A New Era of Treatment Opportunities for Small-Cell Lung Cancer in the Second Line: AN INNOVATIVE 3D VIEW

Wednesday, September 8, 2021

This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM and AMEDCO).
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A New Era of Treatment Opportunities for Small-Cell Lung Cancer in the Second Line: An Innovative 3D View

FACULTY

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PROGRAM OVERVIEW

This live virtual satellite symposium consists of presentations from expert faculty and 3D animation technology to discuss the pathology of small cell lung cancer (SCLC), clinical trial data of therapy in the second-line setting of SCLC, and clinical practice guidelines for the management of extensive disease.

TARGET AUDIENCE

This initiative is designed to meet the educational needs of medical oncologists, radiation oncologists, oncology nurses, and pharmacists who care for patients with small cell lung cancer.

LEARNING OBJECTIVES

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

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

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Stephen Liu, MD reports that he serves as a consultant for Amgen, AstraZeneca, Beigene, Blueprint, Bristol Myers Squibb, Daiichi Sankyo, Elevation Oncology, G1 Therapeutics, Genentech/Roche, Guardant Health, Inivata, Janssen, Jazz Pharmaceuticals, Lilly, Merck/MSD, Pfizer, PharmaMar, Regeneron, Takeda, and Turning Point Therapeutics. He has contracted research (to institution) for Alkermes, Bayer, Blueprint, Bristol Myers Squibb, Elevation Oncology, Erasca, Genentech, Lilly, Merck, Merus, Pfizer, Rain Therapeutics, RAPT, and Turning Point Therapeutics.

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CNE Content Review

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

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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: transcription addiction
d. Animation: hyperactive pathways that drive the pathology of SCLC

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

a. Clinical trials findings of approved treatments
b. Clinical trials findings: developing compounds in the second-line

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

a. Second-line regimens with relapse ≤6 months
b. Current recommendations for relapse >6 months
c. Patient management in the population that has progressed
d. Animation: Adverse events and their management in optimizing tolerability to systemic therapy

IV. Conclusions

V. Questions and Answers

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An Innovative 3D View

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- During this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

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Learning Objectives

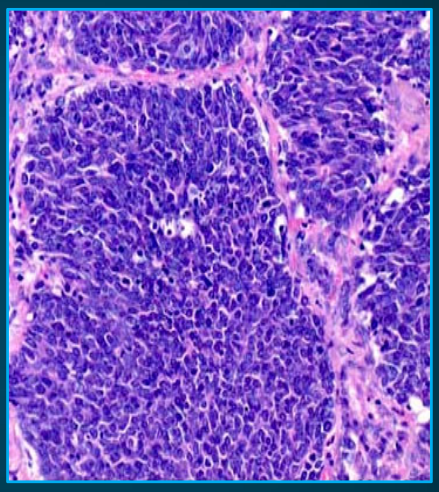
- Discuss biological insights that drive the tumorigenesis of small-cell lung cancer (SCLC)
- Describe the clinical trial findings of combination regimens in the second-line treatment of patients with extensive-stage SCLC
- Apply National Comprehensive Cancer Network (NCCN) clinical practice guidelines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

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

Pathophysiology Primer

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

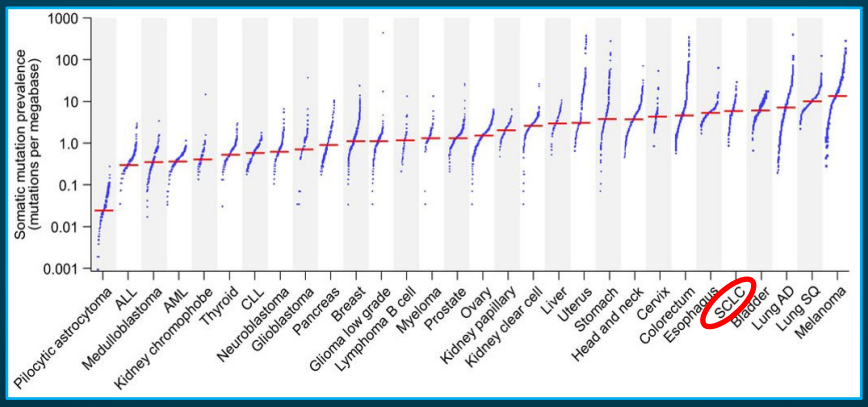


SCLC = small-cell lung cancer; TTF-1 = thyroid transcription factor 1.

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.

