CAMPUS SEOM

Área de formación virtual SEOM

Carcinoma microcítico de pulmón

Dr. Luis Léon
Hospital Clínico Universitario de Santiago de Compostela

SEOM
Sociedad Española
de Oncología Médica

ONCOREPASO
MATERIAL DE APOYO

1. DOCUMENTO PDF: PUNTOS PRINCIPALES SOBRE EL CARCINOMA MICROCÍTICO (SCLC)
2. PRESENTACIÓN PPT
3. PDF CON PREGUNTAS SOBRE SCLC DE EXÁMENES DE OPEs DE DIFERENTES CC.AA
4. ARTÍCULO REVIEW ESMO 2021 (es la referencia del documento de revisión y de la ppt)
5. ARTÍCULO JCO ASCO 2023 (centrado en tratamiento sistémico, con un buen resumen inicial de preguntas clínicas)

GUIÓN DE LA PRESENTACIÓN.

INTRODUCCIÓN

1. EPIDEMIOLOGÍA
2. DIAGNÓSTICO/MOLECULAR
3. ESTADIFICACIÓN/PRONÓSTICO
4. TRATAMIENTO

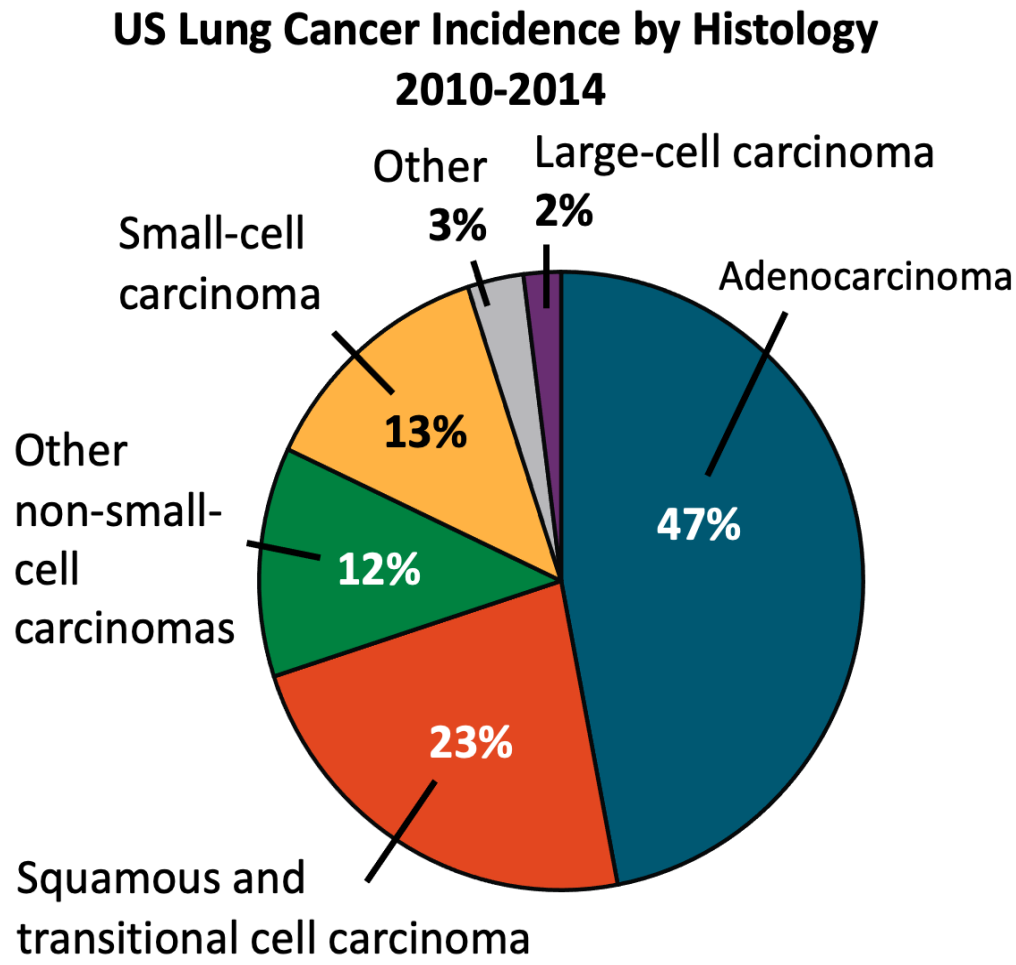
ONCOREPASO

EXÁMENES DE OTRAS OPEs

1. **El SCLC representa alrededor de un 2-3% de las preguntas (5% en la última OPE gallega)**
2. **Qué se pregunta:**
    1. Preguntas generales, epidemiología, incidencia mts SNC….
    2. ICP
    3. Síndromes paraneoplásicos
    4. Tratamiento, más de estadio IV, 1ª y 2ª líneas, sobre fármacos y nº ciclos, uso factor en concomitancia con RT
3. **Sobre qué NO se pregunta (o se pregunta menos):**
    1. Aspectos clínicos
    2. Dosis de fármacos

Small-Cell Lung Cancer

- SCLC accounts for ~ 13% of all lung cancers in the US
- Previously called oat-cell carcinoma
- Associated with a history of significant tobacco use
- Unique biology: rapid proliferation, abrupt presentation, bulky central tumor, hematogenous metastases at onset
- Poor outcomes



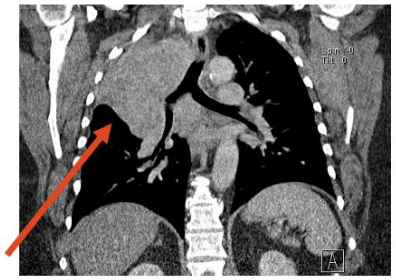
Oronsky. Neoplasia. 2017;19:842. Alvarado-Luna. Transl Lung Cancer Res. 2016;5:26. Howlander. SEER Cancer Statistics Review, 1975-2014.

Slide credit: clinicaloptions.com

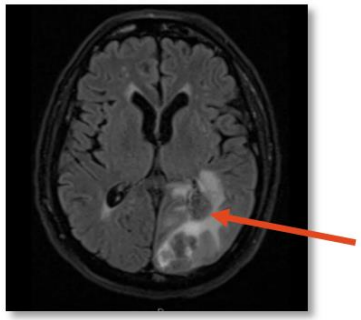
SCLC Clinical Presentation

- Local symptoms: cough, 50%; dyspnea, 40%; chest pain, 35%; hemoptysis, 20%; hoarseness, 10%
- Distant symptoms: weight loss, 50%; weakness, 40%; anorexia, 30%; paraneoplatic syndrome, 15%; fever, 10%
- Paraneoplastic syndromes: ectopic hormone-associated syndromes, immune-mediated neurologic syndromes

Chest CT



Brain MRI



Metastatic Site, %	At Presentation	At Autopsy
Mediastinal LNs	66-80	73-87
Liver	21-27	69
Bone	27-41	54
Adrenal glands	5-31	35-65
Bone marrow	15-30	NA
Brain	10-14	28-50
Retroperitoneal LNs	3-12	29-52
Supraclavicular LNs	17	42
Pleural effusion	16-20	30
Contralateral lung	1-12	8-27
Soft tissues	5	19

Jackman. Lancet. 2005;366:1385. Images courtesy of Anna F. Farago, MD, PhD.

