Project ECHO®

Med Learning Group - Small-Cell Lung Cancer

Leveraging Novel Treatment Options for SMALL-CELL LUNG CANCER in the Second Line

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Jazz Pharmaceuticals, Inc.

Leveraging Novel Treatment Options for SMALL-CELL LUNG CANCER in the Second Line

AGENDA

I. Response to Primary Therapy and Tumorigenesis of Small Cell Lung Cancer: Subsequent Lines of Therapy and Pathophysiology Primer

- a. Time from initial therapy to relapse - determining subsequent therapy
- b. Dose attenuation in the second-line: an appropriate option?
- c. Tumorigenesis

II. Efficacy and Safety Review: Second-Line Regimens for Extensive Stage SCLC

- a. Clinical trials findings
  - i. Topotecan – efficacy, safety, and tolerability
  - ii. Lurbinectedin – efficacy, safety, and tolerability
  - iii. Patient population – comorbidities
- b. Clinical trials findings – developing compounds in the second-line
  - i. Anlotinib
  - ii. Veliparib

III. Applying National Cancer Center Network (NCCN) Guidelines to Practice

- a. Second-line regimens in patients with extensive disease
  - i. Preferred regimens with relapse ≤ 6 months
    - a. Topotecan
    - b. Lurbinectedin
  - ii. Clinical trials data – efficacy and safety in the second-line
- b. Current recommendations for relapse > 6 months
  - i. Original regimen
  - ii. Lurbinectedin – efficacy, safety, and tolerability
- c. Patient management in the population that has progressed

IV. Conclusions

V. Questions and Answers

Leveraging Novel Treatment Options for Small-Cell Lung Cancer in the Second Line

FACULTY

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Physician, Dana-Farber Cancer Institute
Instructor of Medicine
Harvard Medical School
Boston, MA

PROGRAM OVERVIEW
This live virtual TeleECHO program will explore the management of small cell lung cancer (SCLC) in the second-line setting. A brief didactic presentation will discuss treatment options after relapse of SCLC and clinical trial data of the efficacy and safety of second-line treatment regimens. Interactive case studies will illustrate the application of guideline recommendations for treatments approved for managing extensive-stage SCLC.

TARGET AUDIENCE
This activity is intended for community-based oncologists, pulmonologists, oncology nurses, nurse practitioners and other healthcare professionals who treat patients with small cell lung cancer.

LEARNING OBJECTIVES
Upon the completion of this program, attendees should be able to:

- Review the efficacy and safety data of systemic regimens in the second-line treatment of patients with extensive-stage SCLC
- Discuss the clinical trial data supporting the NCCN guidelines in the second-line treatment of patients with extensive-stage SCLC
- Describe how to apply the second-line efficacy and safety data to the management of small-cell lung cancer in the patient care setting

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NURSING CREDIT INFORMATION
Purpose: This program would be beneficial for nurses involved in the management of patients with SCLC in the second-line setting.
CNE Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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CME Content Review

The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

Douglas Cox, MSN, MHA, RN
Ultimate Medical Academy/CCM – Lead Nurse Planner

The reviewer of this activity has nothing to disclose

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2. Participate in the activity.
3. Complete pre-and-post surveys and evaluation.

You will receive your certificate as a downloadable file.

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Learning Objectives

- Discuss biological insights that drive the tumorigenesis of small-cell lung cancer (SCLC)
- Describe the clinical trial findings of combination regimens in the second-line treatment of patients with extensive-stage SCLC
- Apply National Comprehensive Cancer Network (NCCN) clinical practice guidelines in the second-line management of patients with extensive-stage SCLC

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Response to Primary Therapy and Tumorigenesis of Small-Cell lung Cancer

Subsequent Lines of Therapy and Pathophysiology Primer

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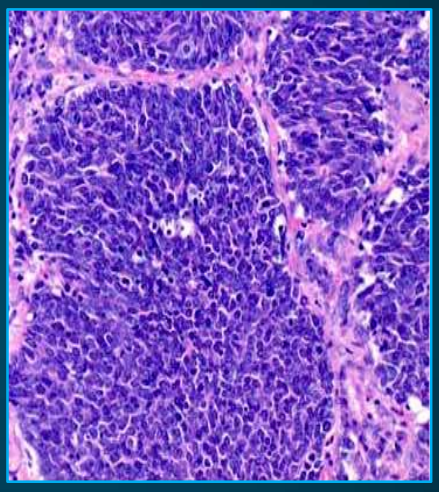
Small-Cell Lung Cancer Diagnosis

- Standard immunohistochemical markers for lung/neuroendocrine tumors
  - Majority express TTF-1
  - ~75% express neuroendocrine differentiation
    - Synaptophysin, chromogranin, and CD56
- SCLC has a high mitotic rate as a transcriptionally active cancer



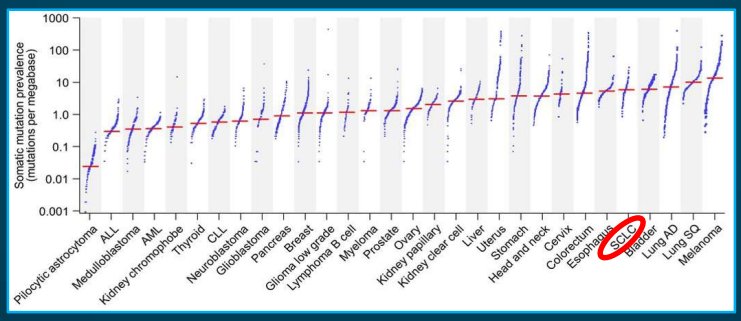
SCLC = small-cell lung cancer; TTF-1 = thyroid transcription factor 1.

George J, et al. *Nature*. 2015;524:47-53. Misch D, et al. *Diagn Pathol*. 2015;10:21. Karachaliou N, et al. *Transl Lung Cancer Res*. 2016;5:2-15.

5

Common Genomic Alterations in Small-Cell Lung Cancer

- Vast majority of individuals with SCLC have a significant smoking history and are without any targeted-therapy options despite having a significant mutational burden
- SCLC is extremely rare in individuals without a smoking history. In a never smoker, molecular profiling may help clarify the diagnosis and demonstrate a target



Pesch B, Kendzia B, Gustavsson P, Jockel KH, Johnen G,et al. Cigarette smoking and lung cancer--relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int J Cancer*. 2012 Sep 1. 131(5):1210-9.

Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561. Büttner R, et al. *ESMO Open*. 2019;4:e000442. Pesch B, et al. *Int J Cancer*. 2012;131:1210-1219.

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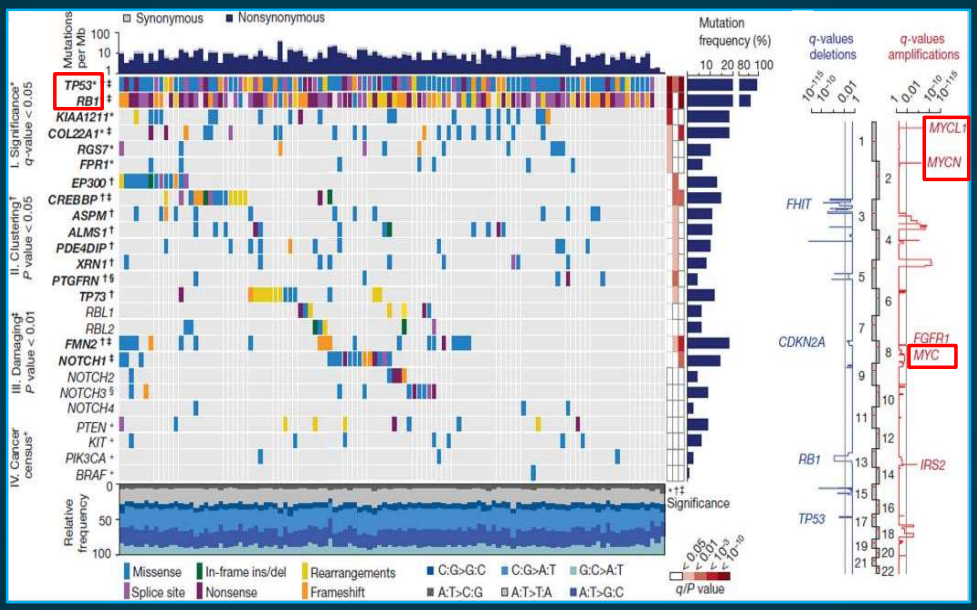
Genomic Alterations in SCLC



George J, et al. *Nature*. 2015;524:47-53.