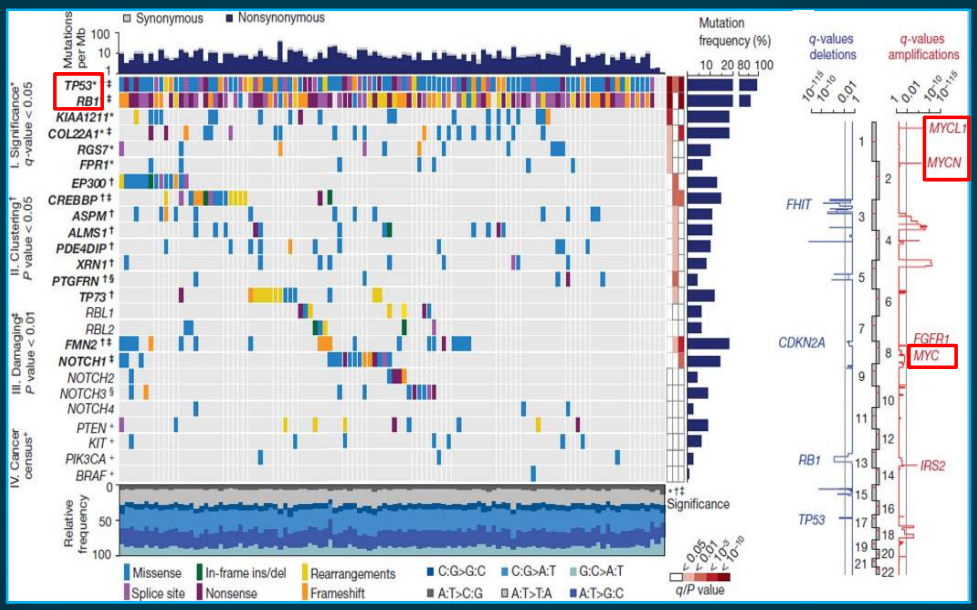
Common Genomic Alterations in Small-Cell Lung Cancer

- 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 reveal a target



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.

Genomic Alterations in SCLC



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

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.

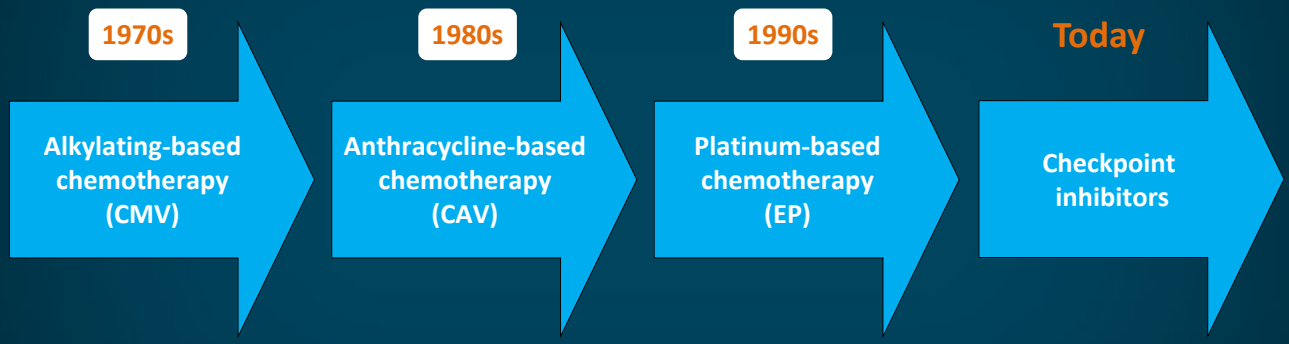
Common Genomic Alterations in Small-Cell Lung Cancer (continued)

- 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.

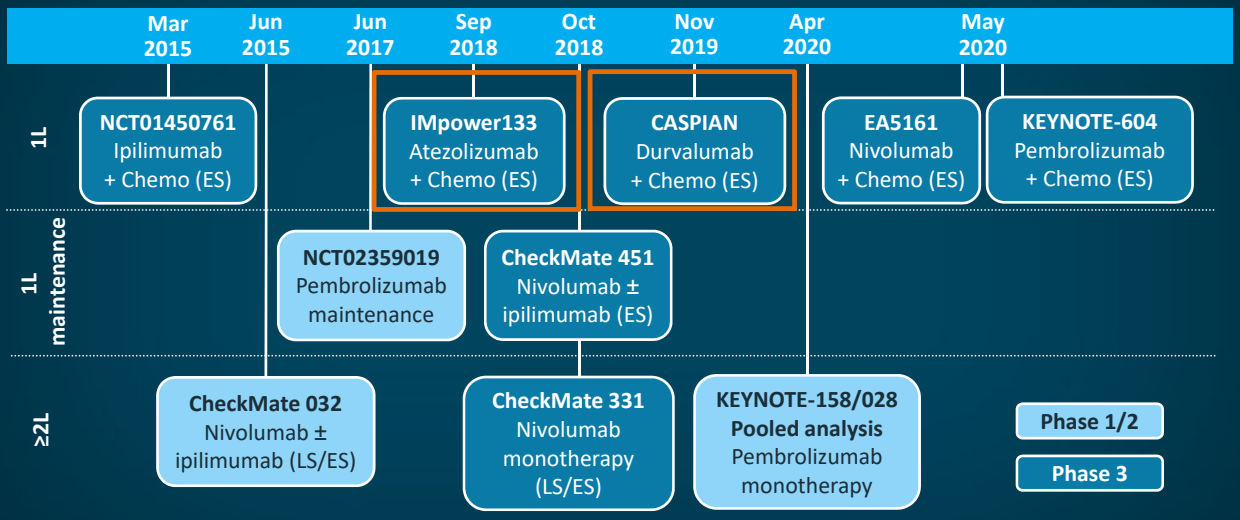
Evolution of Systemic Therapy in Small-Cell Lung Cancer



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.