Slide credit: clinicaloptions.com

ONCOREPASO

Tumor neuroendocrino de alto grado compuesto por células que miden menos de tres linfocitos en reposo, con **escaso citoplasma**, bordes celulares mal definidos, una cromatina nuclear granular finamente dispersa y nucléolos ausentes o poco visibles.

Las **mitosis son numerosas**, con una media de 80 por área de 2 mm2, y la **necrosis es extensa**.

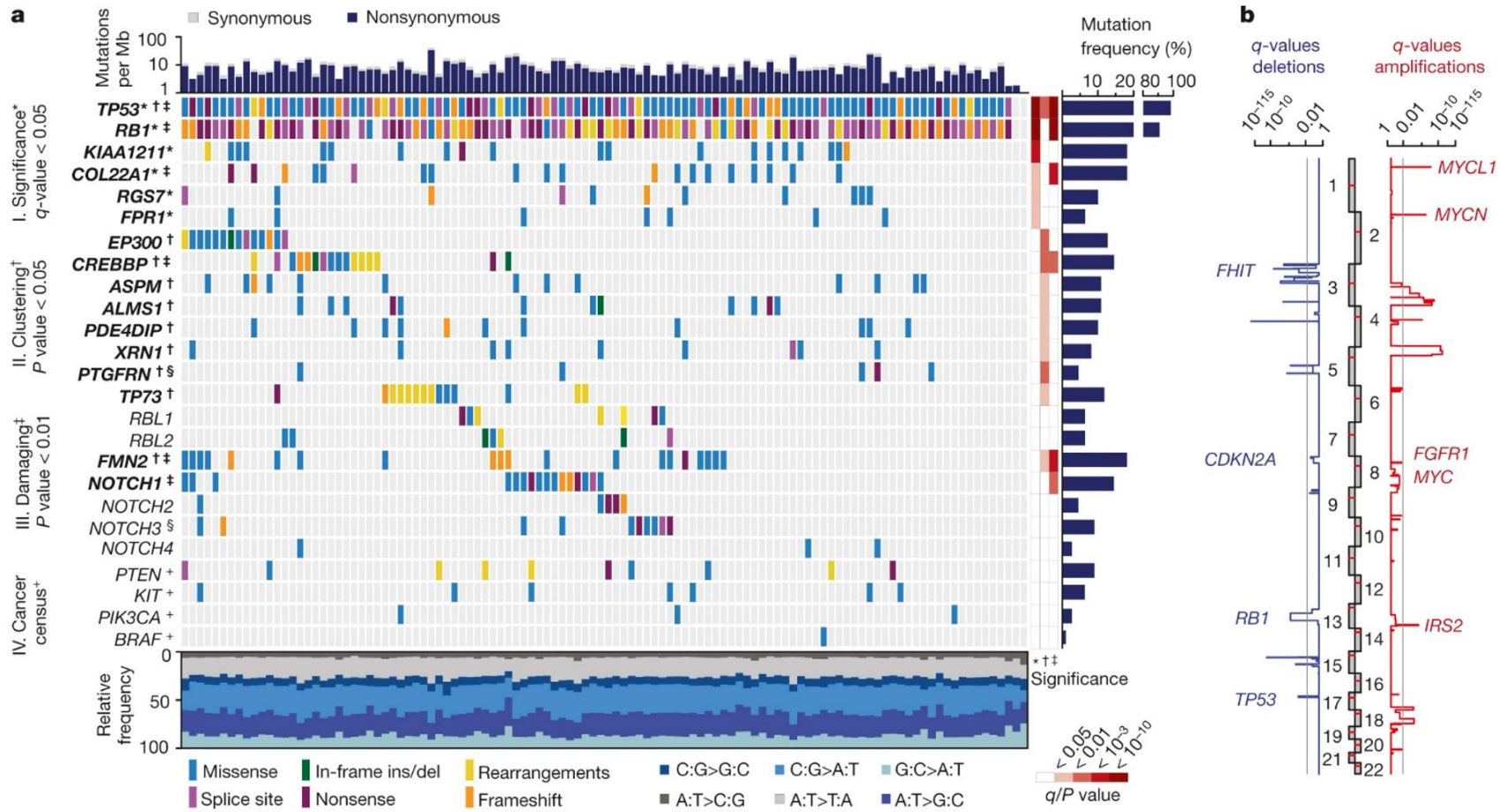
La mayoría expresan **CD56** (tinción membranosa), mientras que la **sinaptofisina y la cromogranina A** presentan tinción citoplasmática en el 54% y el 37% de los casos.

CD56 se considera el marcador más sensible pero menos específico. TTF1 se expresa en el 90% de los SCLC y **>50% de los núcleos se tiñen positivamente para Ki-67**.

Casi todos los SCLC tienen **mutaciones de pérdida de función tanto de TP53 como de RB1**.

Se ha propuesto una clasificación **molecular del SCLC en 4 subtipos: SCLC-A, -N, -P y -Y,**

Why Has Progress Been Slow? Absence of Driver Mutations in SCLC



Slide credit: clinicaloptions.com

ONCOREPASO

Como **factores pronósticos desfavorables** en pacientes SCLC se incluye:

- **Mal PS, pérdida de peso.**
- **Edad avanzada, sexo masculino.**
- **LDH elevada.**
- **Hiponatremia** (en relación con SIADH).

Además, un **gran volumen tumoral** en los pacientes que se tratan con radioquimioterapia se relaciona también con peor pronóstico.

ONCOREPASO

La **estadificación** hay que realizarla siguiendo la **8ª edición del TNM** (no por EL y EE).

Es importante recordar que la realización del **PET-TAC es opcional**, puede ser útil en pacientes que se van a tratar con **radioquimioterapia** (para descartar metástasis a distancia y para ayudar a planificar la radioterapia).

Si el plan terapéutico cambia en función de los hallazgos del PET-TAC se recomienda **biopsiar las localizaciones sospechosas de metástasis.**

La **biopsia de MO** solo se recomienda en caso de que se sospeche y se quiera confirmar invasión de la misma.

La prueba gold estándar para el **estudio del SNC es la RMN**, se acepta realización de TAC si no está disponible.

