J Thorac Oncol.* 2019;14:1447–57; 4. Iams W, et al. *Nat Rev Clin Oncol.* 2020;17:300–12; 5. Rudin C, et al. *Nat Rev Cancer.* 2019 19:289–97.

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What immunotherapy combination approaches are being explored in relapsed small cell lung cancer?

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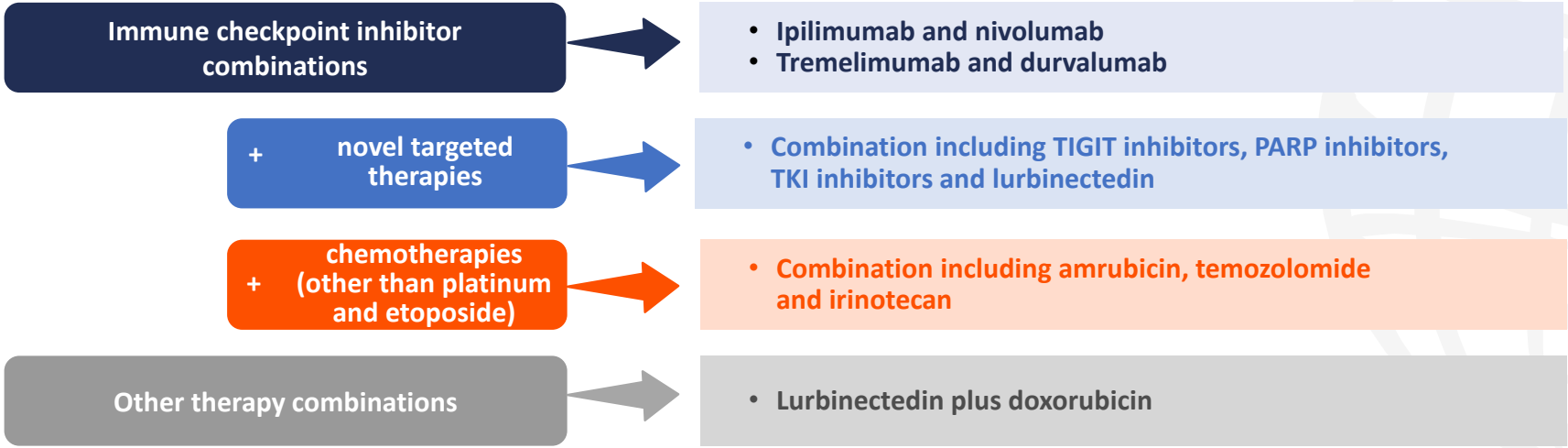
Research efforts seek to identify effective combination regimens in ES-SCLC

Many combined therapies are being explored in preclinical and clinical studies, including:[1–3]



ES-SCLC, extensive-stage small cell lung cancer; PARP, poly-ADP ribose polymerase; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TKI, tyrosine kinase inhibitor.

1. Taniguchi H, et al. *Front Oncol.* 2020;10:741; 2. Saltos A, et al. *Front Oncol*. 2020;10:1074; 3. Rudin CM, et al. *Nat Rev Dis Primers.* 2021;7:3.

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What biomarkers are being investigated to help guide treatment selection for patients with small cell lung cancer?

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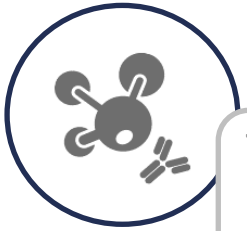
Potential biomarkers in SCLC



Biomarkers of immunotherapy

Tumour PD-L1[1]
- Predictive value currently unknown
- Lack of correlation with effect of immunotherapy

TMB[1]
- High TMB associated with improved outcomes with immunotherapy in CheckMate-032

CTCs, TILs and tumour-stromal PD-L1 expression[1,2]
- Potential biomarkers studied in small numbers of patients

Biomarkers of targeted therapy

SLFN11[1]
- Potential sensitivity to DNA damaging chemotherapy and PARP inhibition

MYC[1]
- High expression or amplification predicted sensitivity to CHK1 inhibition

DLL3[1]
- High expression associated with better response to Rova-T

CHK1, human checkpoint kinase 1; CTC, circulating tumour cell; DLL3, delta-like ligand 3; PARP, poly-ADP ribose polymerase; PD-L1, programmed cell death ligand-1; SCLC, small cell lung cancer; SLFN11, Schlafen family member 11; TIL, tumour infiltrating lymphocyte; TMB, tumour mutational burden.

1. Taniguchi H, et al. *Front Oncol.* 2020;10:741; 2. Iams W, et al. *Nat Rev Clin Oncol.* 2020;17:300–12.

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