Overview of Key Studies of Immune Checkpoint Inhibitors in SCLC



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

Please click here to watch an animation on the pathology of SCLC

Efficacy and Safety Review

Second-Line Regimens for Extensive-Stage SCLC

67-Year-Old Man With Extensive SCLC…

History of disease

- Underwent treatment with 4 cycles carboplatin, etoposide, and atezolizumab
- Experienced a partial response and continued maintenance therapy with atezolizumab

Imaging

- **CT scan after 3 cycles of maintenance immunotherapy:** progressive disease in liver and increase in retroperitoneal LNs

Current clinical status

- Otherwise doing well with no significant symptoms, ECOG PS = 1

What should be the next step in management?

CT = computed tomography; LN = lymph node; ECOG = Eastern Cooperative Oncology Group; PS = performance status.

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 (category 3) • Pembrolizumab (category 3)
Relapse >6 Months	
Preferred regimens • Original regimen	**Other recommended regimen** • Lurbinectedin

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

National Comprehensive Cancer Network (NCCN) version 2.2021 (www.nccn.org/professionals/physician_gls/pdf/sclc.pdf). Accessed 6/20/2021.

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 (category 3) • Pembrolizumab (category 3)
Relapse >6 Months	
Preferred regimens • Original regimen	**Other recommended regimen** • Lurbinectedin

NCCN version 2.2021 (www.nccn.org/professionals/physician_gls/pdf/sclc.pdf). Accessed 6/20/2021.

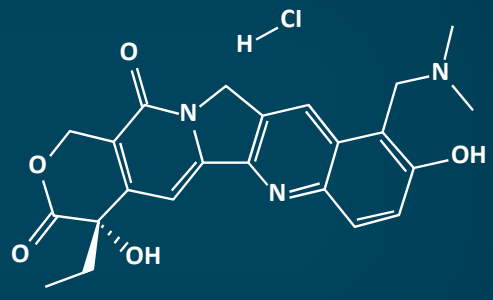
Subsequent Treatment Options for SCLC

SCLC Subsequent Systemic Therapy	
Relapse ≤6 Months, PS 0–2	
Preferred regimens • Topotecan PO or IV—patients who have been chemotherapy-free for >60 days after 1L chemotherapy • Lurbinectedin—metastatic SCLC that has progressed on or after platinum-based chemotherapy • Clinical trial	
Other recommended regimens • Paclitaxel • Docetaxel • Irinotecan • Temozolomide • Cyclophosphamide/doxorubicin/vincristine (CAV)	• Oral etoposide • Vinorelbine • Gemcitabine • Bendamustine (category 2B) • Nivolumab (category 3) • Pembrolizumab (category 3)
Relapse >6 Months	
Preferred regimens • Original regimen	**Other recommended regimen** • Lurbinectedin

NCCN V 2.2021 (www.nccn.org/professionals/physician_gls/pdf/sclc.pdf). Topotecan prescribing information (PI), 2019 (www.accessdata.fda.gov/drugsatfda_docs/label/2019/022453s011lbl.pdf). Lurbinectedin (Zepzelca™) PI 2020 (https://pp.jazzpharma.com/pi/zepzelca.en.USPI.pdf). All URLs accessed 6/20/2021.