SCLC Diagnosis and Staging

El **Screening con TAC NO** es efectivo (demostrado en 3 ensayos clínicos)

- Diagnosis by FNA or biopsy
- Staging workup
  - CT chest/abdomen/pelvis
  - Brain MRI
  - PET scan to rule out distant metastases

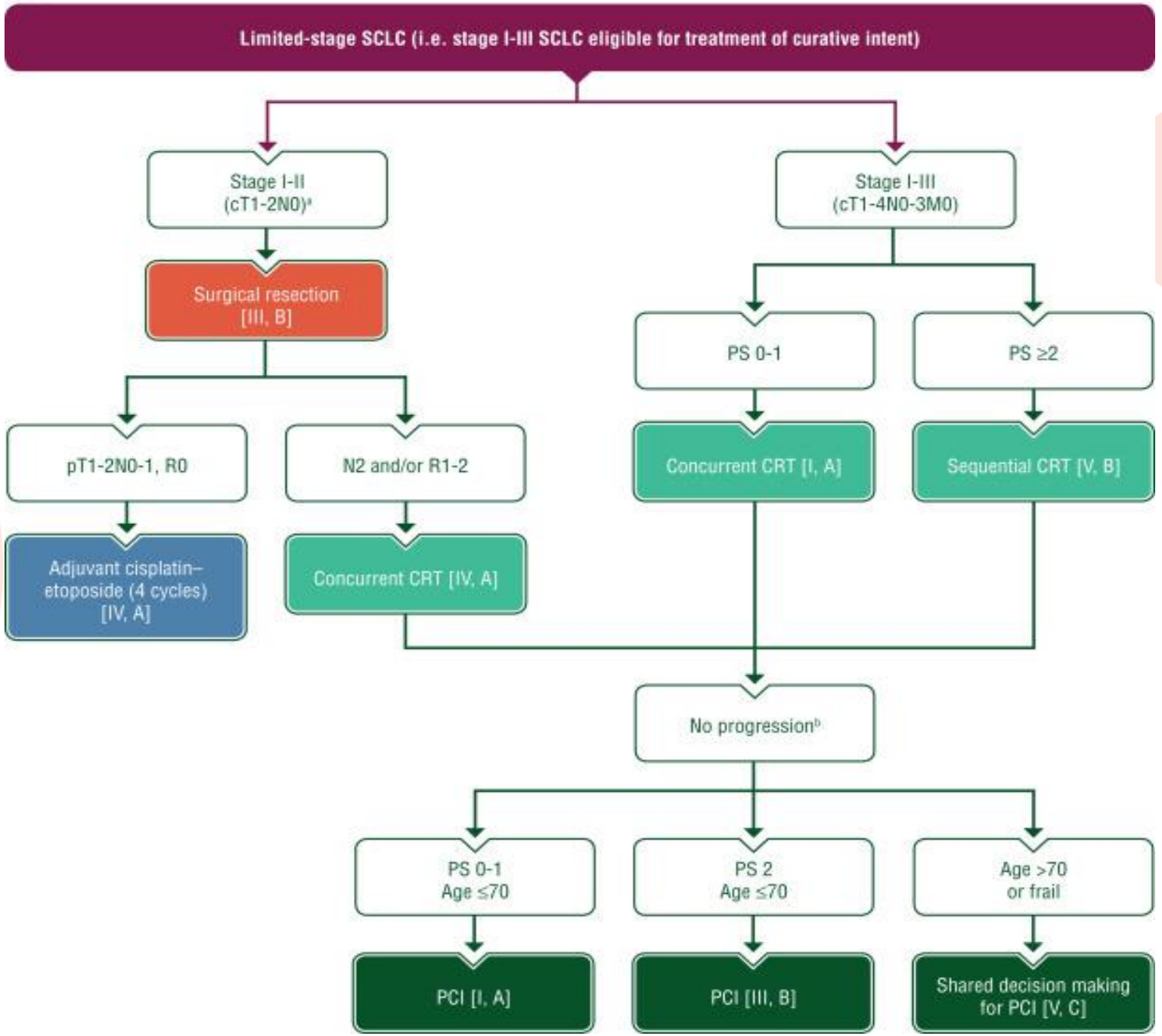
- TNM staging system vs VA staging system

TNM Staging	VA Staging	Incidence, %
T1-T2, N0, M0 (stage I)	Limited stage	~ 5
T any, N any, M0 (stage I-III)	Limited stage; disease burden contained within radiation field	~ 30
T any, N any, M1 (stage IV)	Extensive stage; disease burden beyond radiation field	~ 65

l. Cancer Imaging. 2011;11:253. Alvarado-Luna. Transl Lung Cancer Res. 2016;5:26. Sabari. Nat Rev Clin Oncol. 2017;14:549.

TRATAMIENTO RADICAL ESTADIOS I-III

A


Limited-stage SCLC (i.e. stage I-III SCLC eligible for treatment of curative intent)
Stage I-II (cT1-2N0)[a]
Surgical resection [III, B]
pT1-2N0-1, R0
N2 and/or R1-2
Adjuvant cisplatin–etoposide (4 cycles) [IV, A]
Concurrent CRT [IV, A]
Stage I-III (cT1-4N0-3M0)
PS 0-1
PS ≥2
Concurrent CRT [I, A]
Sequential CRT [V, B]
No progression[b]
PS 0-1 Age ≤70
PS 2 Age ≤70
Age >70 or frail
PCI [I, A]
PCI [III, B]
Shared decision making for PCI [V, C]

ONCOREPASO

RT/QT concomitante.

- Es **preferible el uso de cisplatino** (IA) a carboplatino (IIA).
- **Cisplatino 60-80 mg/m2** día 1 (ó 25 mg/m2 días 1-3) + **Etopósido 100-120 mg/m2** días 1-3; cada 3 semanas. **Total 4 ciclos.**
- **IMPORTANTE.** Se consideraba contraindicado el uso de **CSF** (Bunn JCO 1995) en la concomitancia, pero en un subanálisis del **estudio CONVERT** (Lung Cancer 2021) se ha demostrado no perjuicio en OS, con disminución del % de neutropenia febril.

Esquema de RT.

Los pacientes con T1-4N0-3M0 y buen PS (0-1) se deben tratar con RT/QT concurrente.

Esquema: **30 fracciones, 2 veces al día dosis total 45 Gy**. Este esquema fue superior a 25 fracciones 1 vez/día durante 5 semanas (total 45 Gy), y más recientemente igual a 66 Gy en 33 fracciones durante 6,5 semanas (ensayo **CONVERT**).

El **tratamiento debe iniciarse lo antes posible (1er o 2º ciclo**). Si el PS o comorbilidades del paciente no permiten iniciar RT de modo precoz, puede administrarse con los ciclos 3 y 4. El tratamiento secuencial es también una opción para pacientes con mal PS o gran volumen tumoral.

Irradiación craneal profiláctica (ICP o PCI).

La **PCI disminuye el riesgo de desarrollar metástasis SNC** y aumenta la supervivencia a 3 años en un 5,4 %.