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Common Genomic Alterations in Small-Cell Lung Cancer

P53—"Guardian of the Genome"

- Activates DNA-repair proteins
- Arrests the cell cycle at G1/S to allow for DNA repair
- Can initiate apoptosis in cell with significant DNA damage
- Mutation impacts cellular response to DNA damage
- Mutations present in the majority of SCLCs

P53 = tumor protein P53 (tumor suppressor); DNA = deoxyribonucleic acid; G1 = gap 1 phase; S = synthesis phase.

Sen T, et al. *Transl Lung Cancer Res*. 2018;7:50-68. Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561.

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Common Genomic Alterations in Small-Cell Lung Cancer (continued)

- RB1—Inhibits cell-cycle progression by binding transcription factors in cells with damaged DNA, arresting replication in S-phase
  - Loss of function is almost always noted in SCLC
- MYC—MYC proteins activate expression of genes that enable proliferation
  - Amplified in about 20% of SCLCs

RB = retinoblastoma; MYC = MYC proto-oncogene.

Sen T, et al. *Transl Lung Cancer Res*. 2018;7:50-68. Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561.

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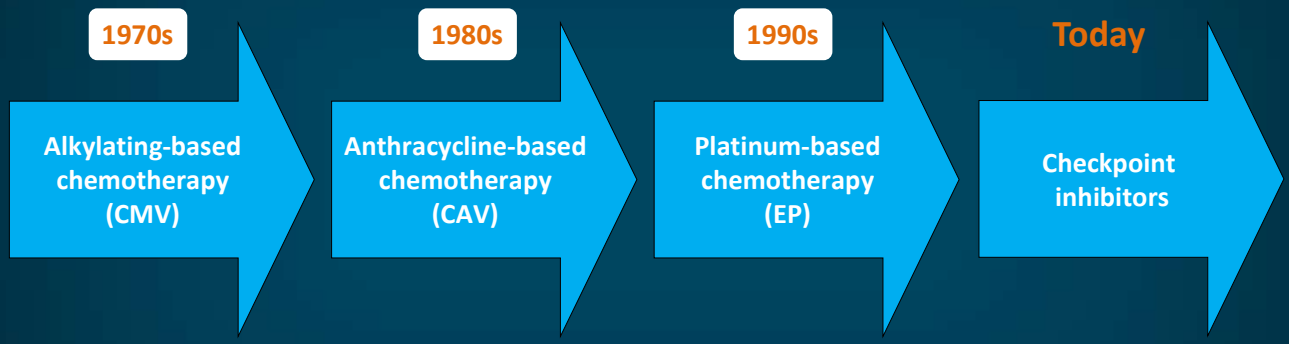
Evolution of Systemic Therapy in Small-Cell Lung Cancer



CMV = cytomegalovirus; CAV = cyclophosphamide, doxorubicin, and vincristine; EP = etoposide and cisplatin.

Modified from Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561. Saleh K, et al. *Immunotherapy*. 2019;11:457-460.

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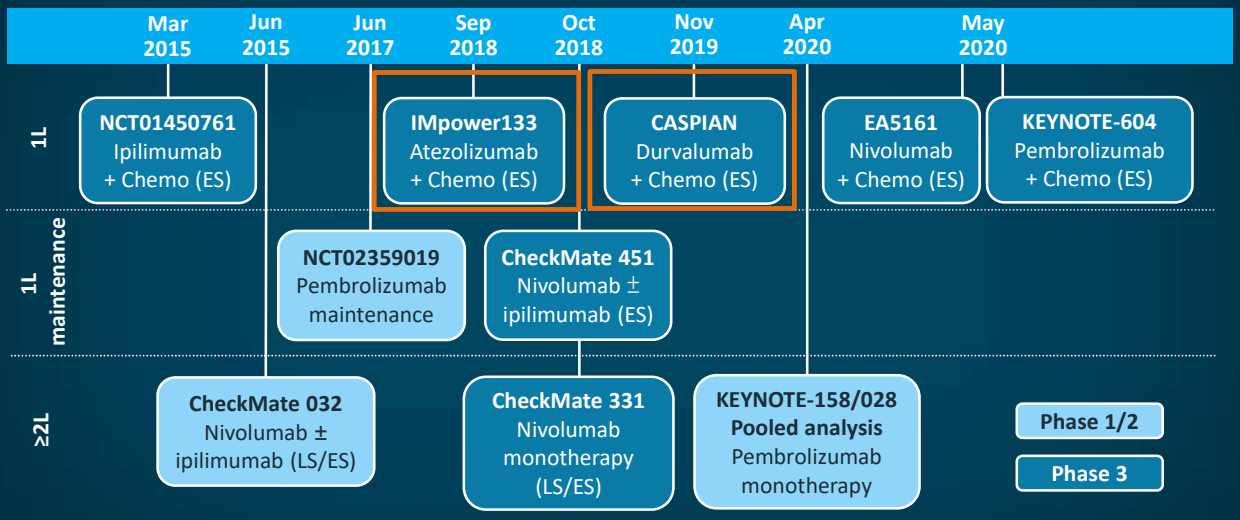
Overview of Key Studies of Immune Checkpoint Inhibitors in SCLC



1L = first line; 2L = second line; Chemo = chemotherapy; ES = extensive stage; LS = limited stage.

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Efficacy and Safety Review

Second-Line Regimens for Extensive-Stage SCLC

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What Are the Key Questions in 2L SCLC?

SCLC Subsequent Systemic Therapy	
Relapse ≤6 Months, PS 0–2	
Preferred regimens • Topotecan PO or IV • Lurbinectedin • Clinical trial	
Other recommended regimens • Paclitaxel • Docetaxel • Irinotecan • Temozolomide • Cyclophosphamide/doxorubicin/vincristine (CAV)	• Oral etoposide • Vinorelbine • Gemcitabine • Bendamustine (category 2B) • Nivolumab • Pembrolizumab
Relapse >6 Months	
Preferred regimens • Original regimen, with omission of checkpoint inhibitor if relapse on IO maintenance	**Other recommended regimens** • As above

PO = by mouth (oral); IV = intravenous.

National Comprehensive Cancer Network (NCCN) version 1.2022 (https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf). Accessed 9/24/2021.

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Current NCCN Guidelines

SCLC Subsequent Systemic Therapy	
Relapse ≤6 Months, PS 0–2	
Preferred regimens • Topotecan PO or IV • Lurbinectedin • Clinical trial	
Other recommended regimens • Paclitaxel • Docetaxel • Irinotecan • Temozolomide • Cyclophosphamide/doxorubicin/vincristine (CAV)	• Oral etoposide • Vinorelbine • Gemcitabine • Bendamustine (category 2B) • Nivolumab • Pembrolizumab
Relapse >6 Months	
Preferred regimens • Original regimen, with omission of checkpoint inhibitor if relapse on IO maintenance	**Other recommended regimens** • As above

NCCN version 1.2022 (https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf). Accessed 6/20/2021.

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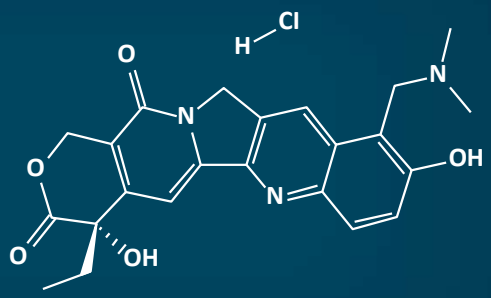
Topotecan

- Topoisomerase I inhibitor
- Prevents re-ligation of the cleaved DNA strand, leading to DNA damage and cell death



Topotecan hydrochloride

O'Brien MER, et al. *J Clin Oncol*. 2006;24:5441-5447. Topotecan PI, 2019 (www.accessdata.fda.gov/drugsatfda_docs/label/2019/022453s011lbl.pdf). Accessed 6/20/2021.