Topotecan

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

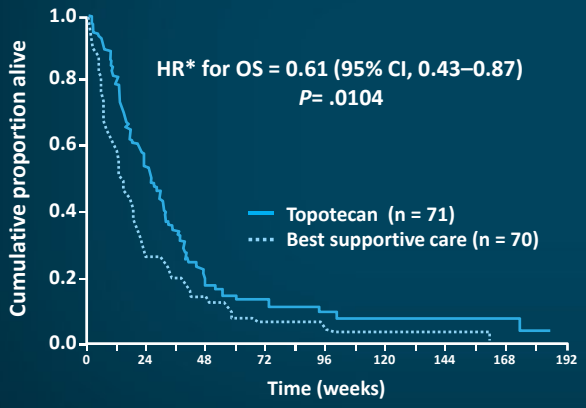


Topotecan hydrochloride

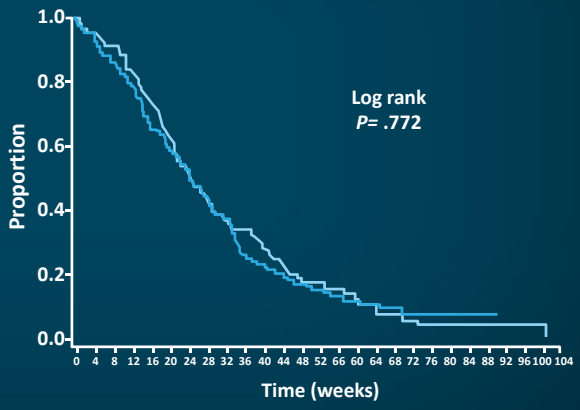
O'Brien MER, et al. *J Clin Oncol.* 2006;24:5441-5447. Topotecan PI, 2019 (www.accessdata.fda.gov/drugsatfda_docs/label/2019/022453s011lbl.pdf). Accessed 6/20/2021.

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.

1. O'Brien MER, et al. *J Clin Oncol.* 2006;24:5441-5447. 2. von Pawel J, et al. *J Clin Oncol.* 1999;17:658-667.

Topotecan Toxicities

Hematologic and Nonhematologic Toxicities

Topotecan 1.5 mg/m^2/d IV for days 1–5 every 21 days

Hematologic Toxicities in 107 Patients

AE	Patients (N = 107) AE/No. of Patients (%)		Courses (N = 446) AE/No. of Patients (%)	
	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%)

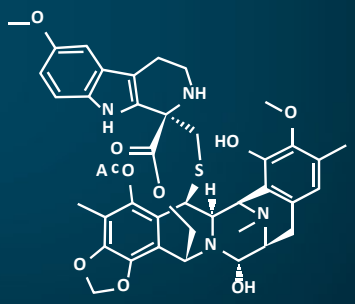
Nonhematologic Toxicities in >10% of 107 Patients

AE, n (%)	Toxicity criteria grade 1/2	Toxicity criteria grade 3/4	Total
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.

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

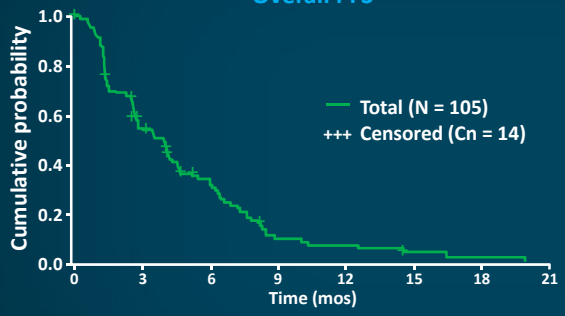


Trigo J, et al. *Lancet Oncol.* 2020;21:645-654. Santamaria Nuñez G, et al. *Mol Cancer Ther.* 2016;15:2399-2412. Cruz C, et al. *J Clin Oncol.* 2018;36:3134-3143. Lurbinectedin (Zepzelca™) PI, 2020 (https://pp.jazzpharma.com/pi/zepzelca.en.USPI.pdf). Lurbinectedin. Drug Approvals International (http://drugapprovalsint.com/lurbinectedin/).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

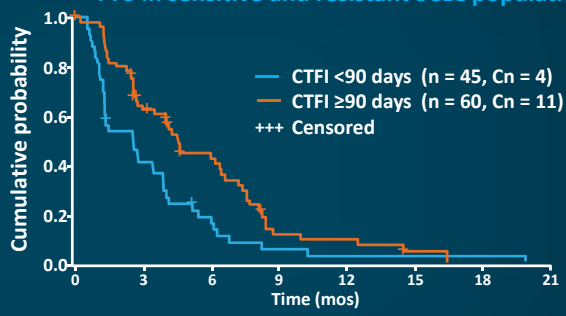
Lurbinectedin Efficacy

- 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.

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.