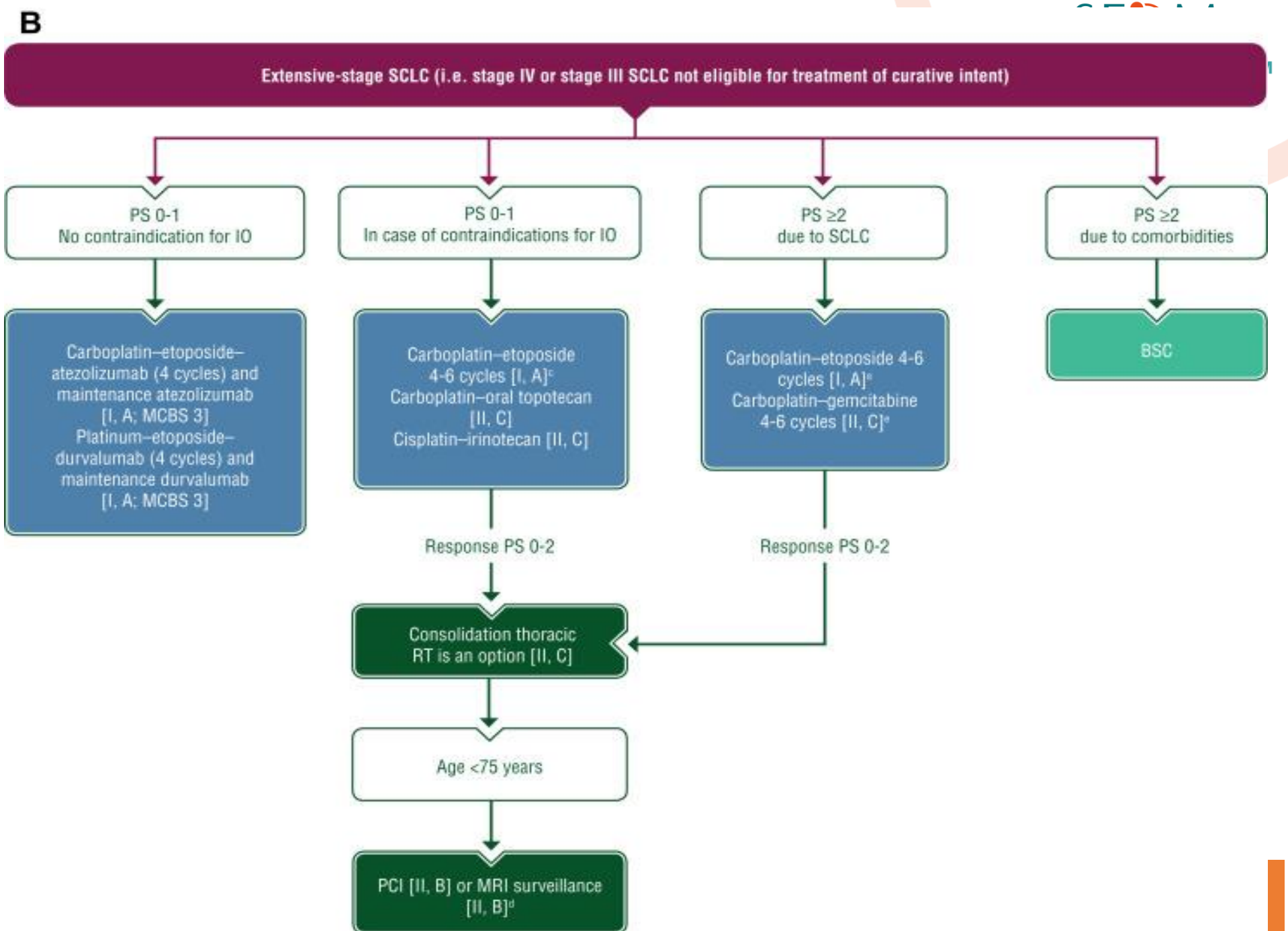
El régimen recomendado es **25 Gy en 10 fracciones.**

Se debe **ofrecer PCI a pacientes con estadio III SCLC con respuesta tras RT/QT y PS 0-1.** Se puede considerar también en pacientes con PS 2.

No está definido el papel de la PCI en pacientes con estadios I-II, mayores de 70 años o frágiles.

TRATAMIENTO NO RADICAL ESTADIOS III-IV

ONCOREPASO



SEOM
Sociedad Española
de Oncología Médica

Quimioterapia. En pacientes no elegibles para IO, el tratamiento estándar en SCLC avanzado (PS 0-1 o PS 2 debido al tumor) es **4-6 ciclos de platino + etopósido** (**EP**).

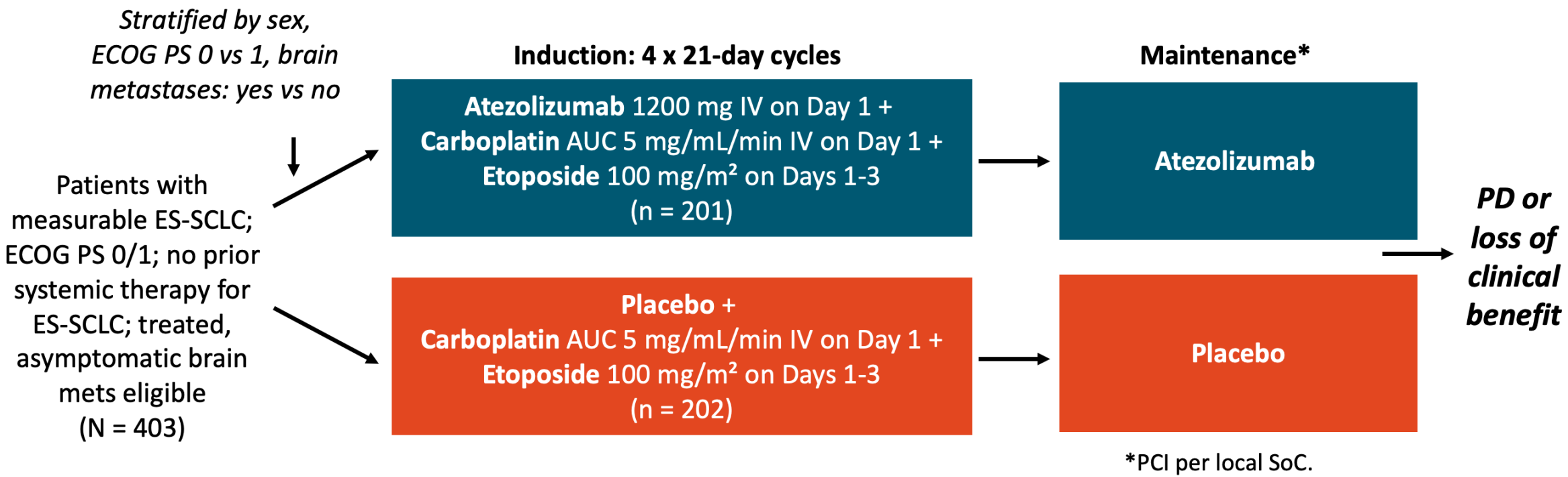
En SCLC avanzado el cisplatino se puede sustituir por carboplatino (IB) (no diferencias en un metaanálisis; cisplatino podría ser ligeramente mejor en pacientes < 70 años, pero son análisis de subgrupos).

Cisplatino con irinotecan o topotecan oral son alternativas de tratamiento (IIC).

En pacientes con mal pronóstico gemcitabina y carboplatino: alternativa de tratamiento (IIC).

IMpower133: Atezolizumab + Chemotherapy for Advanced SCLC

- Double-blind, randomized, placebo-controlled phase I/III trial



- Coprimary endpoints: OS, PFS by investigator assessment
- Secondary endpoints: ORR, DoR, safety

Liu. IASLC WCLC. 2018. Abstr PL0-207. Horn. NEJM. 2018;379:2220.