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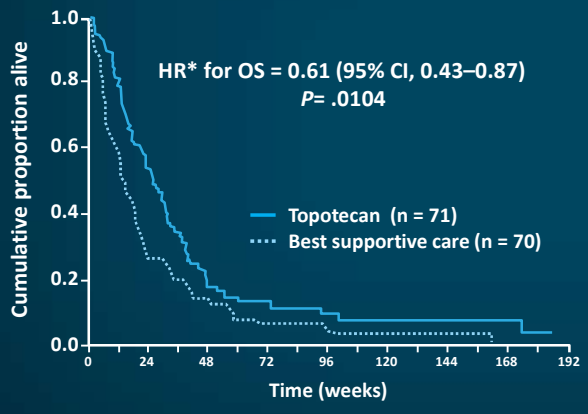
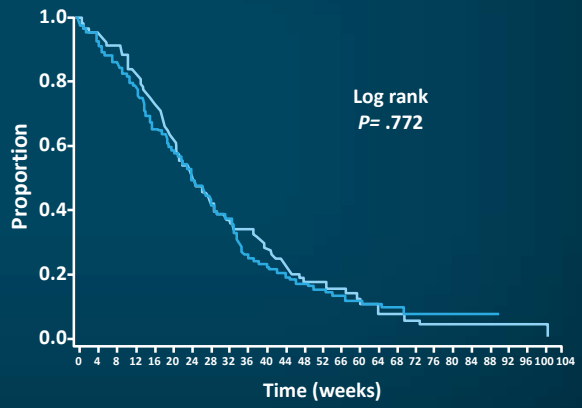
Topotecan Efficacy

- Topotecan 2.3 mg/m^2/day PO for days 1–5 every 21 days[1]
  - Eligibility include chemotherapy-free interval of at least 45 days after 1L therapy



- Topotecan 1.5 mg/m^2/day IV for days 1–5 every 21 days vs CAV[2]
  - Eligibility included chemotherapy-free interval of at least 60 days after 1L therapy



*adjusted for stratification factors.

HR = hazard ratio; OS = overall survival; CI = confidence interval.

O'Brien MER, et al. *J Clin Oncol*. 2006;24:5441-5447. von Pawel J, et al. *J Clin Oncol*. 1999;17:658-667.

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Topotecan Toxicities

Hematologic and Nonhematologic Toxicities by Treatment Group

Topotecan 2.3 mg/m²/day PO for days 1–5 every 21 days

Hematologic AEs	Oral Topotecan n (%)		IV Topotecan n (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Leukopenia	64 (42.7)	34 (22.7)	74 (49.3)	39 (26.0)
Neutropenia	39 (26.2)	70 (47.0)	35 (23.6)	95 (64.2)
Thrombo-cytopenia	30 (20.0)	43 (28.7)	38 (25.3)	27 (18.0)
Anemia	28 (17.3)	8 (5.3)	42 (28.0)	4 (2.7)

Non-hematologic AEs	Oral Topotecan No. of Patients (%)		IV Topotecan No. of Patients (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Diarrhea	11 (7.2)	1 (0.7)	3 (2.0)	1 (0.7)
Fatigue	10 (6.5)	0 (0.0)	10 (6.6)	2 (1.3)
Dyspnea	9 (5.9)	3 (2.0)	10 (6.6)	5 (3.3)
Anorexia	8 (5.2)	0 (0.0)	3 (2.0)	1 (0.7)
Nausea	6 (3.0)	0 (0.0)	3 (2.0)	1 (0.7)
Asthenia	4 (2.6)	3 (2.0)	7 (4.6)	3 (2.0)
Fever	3 (2.0)	3 (2.0)	4 (2.6)	6 (4.0)

AE = adverse event.

O'Brien MER, et al. *J Clin Oncol.* 2006;24:5441-5441.

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Topotecan Toxicities

Hematologic and Nonhematologic Toxicities

Topotecan 1.5 mg/m²/d IV for days 1–5 every 21 days

Hematologic Toxicities in 107 Patients				
	Patients (N = 107) AE/No. of Patients (%)		Courses (N = 446) AE/No. of Patients (%)	
AE	Grade 3	Grade 4	Grade 3	Grade 4
Leukopenia	57/104 (54.8%)	33/104 (31.7%)	196/441 (44.4%)	68/441 (15.4%)
Neutropenia	19/104 (18.3%)	73/104 (70.2%)	137/439 (31.2%)	166/439 (37.8%)
Thrombo-cytopenia	30/104 (28.8%)	30/104 (28.8%)	83/441 (18.8%)	43/441 (9.8%)
Anemia	41/104 (39.4%)	3/104 (2.9%)	73/440 (16.6%)	5/440 (1.1%)

Nonhematologic Toxicities in >10% of 107 Patients			
	Toxicity criteria grade		Total
AE, n (%)	1/2	3/4	
Nausea	38 (35.5%)	4 (3.7%)	42 (39.3%)
Alopecia	38 (35.5%)	0 (0.0%)	38 (35.5%)
Fatigue	23 (21.5%)	5 (4.7%)	28 (26.2%)
Vomiting	24 (22.4%)	2 (1.9%)	26 (24.3%)
Anorexia	19 (17.7%)	1 (0.9%)	20 (18.7%)
Stomatitis	13 (12.2%)	2 (1.8%)	15 (14.0%)
Diarrhea	12 (11.2%)	1 (0.9%)	13 (12.1%)
Fever	11 (10.3%)	2 (1.9%)	13 (12.1%)

von Pawel J, et al. *J Clin Oncol*. 1999;17:658-667.

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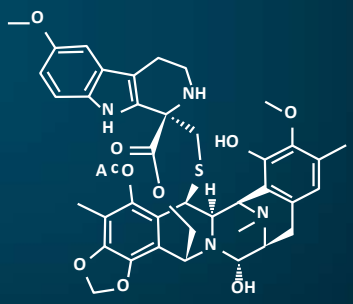
Lurbinectedin

- Synthetically produced agent, originally derived from Ecteinascidia turbinate (sea squirt)
- Binds to DNA gene promoters, preventing binding of transcription factors
  - Inhibits oncogenic transcription leading to apoptosis
  - Induces apoptosis of monocytes and tumor associated macrophages in the tumor microenvironment, inhibits cell migration, and limits production of inflammatory mediators (CCL2 and CXCL8) and angiogenic factors (VEGF)
- FDA-approved in adults with metastatic SCLC whose disease progressed on or after platinum-based chemotherapy



Trigo J, et al. *Lancet Oncol.* 2020;21:645-654. Santamaria Nuñez G, et al. *Mol Cancer Ther.* 2016;15:2399-2412. Cruz C, et al. *J Clin Oncol.* 2018;36:3134-3143. Lurbinectedin (Zepzelca™) PI, 2020 (https://pp.jazzpharma.com/pi/zepzelca.en.USPI.pdf). Lurbinectedin. Drug Approvals International (http://drugapprovalsint.com/lurbinectedin/). Accessed 6/20/2021.

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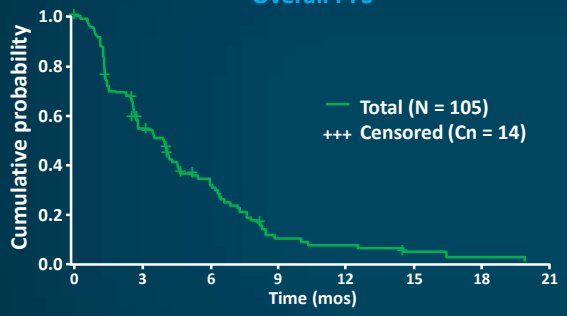
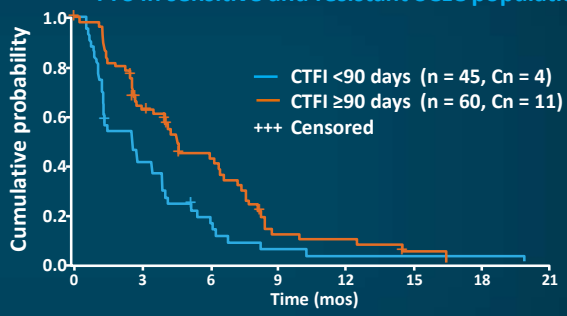
Lurbinectedin Efficacy

- Single-arm phase 2 trial in second-line SCLC
- ORR of 35.2% with stable disease in 33.3% of patients

Overall PFS



PFS in sensitive and resistant SCLC populations



	Overall (n = 105)	Resistant, CTFI <90 days (n = 45)	Sensitive, CTFI ≥90 days (n = 60)
PFS mos, median, (95% CI)	3.5 (2.6–4.3)	2.6 (1.3–3.9)	4.6 (2.8–6.5)
PFS at 6 mos, %, (95% CI)	32.9 (23.3–42.5)	18.8 (6.8–30.9)	43.5 (30.1–56.9)

ORR = overall/objective response rate; PFS = progression-free survival; Cn = censored number; mo(s) = month(s); CTFI = chemotherapy-free interval.