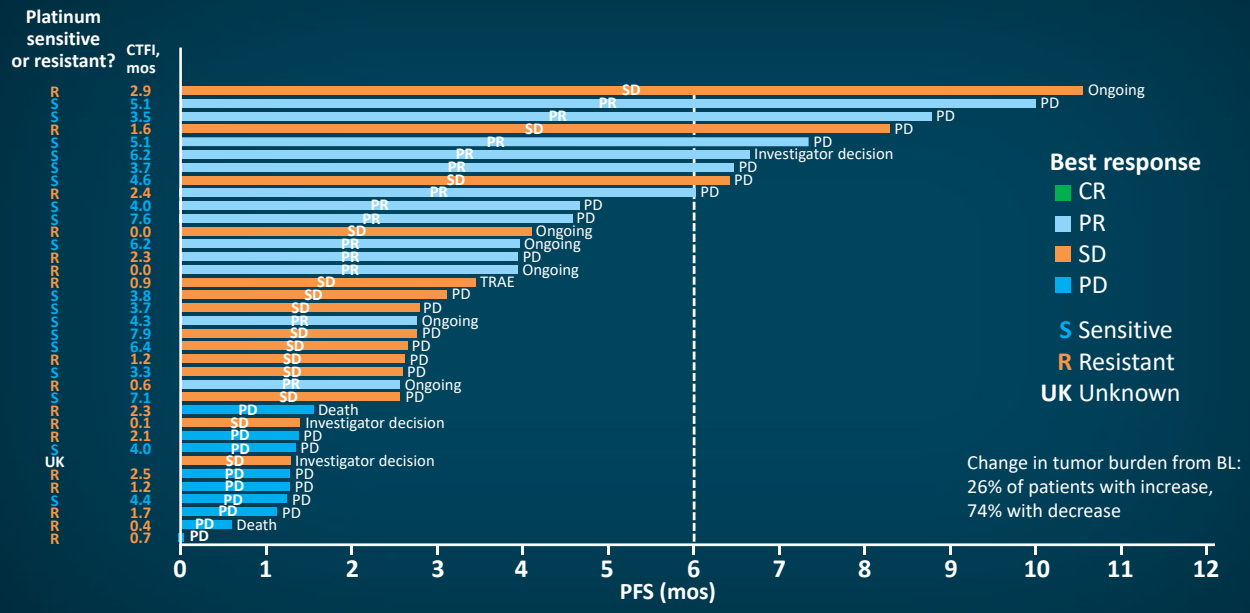
Lurbinectedin Has Efficacy in Sensitive and Resistant SCLC

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.

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.

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.

Lurbinectedin Is Approved and Available for Use

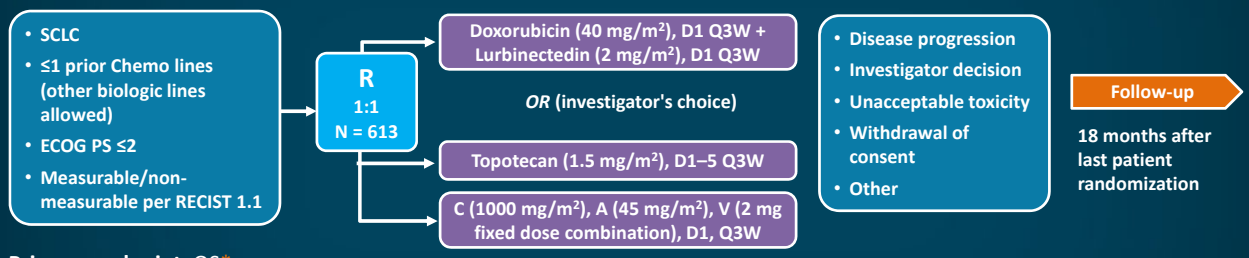
- Confirmed ORR of 35.2% with 2L lurbinectedin surpassed ≥30% statistical cutoff for a positive trial
  - Follow-up: 17.1 months (IQR: 6.5–25.3),
- Outcomes with 2L lurbinectedin numerically higher than historical outcomes with 2L topotecan
- Results from phase 3 ATLANTIS trial of second-line lurbinectedin plus doxorubicin versus investigator's choice of topotecan or CAV are awaited

IQR = interquartile range.

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

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.

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

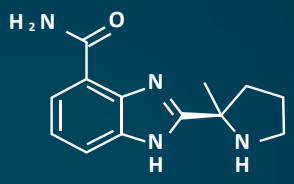
G-CSF = granulocyte colony-stimulating factor.

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

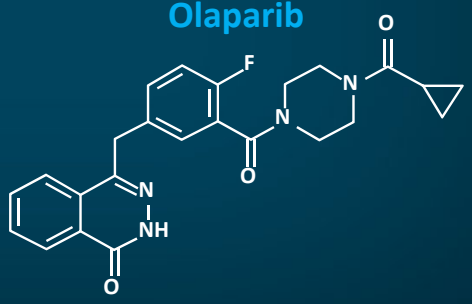
PARP Inhibitors

- 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



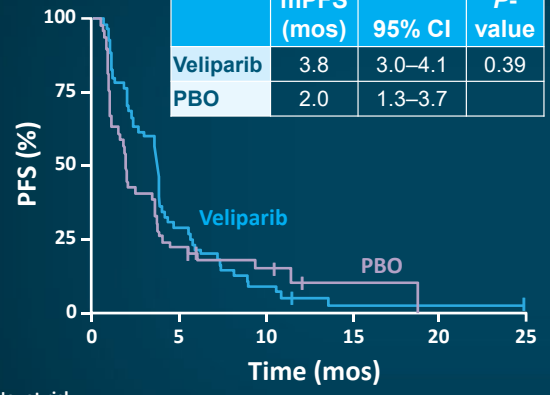
ADP = adenosine diphosphate.