Slide credit: clinicaloptions.com

IMPOWER 133

En el análisis actualizado de supervivencia, la **mediana de la SG fue de 12,3 meses** (IC 95% = 10,8-15,8) en el grupo de atezolizumab **frente a 10,3** meses (IC 95% = 9,3-11,3) en el grupo de control (HR = 0,76, IC del 95% = 0,60-0,95, p = 0,0154), con porcentajes a los 12 y 18 meses del 51,9% vsl 39 % y del 34 % frente al 21 %.

En el análisis actualizado en 2021, la mediana de **supervivencia libre de progresión fue de 5,2 meses vs 4,3 meses** (HR = 0,77, IC del 95% = 0,63-0,95) a favor de la IO. No hubo diferencias ni en el porcentaje de respuestas ni en la mediana de duración de las mismas.

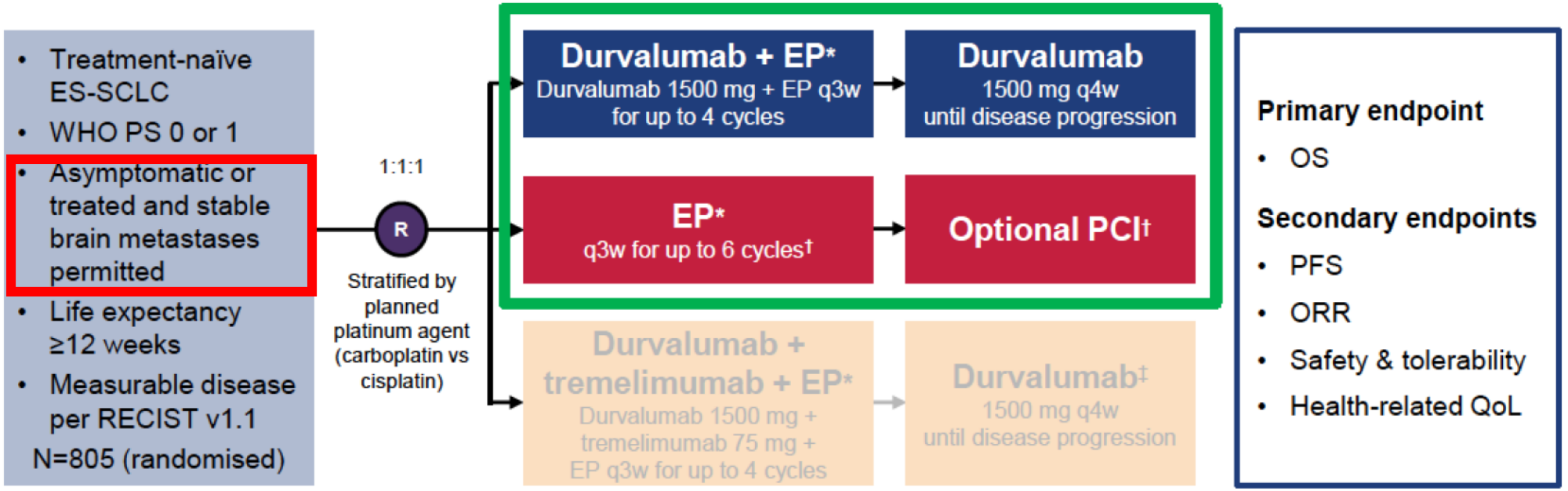
IMbrella A: extensión Impower 133, 12% supervivientes a 5 años (históricamente 2 %)

Overall survival with durvalumab plus platinum-etoposide in first-line extensive-stage SCLC: Results from the CASPIAN study

DIFERENCIAS CON IM 133: Se permite Cis o Carbo
Se permiten 6 ciclos en brazo control, y uso de PCI SOLO en este brazo

CASPIAN Study Design

Phase 3, global, randomised, open-label, sponsor-blind multicentre study



The durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

*EP consists of etoposide 80–100 mg/m² with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m²
†Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion
‡Patients received an additional dose of tremelimumab post-EP

Paz Ares WCLC 19

CASPIAN

CASPIAN: **mejoría clínica y estadísticamente significativa de la SG en comparación con EP** solo en pacientes con SCLC avanzado, con un **HR de 0,73** (IC del 95%: 0,59-0,91; p = 0,0047), objetivo principal del estudio.

Dicho beneficio también se observa en criterios de valoración secundarios como la SLP y la TR. Los datos recientemente publicados con más de 2 años de seguimiento, confirman no sólo el **beneficio** en SG, sino **en supervivencia a 12 meses:** 52,8% para los pacientes tratados con D+PE frente a 39,3% para los pacientes que reciben PE, y **la supervivencia a 24 meses** fue de 22,2% para los que recibieron D + PE frente a 14,4% alcanzado por los pacientes que recibieron PE.

ENSAYOS NEGATIVOS CON INMUNOTERAPIA

En otros 3 ensayos fase III ni Ipilimumab con EP (**Reck JCO 2016**), ni EP + Pembrolizumab (**ensayo Keynote 604**) ni Nivolumab + Ipilimumab como tratamiento de mantenimiento (**Checkmate 451**) han demostrado beneficio en supervivencia para el brazo experimental.

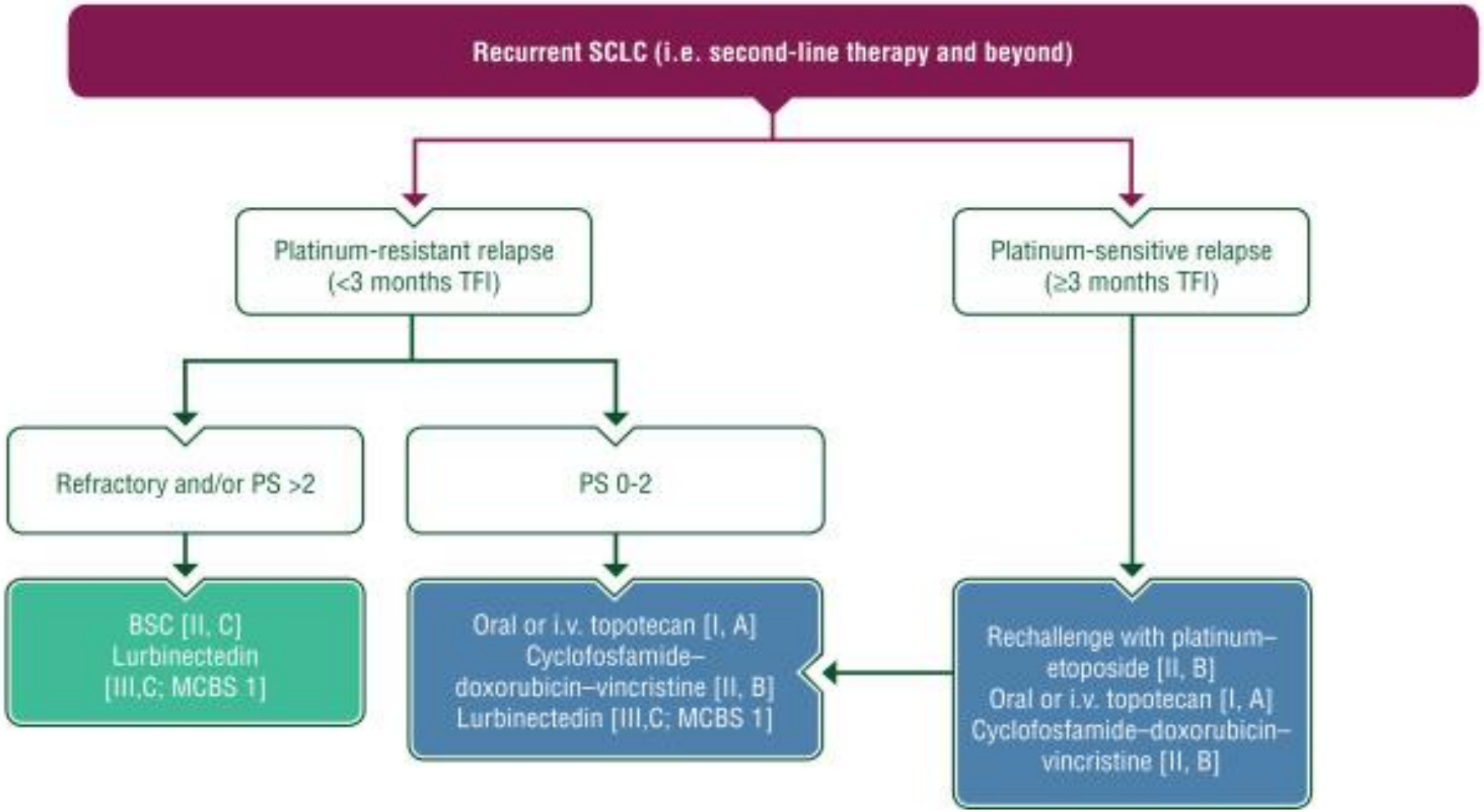
RT torácica de consolidación en SCLC metastásico.