Trigo J, et al. *Lancet Oncol.* 2020;21:645-654 and supplement. Paz-Ares LG, et al. *J Clin Oncol.* 2019;37(suppl 15): abstract 8506.

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Lurbinectedin Has Efficacy in SCLC

Outcome	All Patients (N = 105)
ORR, %	35.2
DCR, %	68.6
Median DoR, mos	5.3
Median PFS, mos 6-mo PFS, %	3.5 32.9
Median OS, mos 12-mo OS, %	9.3 34.2

DCR = disease control rate; DoR = duration of response; OS = overall survival.

Trigo J, et al. *Lancet Oncol.* 2020;21:645-654.

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Lurbinectedin Has Efficacy in Sensitive and Resistant SCLC

Outcome	All Patients (N = 105)	Platinum Sensitive* (n = 60)	Platinum Resistant† (n = 45)
ORR, %	35.2	45.0	22.2
DCR, %	68.6	81.7	51.1
mDoR, mos	5.3	6.2	4.7
mPFS, mos 6-mo PFS, %	3.5 32.9	4.6 43.5	2.6 18.8
mOS, mos 12-mo OS, %	9.3 34.2	11.9 48.3	5.0 15.9

*platinum sensitive = CTFI ≥90 days; †platinum resistant = CTFI <90 days.
mDoR = median DoR; mPFS = median PFS; mOS = median OS.

Trigo J, et al. *Lancet Oncol.* 2020;21:645-654.

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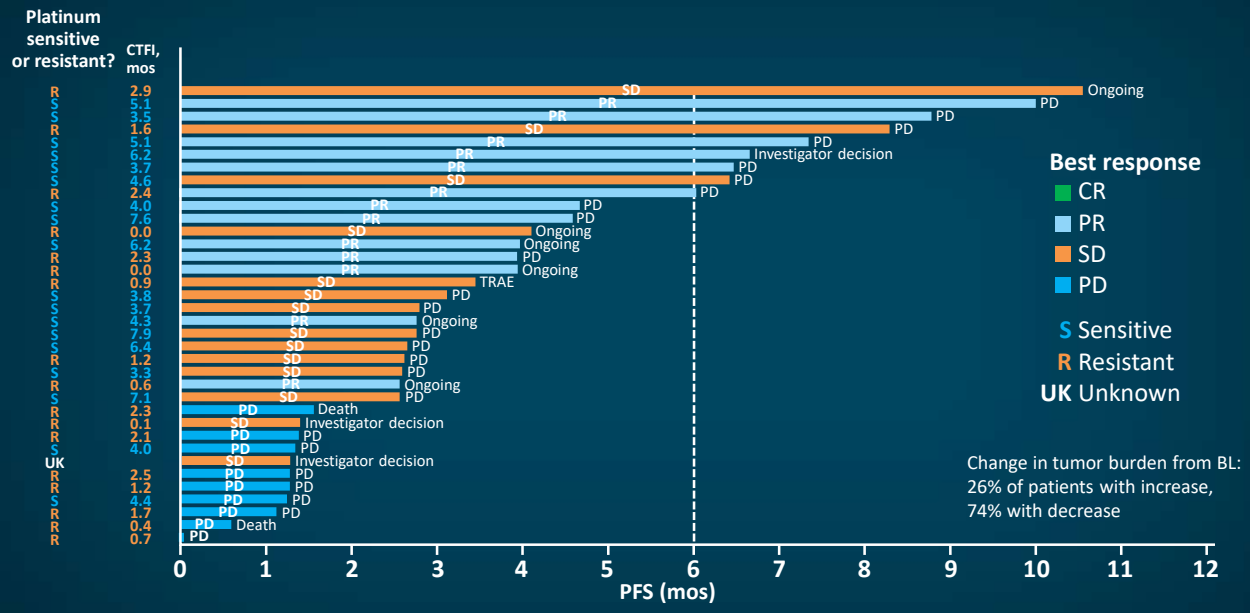
Lurbinectedin Has Efficacy in Sensitive and Resistant SCLC: Response



CR = complete response; PR = partial response; SC = stable disease; PD = progressive disease.

Trigo J, et al. *Lancet Oncol.* 2020;21:645-654.

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Efficacy Is Comparable, if Not Superior To Historical Trials

Outcome	Lurbinectedin	Topotecan	Amrubicin
ORR	**35.2%**	**16.9%**	**31.1%**
ORR Sens	45.0%	23.1%	40.9%
ORR Res	22.2%	9.4%	20.1%
Median PFS, mos	**3.5**	**3.5**	**4.1**
Median PFS, Sens, mos	4.6	4.3	5.5
Median PFS, Res, mos	2.6	2.6	2.8
Median OS, mos	**9.3**	**7.8**	**7.5**
Median OS, Sens, mos	11.9	9.9	9.2
Median OS, Res, mos	5.0	6.2	5.7

Sens = sensitive; Res = resistant.

Trigo J, et al. *Lancet Oncol.* 2020;21:645-654. von Pawel J, et al. *J Clin Oncol*. 2014;32:4012-4019.

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Lurbinectedin Is FDA Approved For SCLC after progression on or after a platinum doublet

- Confirmed ORR of 35.2% with 2L lurbinectedin surpassed ≥30% statistical cutoff for a positive trial
  - Follow-up: 17.1 months (IQR: 6.5–25.3),
- Outcomes with 2L lurbinectedin numerically higher than historical outcomes with 2L topotecan
- Results from phase 3 ATLANTIS trial of second-line lurbinectedin plus doxorubicin versus investigator's choice of topotecan or CAV are awaited, however per press communications the primary endpoint of improved OS was not met

IQR = interquartile range.

Trigo J, et al. *Lancet Oncol*. 2020;21:645-654. Farago AF, et al. *Future Oncol*. 2019;15:231-239.

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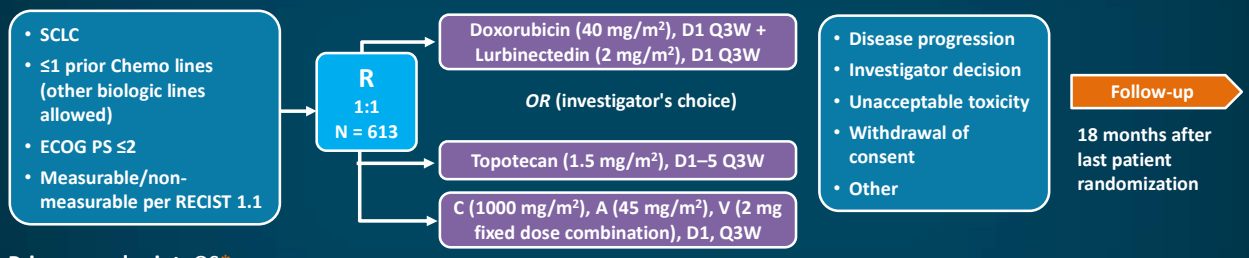
Lurbinectedin + Doxorubicin: ATLANTIS

- Lurbinectedin is an RNA polymerase II inhibitor that targets active transcription
- Has direct cytotoxic effect inducing apoptosis and may impact TME targeting TAM
- Phase 2 study of single-agent lurbinectedin (N = 105): ORR = 35%. mPFS = 3.5 mos, and mOS = 9.3 mos
- Lurbinectedin + doxorubicin has ORR of 92% with mPFS of 5.8 mos in platinum-sensitive SCLC