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

Veliparib + Temozolomide for Recurrent ES-SCLC

No significant difference between veliparib + temozolomide and PBO + temozolomide

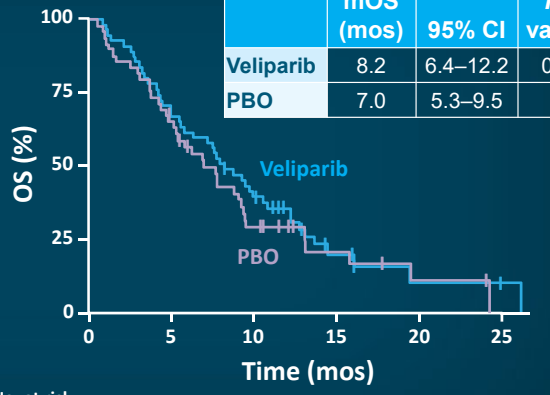
	mPFS (mos)	95% CI	*P*-value
Veliparib	3.8	3.0–4.1	0.39
PBO	2.0	1.3–3.7	



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.

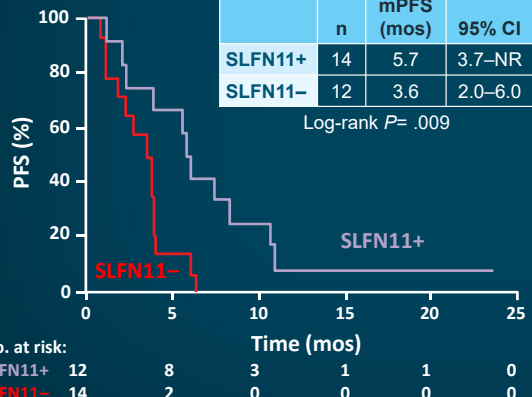
Pietanza MC, et al. *J Clin Oncol*. 2018;36:2386-2394.

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

Veliparib + Temozolomide	n	mPFS (mos)	95% CI
SLFN11+	14	5.7	3.7–NR
SLFN11–	12	3.6	2.0–6.0

Log-rank *P*= .009

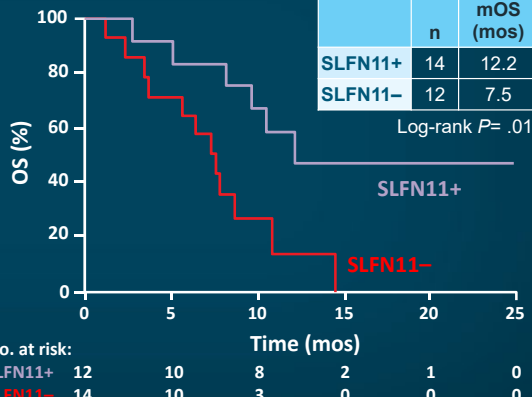


No. at risk:

SLFN11+	12	8	3	1	1	0
SLFN11–	14	2	0	0	0	0

Veliparib + Temozolomide	n	mOS (mos)	95% CI
SLFN11+	14	12.2	9.7–NR
SLFN11–	12	7.5	5.6–NR

Log-rank *P*= .014



No. at risk:

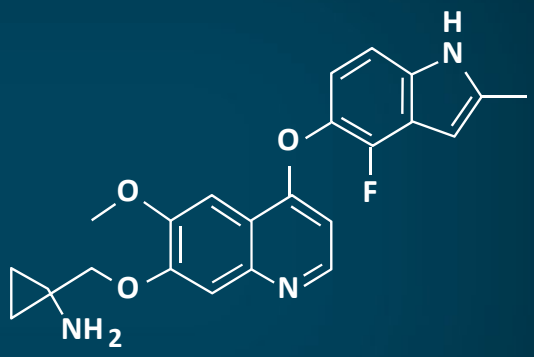
SLFN11+	12	10	8	2	1	0
SLFN11–	14	10	3	0	0	0

SLN11 = Schlafen-11; NR = not reached.

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

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

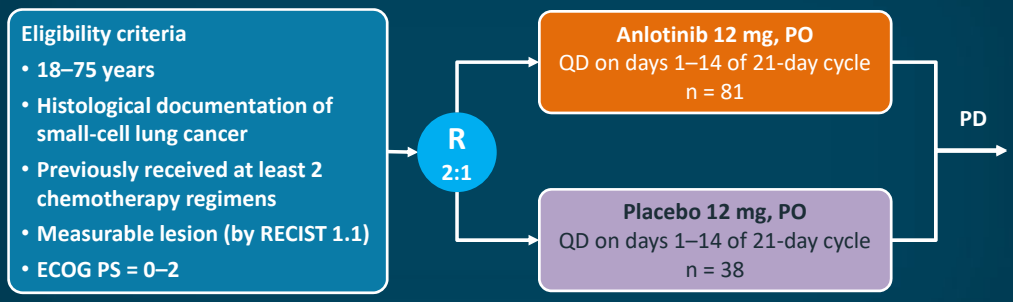


VEGFR = vascular endothelial growth factor receptor; PDGFR= platelet-derived growth factor receptor, KIT = stem cell factor receptor.

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

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.