En base a los resultados de 2 ensayos (Jeremic JCO 99 y el ensayo CREST), se puede considerar la administración de **RT torácica de consolidación en pacientes que responden al tto sistémico y con PS 0-2.**

Irradiación craneal profiláctica en SCLC avanzado.

Pacientes **PS 0-2, < 75 años, con respuesta tras QT** y sin RNM SNC de estadificación se puede plantear **PCI** (20 Gy/5 fracciones o 25/Gy en 10 fracciones) (IIB).

C


Recurrent SCLC (i.e. second-line therapy and beyond)
Platinum-resistant relapse (<3 months TFI)
Platinum-sensitive relapse (≥3 months TFI)
Refractory and/or PS >2
PS 0-2
BSC [II, C]
Lurbinectedin [III,C; MCBS 1]
Oral or i.v. topotecan [I, A]
Cyclofosfamide–doxorubicin–vincristine [II, B]
Lurbinectedin [III,C; MCBS 1]
Rechallenge with platinum–etoposide [II, B]
Oral or i.v. topotecan [I, A]
Cyclofosfamide–doxorubicin–vincristine [II, B]

ONCOREPASO. 2ª LÍNEA

Topotecan IV u oral están aprobados por la EMA como tratamiento de la enfermedad platino resistente (progresión < 3 meses desde fin de EP) o platino sensible (progresión > 3 meses). **CAV** es otra alternativa válida, con eficacia similar a topotecan, pero mayor toxicidad.

Lurbenictidina es otra opción para paciente en progresión durante o tras terapia basada en platino. En el estudio fase III **ATLANTIS** la combinación de **Lurbenictinida y doxorrubicina no** ha demostrado superioridad respecto a CAV o topotecan. La amrrubicina también fracasó en la comparación frente a Topotecan en un ensayo fase III.

En caso de enfermedad sensible al platino el **rechallenge** con EP también puede valorarse. Otros agentes como paclitaxel, irinotecan o temozolamida han conseguido porcentajes de respuestas en torno al 15-30% en ensayos fases II.

No hay datos sólidos que avalen a día de hoy el uso de **inmunoterapia en segunda o posteriores líneas** en pacientes con SCLC avanzado.

Paraneoplásicos

Table 1. Paraneoplastic Syndromes Associated With Small Cell Lung Cancer

ECTOPIC HORMONE –ASSOCIATED SYNDROMES

Clinical Syndrome	*Incidence*	*SCLC-Produced Hormone*
Ectopic Cushing syndrome	5%	ACTH
		CRH (rare)
Hyponatremia of malignancy	15%	AVP
		ANP
Hypertension	<1%	Renin
Amenorrhea, galactorrhea	<1%	prolactin, GH
Hyperamylasemia	<1%	salivary amylase

IMMUNE-MEDIATED NEUROLOGIC SYNDROMES

Clinical Syndrome	*Incidence*	*Antibody*	*SCLC-Expressed Gene/Protein*
Lambert-Eaton myasthenic syndrome (LEMS)	1%	anti-VGCC	Synaptotagmin, MysB
Encephalomyelitis	<1%	anti-Hu	HuD, HuC, Hel-N1, N2
Sensory neuronopathy	<1%	anti-Hu	HuD, HuC, Hel-N1, N2
Cerebellar degeneration	<1%	anti-Hu	HuD, HuC, Hel-N1, N2
		anti-VJCC MysB	Synaptotagmin,
		anti-Ri	Nova-1
		anti-Yo	CDR-34
Retinopathy	<1%	anti-CAR	Recoverin
Stiff-person syndrome (encephalitis)	<1%	anti-amphiphysin	Amphiphysin
Opsoclonus, myoclonus	<1%	anti-Hu,	HuD, HuC, Hel-N1, N2
		anti-Ri	Nova-1

Abbreviations: ACTH, adrenocorticotropic hormone; ANP, atrial natriuretic peptides; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; GH, growth hormone; VGCC, voltage-gated calcium channel.

Gandhi JNCCN 2006

Muchas gracias por vuestra atención

SEOM
Sociedad Española de Oncología Médica

OPE 2021. CARCINOMA MICROCÍTICO.

EPIDEMIOLOGÍA.

Es la forma más agresiva de cáncer de pulmón. En torno a un **15% del total de tumores de pulmón**. Alto porcentaje de respuestas a radio y quimio con resistencia precoz.

Fuerte relación con **tabaco** (en más del 95% de los casos).

Supervivencia a 5 años (todos los estadios) < 10%. Prevalencia de 1-5/10.000 en el UE.

Prevalencia similar en hombres y mujeres, pero ha aumentado en > 70 años (del 23% en 1975 al 44% en 2010). Hasta un **10% de pacientes tiene mts SNC al diagnóstico** y un 50% en la evolución de la enfermedad.

El **Screening con TAC NO** es efectivo (demostrado en 3 ensayos clínicos).

DIAGNÓSTICO/PATOLOGÍA MOLECULAR Y BIOLOGÍA.

El SCLC es un **tumor neuroendocrino de alto grado** compuesto por células tumorales que miden menos de tres linfocitos en reposo, con **escaso citoplasma**, bordes celulares mal definidos, una cromatina nuclear granular finamente dispersa y nucleolos ausentes o poco visibles.

Las **mitosis son numerosas**, con una media de 80 por área de 2 mm2, y la **necrosis es extensa**.