Primary endpoint: OS*
Key secondary endpoints: PFS, DoR, best tumor response
Stratified by ECOG PS (0 vs 2 1), CTFI (≥180, 180–90, <90), CNS involvement (Yes/No), prior PD-L1/PD-1 (Yes/No), investigator's preference for control arm

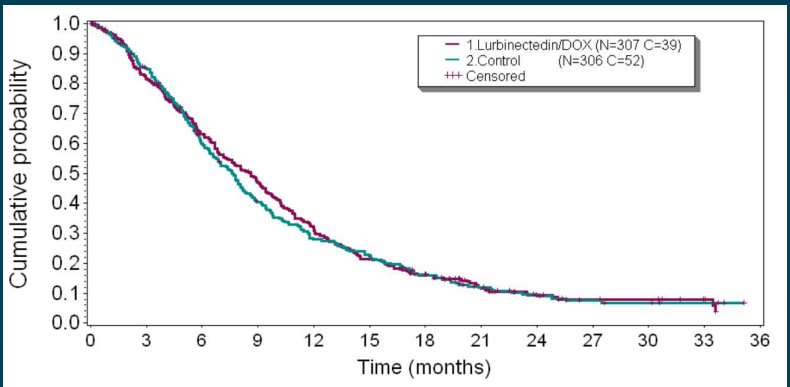
*Study failed to meet its primary endpoint.

RNA = ribonucleic acid; TME = tumor microenvironment; TAM = tumor-associated macrophages; RECIST = Response Evaluation Criteria in Solid Tumors; R = randomization; D = day; Q3W = every 3 weeks; C = cyclophosphamide; A = doxorubicin; V = vincristine; CNS = central nervous system; PD-1 = programmed (cell) death 1; PD-L1 = PD-1 ligand.

Trigo J et al, *Lancet Oncol* 2020;21:645-645. Farago AF, et al *Future Oncol*. 2019;15:231-239. NCT02566993 (https://clinicaltrials.gov/ct2/show/NCT02566993). Rosa K. OncLive. 2020 (www.onclive.com/view/lurbinectedin-doxorubicin-combo-misses-os-end-point-in-phase-3-sclc-trial). Accessed 6/20/2021.

26

Overall Survival Equivalent Lurbinectedin/Doxorubicine vs Control



Overall Survival: 8.6 vs 7.6 months
(HR 0.967, 95% CI 0.815-1.148)

Ares P, et al. IASLC 2021 World Conference on Lung Cancer: Abstract PL02.03. Presented September 10, 2021.

27

Managing Adverse Events with Lurbinectedin

- Consider administering premedications for antiemetic prophylaxis
  - Dexamethasone 8 mg IV or equivalent
  - Ondansetron 8 mg IV or equivalent
- Administer lurbinectedin only to patients with baseline neutrophil count >1500 cells/mm^3 and platelet counts >100,000/mm^3
  - Monitor blood counts prior to each administration
  - G-CSF recommended if neutrophil count <500 cells/mm^3 or less than lower limit of normal
- Withhold, reduce dose, or permanently discontinue based on severity of hepatotoxicity or myelosuppression
- Lurbinectedin can cause fetal harm; advise use of contraception

G-CSF = granulocyte colony-stimulating factor.

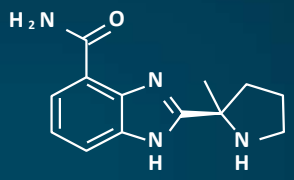
Lurbinectedin (Zepzelca™) PI 2020 (https://pp.jazzpharma.com/pi/zepzelca.en.USPI.pdf). Accessed 6/20/2021.

28

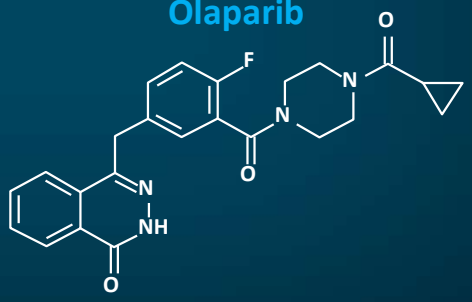
PARP Inhibitors

- Poly-ADP-ribose polymerase (PARP) inhibitors (eg, olaparib and veliparib) prevent repair of single-strand DNA breaks, leading to multiple double-strand DNA breaks
- Trapping of PARP proteins on DNA interferes with replication, causing cell death

Veliparib



Olaparib



ADP = adenosine diphosphate.

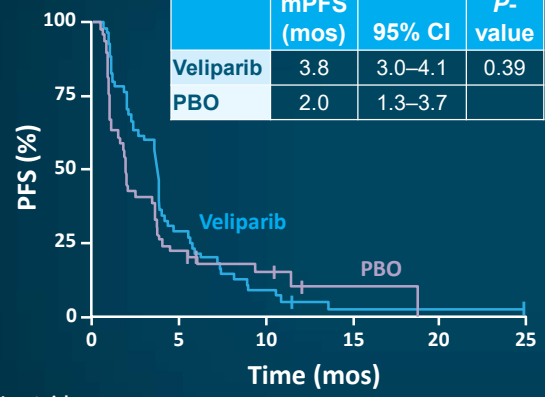
Sen T, et al. *Transl Lung Cancer Res*. 2018;7:50-68. Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561.

29

Veliparib + Temozolomide for Recurrent ES-SCLC

No significant difference between veliparib + temozolomide and PBO + temozolomide

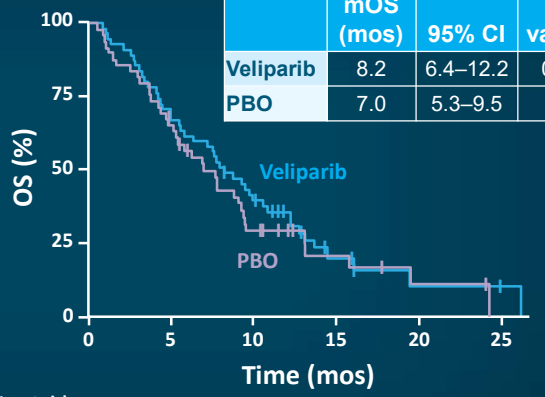
	mPFS (mos)	95% CI	*P*-value
Veliparib	3.8	3.0–4.1	0.39
PBO	2.0	1.3–3.7	



No. at risk:

Veliparib	55	16	5	1	1	0
Placebo	49	11	6	1	0	0

	mOS (mos)	95% CI	*P*-value
Veliparib	8.2	6.4–12.2	0.5
PBO	7.0	5.3–9.5	



No. at risk:

Veliparib	55	37	21	6	2	1
Placebo	49	31	13	5	2	0

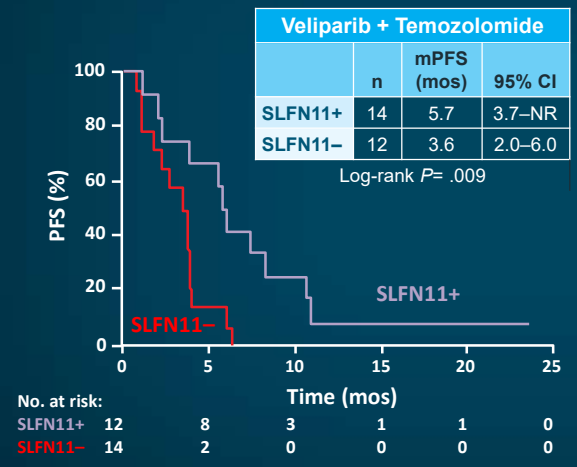
PBO = placebo.