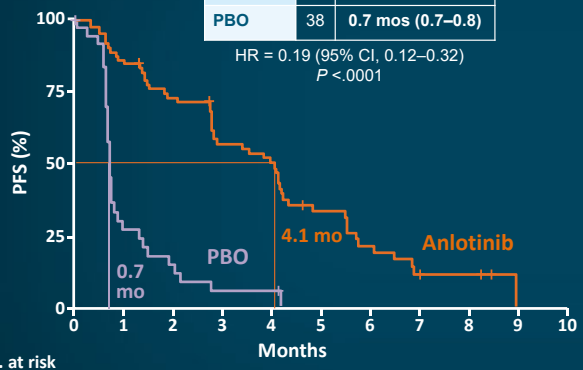
Cheng Y, et al. *Ann Oncol*. 2019;30(suppl 5):v711 (abstract 17380). Si X, et al. *Thorac Cancer*. 2019;10:551-556.

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

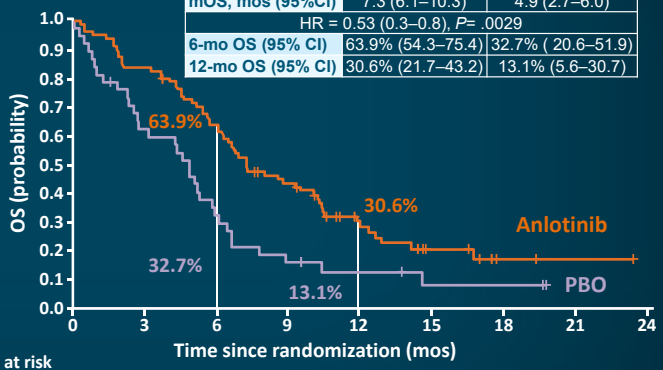


No. at risk

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

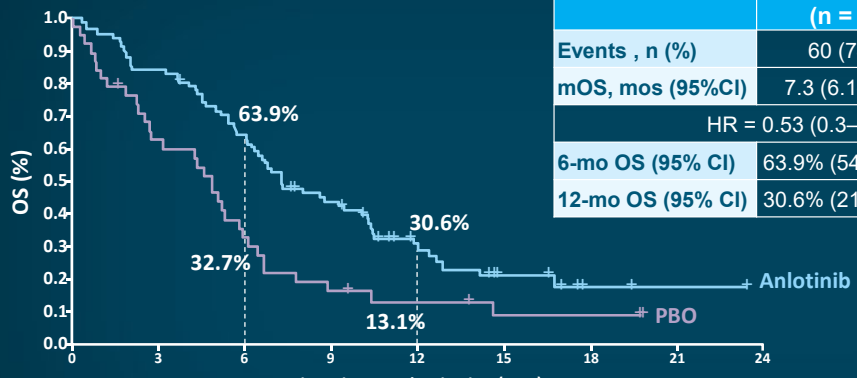
Anlotinib	81	68	51	33	16	7	2	1	0
Placebo	38	23	12	6	4	2	2	0	0

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).

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		
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

Grade 3 adverse events include hypertension and hyponatremia

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

Applying National Cancer Center Network Guidelines to Practice

73-Year-Old Woman With Extensive SCLC…

History of disease

- Underwent 4 cycles of carboplatin, etoposide, and durvalumab
- At the end of induction chemoimmunotherapy, underwent whole brain radiation for brain metastases
- Tolerated therapy well and went on to maintenance durvalumab administered every 4 weeks for 10 cycles

Imaging

- CT scans: increase in RUL mass, increase in mediastinal and hilar LAD, new symptomatic bony metastases at L2
- MRI of brain: no evidence of progression

RUL = right upper lobe; LAD = lung adenocarcinoma; L12 = 12th lumbar vertebra; MRI = magnetic resonance imaging.

Second Case Study
(continued)

Treatment course

- She undergoes palliative radiation to T12-L2
- She is otherwise doing well
  - No significant symptoms, ECOG PS = 1

What should be the next step in management?

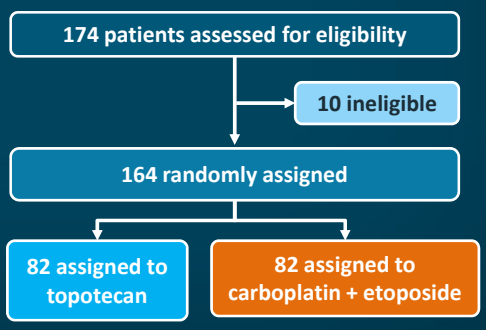
T12 = 12th thoracic vertebra; L2 = second lumbar vertebra.