La transformación a SCLC es un mecanismo de resistencia conocido en el adenocarcinoma de pulmón con mutación del receptor del factor de crecimiento epidérmico (EGFR) tratado con inhibidores de la tirosina quinasa del EGFR. Ocurre en el 3%-5% de los pacientes y se asocia con **la pérdida de RB1 y TP53**.

La mayoría de los SCLC expresan de forma difusa la CD56 (tinción membranosa), mientras que la **sinaptofisina y la cromogranina A** presentan tinción citoplasmática en el 54% y el 37% de los casos, respectivamente. La expresión de la CD56 se considera el marcador más sensible pero menos específico. El factor de transcripción tiroidea 1 (TTF1) se expresa en el 90% de los SCLC y **>50% de los núcleos se tiñen positivamente para Ki-67**.

Casi todos los SCLC tienen **mutaciones de pérdida de función tanto de TP53 como de RB1**.

Una reciente revisión de consenso ha propuesto una clasificación **molecular del SCLC en 4 subtipos: SCLC-A, -N, -P y -Y**, para los subtipos con expresión dominante de ASCL1, NEUROD1, POU2F3 y YAP1, respectivamente.

Aunque se necesitan más estudios, los datos disponibles de los ensayos IMpower133, CASPIAN y KEYNOTE-158 y -028 no apoyan la evaluación de la tinción de PD-L1 como biomarcador predictivo de la eficacia de la inmunoterapia. Tampoco hay datos que soporten la utilidad de la MTB.

ESTADIFICACIÓN Y FACTORES PRONÓSTICOS.

Como **factores pronósticos desfavorable**s en pacientes SCLC se incluye:

- **Mal PS, pérdida de peso.**

- **Edad avanzada, sexo masculino**.
- **LDH elevada**.
- **Hiponatremia** (en relación con SIADH).

Además, un **gran volumen tumoral** en los pacientes que se tratan con radioquimioterapia se relaciona también con peor pronóstico.

En la **tabla 1** se recogen los principales puntos a considerar en el diagnóstico/estadificación:

Table 1. Diagnostic and staging work-up of SCLC

History and clinical examination
Medical history (including smoking history and comorbidities)
PS
Physical examination
Assessment of paraneoplastic syndromes (especially when initiating immunotherapy)
Laboratory analysis
CBC, liver enzymes, sodium, potassium, calcium, glucose, LDH and renal functions tests should be carried out
Imaging
CT of the thorax and abdomen should be carried out in all patients; an FDG—PET—CT is optional
In case of a suspicion of bone metastasis and no other metastasis, a bone scintigraphy should be carried out unless FDG—PET is available
Imaging of the brain (preferably MRI) is mandated in patients with stage I-III disease
MRI of the brain is recommended for patients with stage IV disease who are eligible for PCI but who choose not to undergo PCI
Tumour biopsy
A diagnosis of SCLC is preferably assessed based on histological examination of a biopsy
In case of planned surgery, invasive mediastinal staging is required
Functional assessment
Pulmonary function testing (FEV1, VC, DLCO) is required for patients with stage I-III SCLC who are candidates for surgery or RT
VO2 max assessment by cycle ergometry should be carried out if surgery is planned when pulmonary function tests are limited

La estadificación hay que realizarla siguiendo la **8ª edición del TNM** (no por EL y EE).

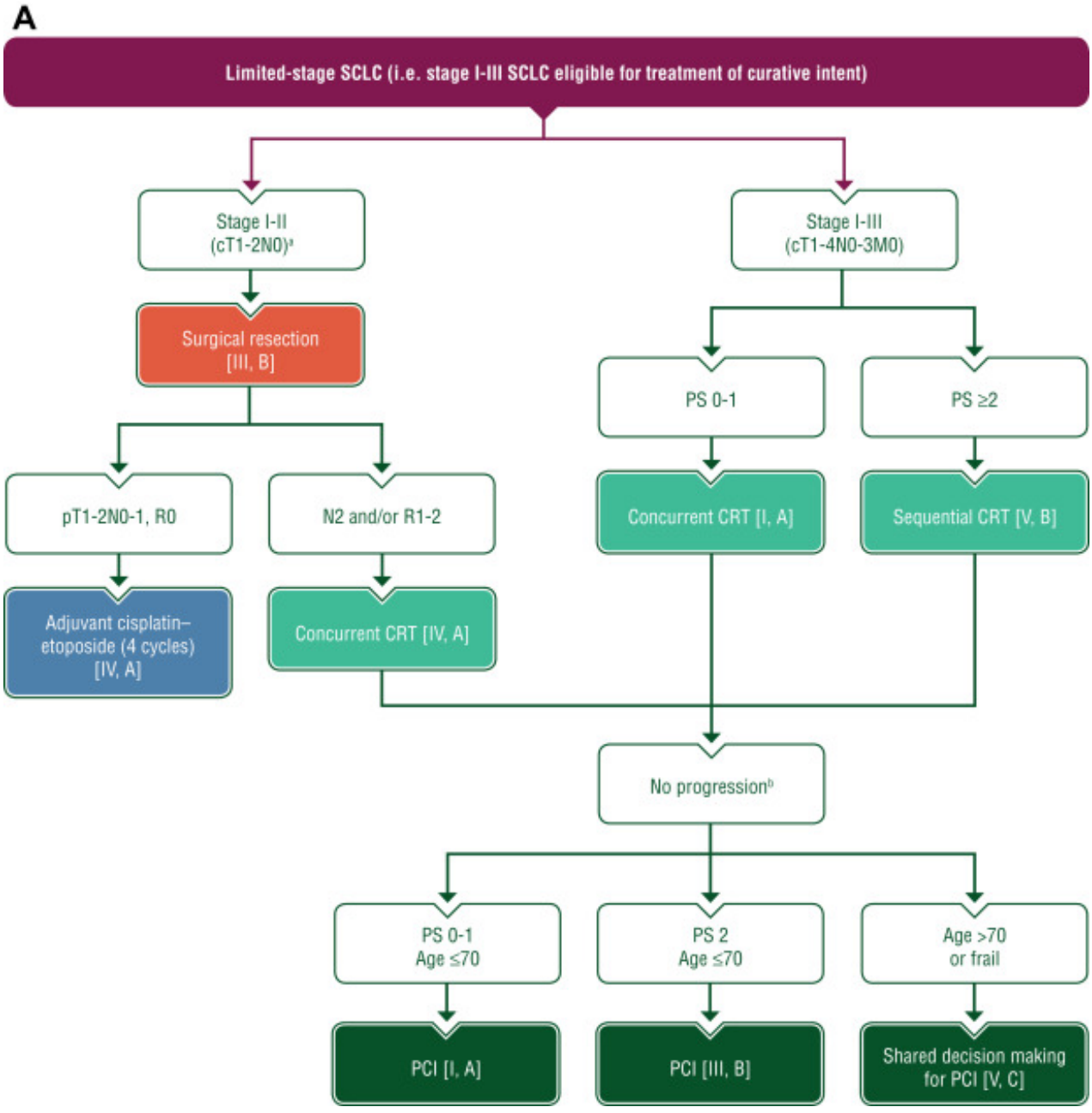
Es importante recordar que la realización del **PET-TAC es opcional**, puede ser útil en pacientes que se van a tratrar con radioquimioterapia (para descartar metástasis a distancia y para ayudar a planificar la radioterapia). Si el plan terapéutico cambia en función de los hallazgos del PET-TAC se recomienda **biopsiar las localizaciones sospechosas de metástasis.**

La **biopsia de MO** solo se recomienda en caso de que se sospeche y se quiera confimar invasión de la misma. La prueba gold estándar para el **estudio del SNC es la RMN;** se acepta realización de TAC si no está disponible.