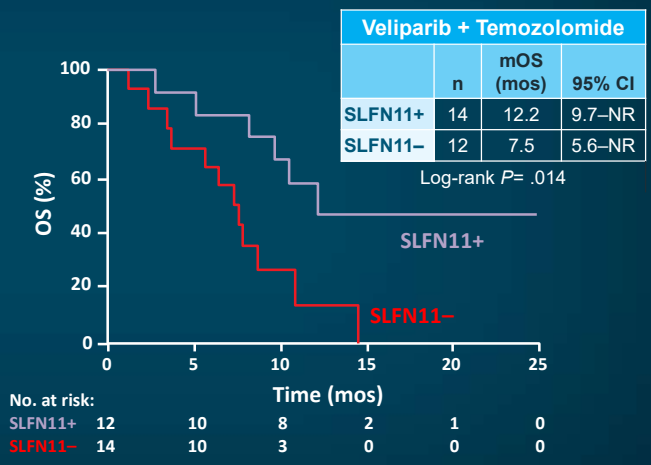
Pietanza MC, et al. *J Clin Oncol*. 2018;36:2386-2394.

30

Veliparib + Temozolomide: Biomarker Analysis

- SLFN11-positive tumors had significantly prolonged PFS and OS
- SLFN11 has potential to serve as a biomarker, but further study is needed





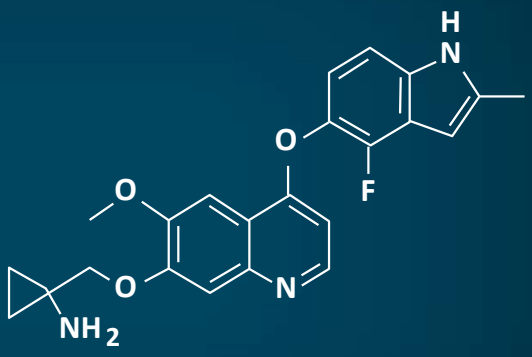
SLN11 = Schlafen-11; NR = not reached.

Pietanza MC, et al. *J Clin Oncol*. 2018;36:2386-2394.

31

Anlotinib

- Multi-targeted tyrosine kinase inhibitor
- Selective inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, cKIT
  - Receptors mediate proangiogenic pathways and tumor proliferation
- Randomized trial: anlotinib vs placebo in 3rd-line small-cell lung cancer



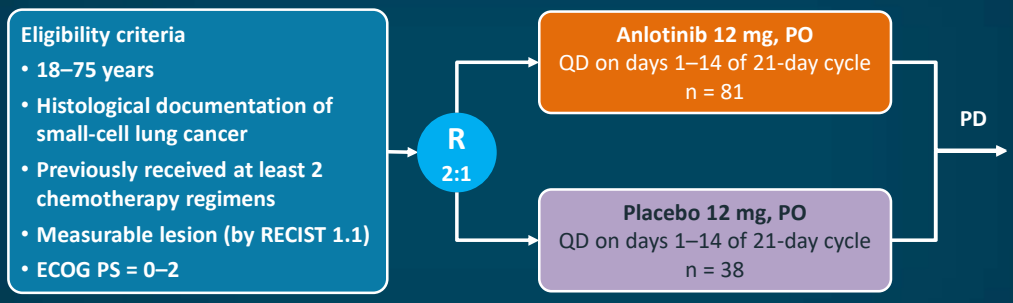
VEGFR = vascular endothelial growth factor receptor; PDGFR= platelet-derived growth factor receptor, KIT = stem cell factor receptor.

Si X, et al. *Thorac Cancer*. 2019;10:551-556. Zhao Y, Adjei AA. *Oncologist*. 2015;20:660-673.

32

Antiangiogenic Agents: Anlotinib in Relapsed SCLC (ALTER1202)

- VEGF plays a central role in angiogenesis, and high VEGF levels are poor prognosis in SCLC
- Anlotinib is multi-kinase inhibitor with activity at VEGFR 2-3, FGFR1-4, PDGF a/B and c-kit



Primary endpoint: PFS

Secondary endpoint: OS, ORR, DCR, quality of life, safety/tolerability

Stratification: stage (limited vs extensive, relapse (sensitive vs refractory)

QD = once daily, every day.

Cheng Y, et al. *Ann Oncol*. 2019;30(suppl 5):v711 (abstract 17380). Si X, et al. *Thorac Cancer*. 2019;10:551-556.

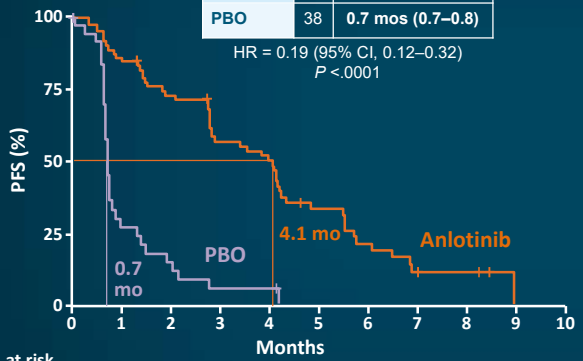
33

Antiangiogenic Agents: Anlotinib in Relapsed SCLC (ALTER1202)

Progression-free survival

	n	mPFS (95% CI)
Anlotinib	81	4.1 mos (2.8–4.2)
PBO	38	0.7 mos (0.7–0.8)

HR = 0.19 (95% CI, 0.12–0.32)
P <.0001

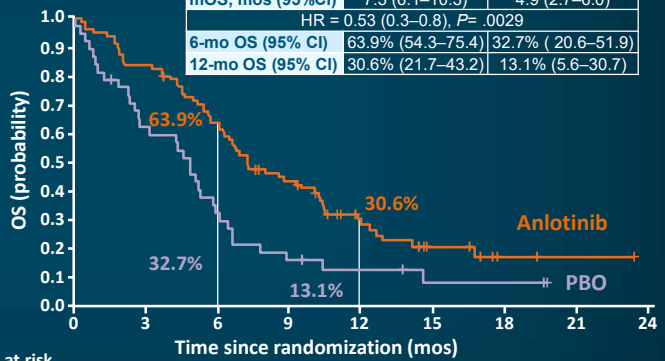


No. at risk

Anlotinib	81	65	49	34	29	16	9	3	3	0
Placebo	38	9	5	2	2	0				

Overall survival

	Anlotinib (n = 81)	PBO (n = 38)
Events , n (%)	60 (74.1)	33 (86.8)
mOS, mos (95%CI)	7.3 (6.1–10.3)	4.9 (2.7–6.0)
HR = 0.53 (0.3–0.8), *P*= .0029		
6-mo OS (95% CI)	63.9% (54.3–75.4)	32.7% (20.6–51.9)
12-mo OS (95% CI)	30.6% (21.7–43.2)	13.1% (5.6–30.7)



No. at risk

Anlotinib	81	68	51	33	16	7	2	1	0	
Placebo	38	23	12	6	4	2	2	0	0	

ORR = 4.9% vs 2.6%, DCR = 71.6% vs 13.2%

Cheng Y, et al. *Ann Oncol*. 2019;30(suppl 5):v711 (abstract 17380).

34

Anlotinib vs Placebo

	Anlotinib (n = 81)	PBO (n = 38)
Events , n (%)	60 (74.1)	33 (86.8)
mOS, mos (95%CI)	7.3 (6.1–10.3)	4.9 (2.7–6.0)
HR = 0.53 (0.3–0.8), *P*= .0029		
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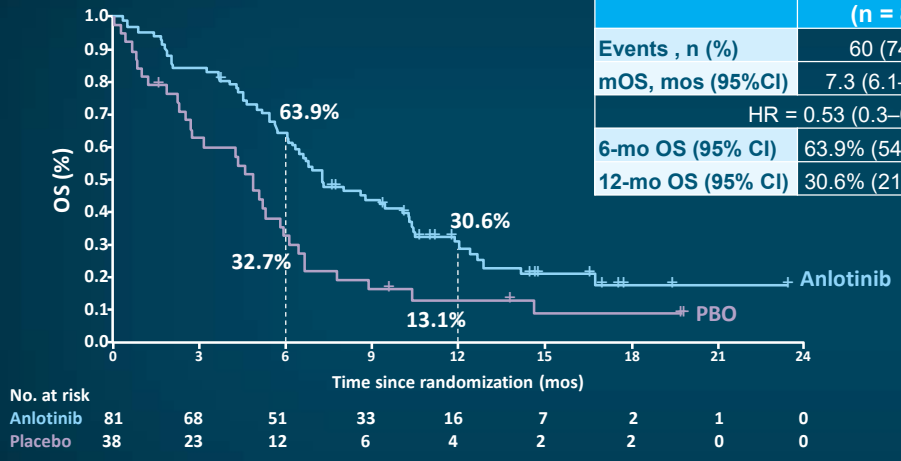
12-mo OS (95% CI)	30.6% (21.7–43.2)	13.1% (5.6–30.7)



Grade 3 adverse events include hypertension and hyponatremia

Cheng Y, et al. *Ann Oncol*. 2019;30(suppl 5):v711 (abstract 17380).