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**



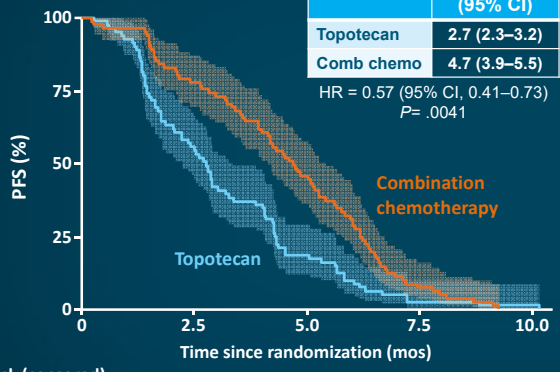
Baize N, et al. *Lancet Oncol*. 2020;21:1224-1233.

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

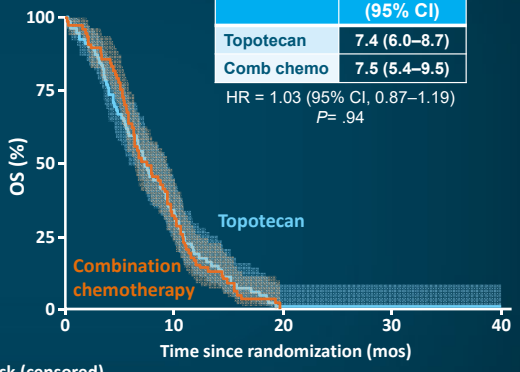


No. at risk (censored)					
Topotecan	81 (0)	45 (0)	15 (0)	2 (0)	1 (0)
Comb chemo	81 (0)	63 (0)	7 (0)	6 (2)	0 (2)

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



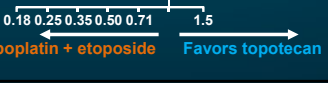
No. at risk (censored)					
Topotecan	79 (0)	27 (0)	15 (0)	2 (2)	1 (2)
Comb chemo	77 (0)	25 (0)	0 (0)	0 (4)	0 (5)

Comb chemo = combination chemotherapy (carboplatin + etoposide).

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

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.

Please click here to watch an animation on adverse events of SCLC

Summary

- In considering 2L therapy for SCLC, many factors should be considered, including prior therapy and nature of the disease, i.e. resistant vs sensitive disease
- ICI monotherapy is not recommended for those patients who progressed after chemo/IO
- Lurbinectedin is now approved for therapy for 2L disease

ICI = immune-checkpoint inhibitor; IO = immuno-oncology.

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/
O'Brien MER, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol*. 2006;24:5441-5447.	https://mct.aacrjournals.org/content/15/10/2399.full-text.pdf
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
Pietanza MC, et al. Randomized, double-blind, phase II study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. *J Clin Oncol*. 2018;36:2386-2394.	https://ascopubs.org/doi/pdf/10.1200/JCO.2018.77.7672
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
Si X, et al. Management of anlotinib-related adverse events in patients with advanced non-small cell lung cancer: experiences in ALTER-0303. *Thorac Cancer*. 2019;10:551-556.	www.ncbi.nlm.nih.gov/pmc/articles/PMC6397894/
Trigo J, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol*. 2020;21:645-654.	https://pubmed.ncbi.nlm.nih.gov/32224306/
von Pawel J, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell	https://ascopubs.org/doi/pdf/10.1200/JCO.2013.54.5392

lung cancer. *J Clin Oncol*. 2014;32:4012-4019.	
von Pawel J, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol*. 1999;17:658-667.	https://pubmed.ncbi.nlm.nih.gov/10080612/

Applying National Cancer Center Network guidelines to practice

Resource	Address
Baize N, et al. 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. *Lancet Oncol*. 2020;21:1224-1233.	https://pubmed.ncbi.nlm.nih.gov/32888454/

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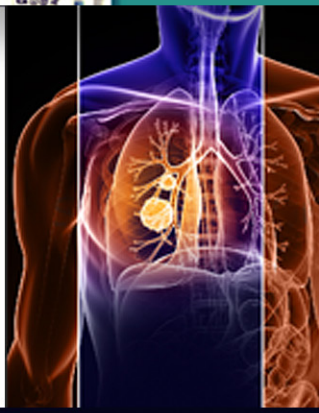
A New Era of Treatment Opportunities for Small-Cell Lung Cancer in the Second Line: AN INNOVATIVE 3D VIEW



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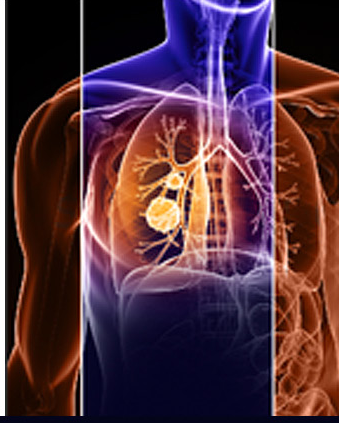
A New Era of Treatment Opportunities for Small-Cell Lung Cancer in the Second Line: AN INNOVATIVE 3D VIEW



WHITEBOARD ANIMATIONS

SCLC – Path: https://youtu.be/LVBrioOrqi4

SCLC – Adversarial Events: https://youtu.be/4q7zfZwr3j4

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