35

Checkpoint Inhibitors for 2L+ in NSCLC
FDA Approvals Withdrawn for Pembrolizumab and Nivolumab

Pembrolizumab

Accelerated Approval
KEYNOTE-158/028
ORR 19% (95%CI 11-29%)

⇨

Indication Withdrawn
KEYNOTE-604, 1L Chemo +/- Pembro
No OS Benefit

Nivolumab

Accelerated Approval
CheckMate 032, 3L+ Nivo
ORR 11.9%, DoR 17.9 mo

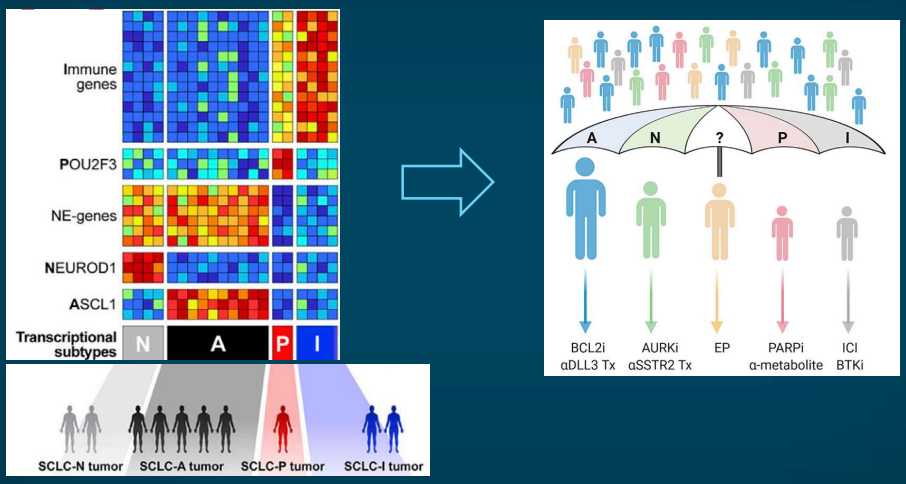
⇨

Indication Withdrawn
CheckMate 331, 2L Nivo vs Chemo
No OS Benefit

Rudin CM, et al. *J Clin Oncol*. 2020;38(21):2369-2379. Ready N, et al. *J Thorac Oncol*. 2019;14(2):237-44. Spigel DR, et al. *Ann Oncol*. 2021;32(5):631-641.

36

Will Molecular Profiling Guide SCLC Treatment in the Future?



Gay CM, et al. *Cancer Cell*. 2021;39(3):346-360. Frese KK, et al. *Cancer Cell*. 2021;39:297-299

37

Applying National Cancer Center Network Guidelines to Practice

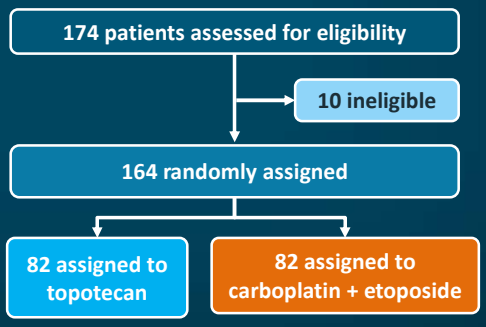
38

Role of Platinum Re-exposure?

- For platinum-sensitive disease, usual practice is to rechallenge with first-line platinum-based treatment
- However, this practice relies on studies older than 20 years with small sample sizes
- Two strategies are available for second-line treatment: rechallenge with the initial chemotherapy or treatment with topotecan

Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial

*Nathalie Baize, Isabelle Monnet, Laurent Greillier, Margaux Geier, Hervé Lena, Henri Janicot, Alain Vergnenegre, Jacky Crequit, Regine Lamy, Jean-Bernard Auliac, Jacques Letreut, Hervé Le Caer, Radj Gervais, Eric Dansin, Anne Madroszyk, Patrick-Aldo Renault, Gwenaëlle Le Garff, Lionel Falchero, Henri Berard, Roland Schott, Patrick Saulnier, Christos Chouaid, on behalf of the Groupe Français de Pneumo-Cancérologie 01–13 investigators**



Baize N, et al. *Lancet Oncol.* 2020;21:1224-1233.

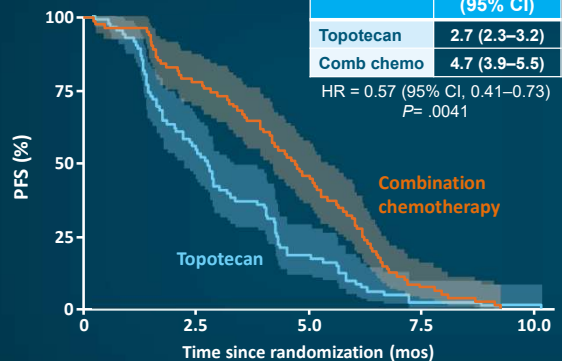
39

Improved PFS with Platinum Re-exposure

PFS

	mPFS (95% CI)
Topotecan	2.7 (2.3–3.2)
Comb chemo	4.7 (3.9–5.5)

HR = 0.57 (95% CI, 0.41–0.73)
P= .0041

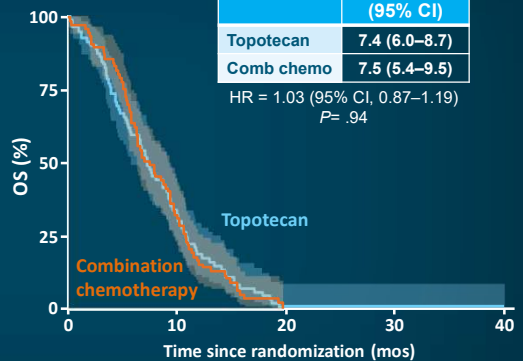


No. at risk (censored)					
Topotecan	81 (0)	45 (0)	15 (0)	2 (0)	1 (0)
Comb chemo	81 (0)	63 (0)	7 (0)	6 (2)	0 (2)

OS

	mOS (95% CI)
Topotecan	7.4 (6.0–8.7)
Comb chemo	7.5 (5.4–9.5)

HR = 1.03 (95% CI, 0.87–1.19)
P= .94



No. at risk (censored)					
Topotecan	79 (0)	27 (0)	15 (0)	2 (2)	1 (2)
Comb chemo	77 (0)	25 (0)	0 (0)	0 (4)	0 (5)

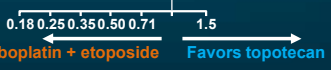
Comb chemo = combination chemotherapy (carboplatin + etoposide).

Baize N, et al. *Lancet Oncol.* 2020;21:1224-1233.

40

Improved PFS with Platinum Re-Exposure

	Topotecan Events/patients	Carboplatin + etoposide Events/patients	HR (95% CI)
Time from first-line chemo to progression			
≥90 days to <180 days	56/56	56/57	0.70 (0.57–1.05)
≥180 days	25/25	23/24	0.23 (0.18–0.62)
Age (years)			
<70	59/59	61/63	0.58 (0.41–0.84)
≥70	22/22	18/18	0.60 (0.31–1.18)
Sex			
Male	59/59	49/50	0.73 (0.42–1.20)
Female	22/22	30/31	0.52 (0.35–0.79)
ECOG performance status			
0	26/26	27/28	0.48 (0.27–0.86)
1–2	55/55	52/53	0.60 (0.41–0.89)
Disease stage at entry			
Limited	30/30	29/29	0.40 (0.22–0.71)
Extensive	51/51	50/52	0.67 (0.41–0.99)
Response to first-line chemotherapy			
Complete	13/13	18/18	0.36 (0.16–0.82)
Partial	68/68	61/63	0.61 (0.43–0.87)
History of thoracic radiotherapy			
Yes	47/47	45/45	0.42 (0.26–0.66)
No	34/34	34/36	0.72 (0.40–1.20)
Brain metastasis			
No	51/51	52/54	0.68 (0.51–0.98)
Yes	30/30	27/27	0.32 (0.24–0.78)
Prophylactic brain irradiation			
Yes	19/19	20/20	0.56 (0.41–0.99)
No	62/62	59/61	0.55 (0.41–0.82)
Overall	81/81	79/81	0.57 (0.41–0.73)



Baize N, et al. *Lancet Oncol.* 2020;21:1224-1233.

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Case Study

Multifocal, Systemic, SCLC Relapse

42

A 57-Year-Old Man Previously Diagnosed With SCLC…

History of Disease

- First diagnosed with SCLC in December 2018
- Treated with 6 cycles of cisplatin and etoposide
- Concurrent 70 Gy radiation with the first 2 chemotherapy cycles
- Began to experience dyspnea and hemoptysis 3 months after therapy completion
- Imaging and biopsy confirm multifocal systemic SCLC relapse, without CNS involvement
- He began treatment with lurbinectedin 3.2 mg/m^2

43

A 57-Year-Old Man Previously Diagnosed With SCLC (continued)…

Cycle 2, Day 1 Appointment

- Absolute neutrophil count is 1,200 cells/mm^3
- He is not experiencing fever

What is the best course of action?

44

Lurbinectedin Dose Adjustments

Neutropenia

ANC <500/mm^3 or febrile neutropenia → Hold to ANC >1500/mm^3 and dose reduce

- Option to add GCSF and defer dose reduction if isolated ANC <500/m^3
- GCSF recommended if any ANC < LLN

Thrombocytopenia

Platelets 25-50K/mm^3 +bleeding or < 25K/mm^3 → Hold until 100K/mm^3 and dose reduce

Lurbinectedin. Package insert. Jazz Pharmaceuticals, Inc.; 2020. [https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213702s000lbl.pdf]

45

Case Study

SCLC with Multifocal CNS Metastasis

46

A 64-Year-Old Woman Presents to the Emergency Department…

Presentation and Medical History

- Complains of cough and dyspnea
- Current smoker
  - Smokes 1 pack per day since 21 years of age

Imaging

- Chest x-ray
  - Abnormal hilar shadow in the left lung
- CT scan
  - A 4.0 x 3.2 cm hilar mass in the left lung
  - Enlarged mediastinal lymph nodes bilaterally, with several hepatic lesions
- Brain MRI
  - Multifocal CNS metastases

47

A 64-Year-Old Woman Presents to the Emergency Department (continued)…

Clinical Course

- Received 4 cycles of carboplatin/etoposide/atezolizumab
- Whole brain radiation therapy
  - Post-treatment CT scans showed a partial response ongoing after 4 cycles therapy
- Continued atezolizumab maintenance therapy

3-month Follow-up

- CT scans
  - Progression in the liver and mediastinal LN
- Brain MRI
  - Numerous new small CNS metastases
- ECOG PS 2

48

A 64-Year-Old Woman Presents to the Emergency Department (continued)…

What treatment option would you recommend for this patient?

49

What treatment option would you recommend for this patient?

- In the 2L platinum-resistant setting, topotecan has demonstrated CNS activity and therefore is a preferred option
- Temozolomide has also demonstrated CNS activity and would be a reasonable subsequent treatment option
- Topotecan may also be a preferred option for patients who specifically desire an oral dosing schedule

50

Case Study

Extensive-stage SCLC

51

A 79-Year-Old Man With Extensive-stage SCLC…

Presentation

- Multifocal disease involving the lungs, lymph nodes, liver, following biopsy of a hepatic lesion

Medical History

- Tobacco use
- Coronary artery disease
- Congestive heart failure
- He lives in an assisted living facility
- ECOG PS is 2 at diagnosis

Clinical Course

- 4 cycles carboplatin/etoposide/atezolizumab
- Atezolizumab maintenance
- Course complicated by hospitalizations for CHF exacerbations and by neutropenic fever

52

A 79-Year-Old Man With Extensive-stage SCLC…

3-month Follow-up

- CT scans
  - Multifocal disease progression including in the lungs and liver
  - New bone metastasis at L3 without epidural extension
- Clinically declined and spend most of the day in bed
- New midline lower back pain which is requiring increased doses of opioids

What treatment option would you recommend for this patient?

53

Thank You!

54

Build your own complimentary poster for the office!

Supplement your Course Learning.
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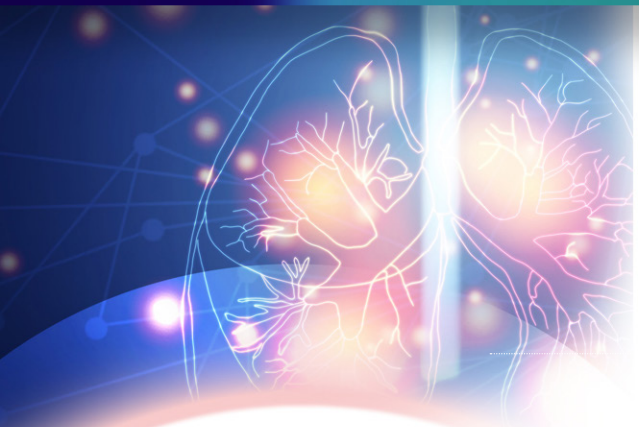

Project ECHO®
Med Learning Group - Small-Cell Lung Cancer

Leveraging Novel Treatment Options for SMALL-CELL LUNG CANCER in the Second Line

PLEASE VISIT **sclc.posterprogram.com**

Response to primary therapy and tumorigenesis of small-cell lung cancer: subsequent lines of therapy and pathophysiology primer

Resource	Address
Büttner R, et al. Implementing TMB measurement in clinical practice: considerations on assay requirements. *ESMO Open*. 2019;4:e000442.	www.ncbi.nlm.nih.gov/pmc/articles/PMC6350758/pdf/esmoopen-2018-000442.pdf
George J, et al. Comprehensive genomic profiles of small cell lung cancer. *Nature*. 2015;524:47-53.	https://pubmed.ncbi.nlm.nih.gov/26168399/
Misch D, et al. Value of thyroid transcription factor (TTF)-1 for diagnosis and prognosis of patients with locally advanced or metastatic small cell lung cancer. *Diagn Pathol*. 2015;10:21.	https://diagnosticpathology.biomedcentral.com/track/pdf/10.1186/s13000-015-0250-z.pdf
Sabari JK, et al. Unravelling the biology of SCLC: implications for therapy. *Nat Rev Clin Oncol*. 2017;14:549-561.	https://pubmed.ncbi.nlm.nih.gov/28534531/
Sen T, Gay CM, Byers LA. Targeting DNA damage repair in small cell lung cancer and the biomarker landscape. *Transl Lung Cancer Res*. 2018;7:50-68.	https://tlcr.amegroups.com/article/view/19133/15089

Efficacy and safety review

Resource	Address
Cruz C, et al. Multicenter phase II study of lurbinectedin in BRCA-mutated and unselected metastatic advanced breast cancer and biomarker assessment substudy. *J Clin Oncol*. 2018;36:3134-3143.	https://ascopubs.org/doi/pdf/10.1200/JCO.2018.78.6558
Farago AF, et al. ATLANTIS: a phase III study of lurbinectedin/doxorubicin versus topotecan or cyclophosphamide/doxorubicin/vincristine in patients with small-cell lung cancer who have failed one prior platinum-containing line. *Future Oncol*. 2019;15:231-239.	https://pubmed.ncbi.nlm.nih.gov/30362375/

Santamaria Nuñez G, et al. Lurbinectedin specifically triggers the degradation of phosphorylated RNA polymerase II and the formation of DNA breaks in cancer cells. *Mol Cancer Ther*. 2016;15:2399-2412.	https://pubmed.ncbi.nlm.nih.gov/27630271/
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Paz-Ares LG, et al. Efficacy and safety profile of lurbinectedin in second-line SCLC patients: results from a phase II single-agent trial. *J Clin Oncol*. 2019;37(suppl 15): abstract 8506.	https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.8506
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