TRATAMIENTO.

Dividimos este apartado en 2 partes, el manejo de la enfermedad estadio I-III susceptible de tratamiento radical, y la enfermedad estadio IV o III no radical.

1. **SCLC estadio I-III con intención radical.**



Papel de la cirugía. Aunque historicamente no se ha considerado la cirugía como tratamiento de elección en estadios I-II, en datos retrospectivos y de bases de pacientes se ha comunicado beneficio en supervivencia comparando con la estrategia de RT/QT. Por tanto, aunque no hay datos sólidos, se acepta el **uso de la cirugía en estadios**

iniciales cuando sea factible la resección R0, que debe acompañarse siempre de un **estudio del mediastino prequirúrgico y de una linfadenectomía sistemática**. Se debe considerar **QT adyuvante** en tumores pT1-2N0-1R0, **y QT + RT** en N2 y/o R1-2 (importante, recordad que la **RT adyuvante no está actualmente indicada en NSCLC**, salvo rotura capsular).

RT/QT concomitante.

- Es **preferible el uso de cisplatino** (IA) a carboplatino (IIA).
- **Cisplatino 60-80 mg/m2** día 1 (ó 25 mg/m2 días 1-3) + **Etopósido 100-120 mg/m2** días 1-3; cada 3 semanas. **Total 4 ciclos.**
- **IMPORTANTE.** Se consideraba contraindicado el uso de **CSF** (Bunn JCO 1995) en la concomitancia, pero en un subanálisis del **estudio CONVERT** (Lung Cancer 2021) se ha demostrado no perjuicio en OS, con disminución del % de neutropenia febril.

Esquema de RT.

Los pacientes con T1-4N0-3M0 y buen PS (0-1) se deben tratar con RT/QT concurrente.

El esquema recomendado es **30 fracciones, 2 veces al día dosis total 45 Gy (**Turrisi N Eng J Med 1999**)**. Este esquema fue superior en supervivencia a 2 y 5 años respecto a 25 fracciones 1 vez/día durante 5 semanas (total 45 Gy). Más recientemente se comparó con **66 Gy en 33 fracciones** durante 6,5 semanas (ensayo **CONVERT** Falvre-Finn Lancel Oncol 2017), con resultados similares en toxicidad, y supervivencia del 56% y 51% a 2 años para el hiperfraccionamiento y normofraccionamiento, respectivamente (diferencias estadísticamente no significativas).

El t**ratamiento debe iniciarse lo antes posible (1er o 2º ciclo**). Si el PS o cormobilidades del paciente no permiten iniciar RT de modo precoz, puede administrarse con los ciclos 3 y 4. El tratamiento secuencial es también una opción para pacientes con mal PS o gran volumen tumoral.

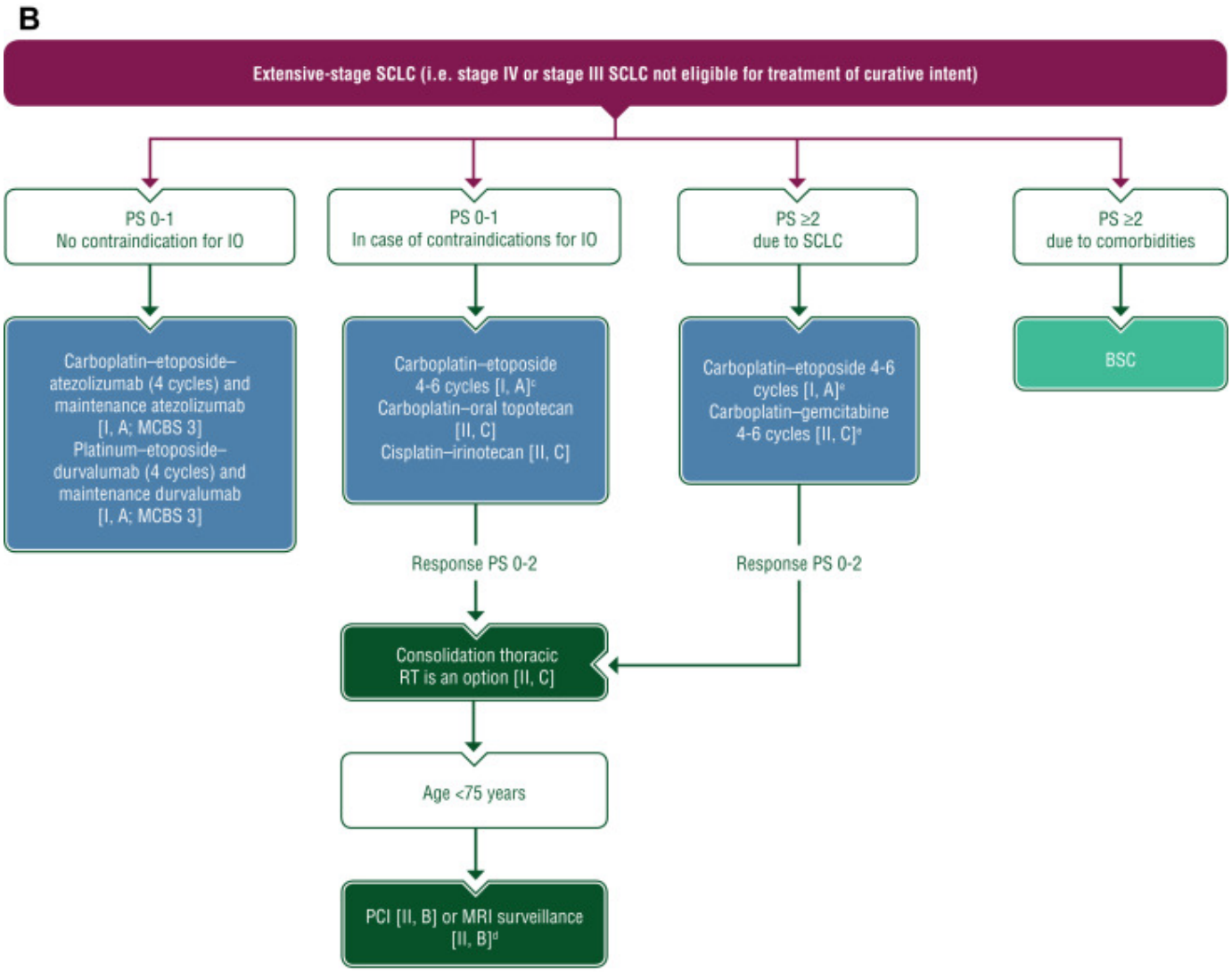
Irradiación Craneal Profiláctica (PCI).

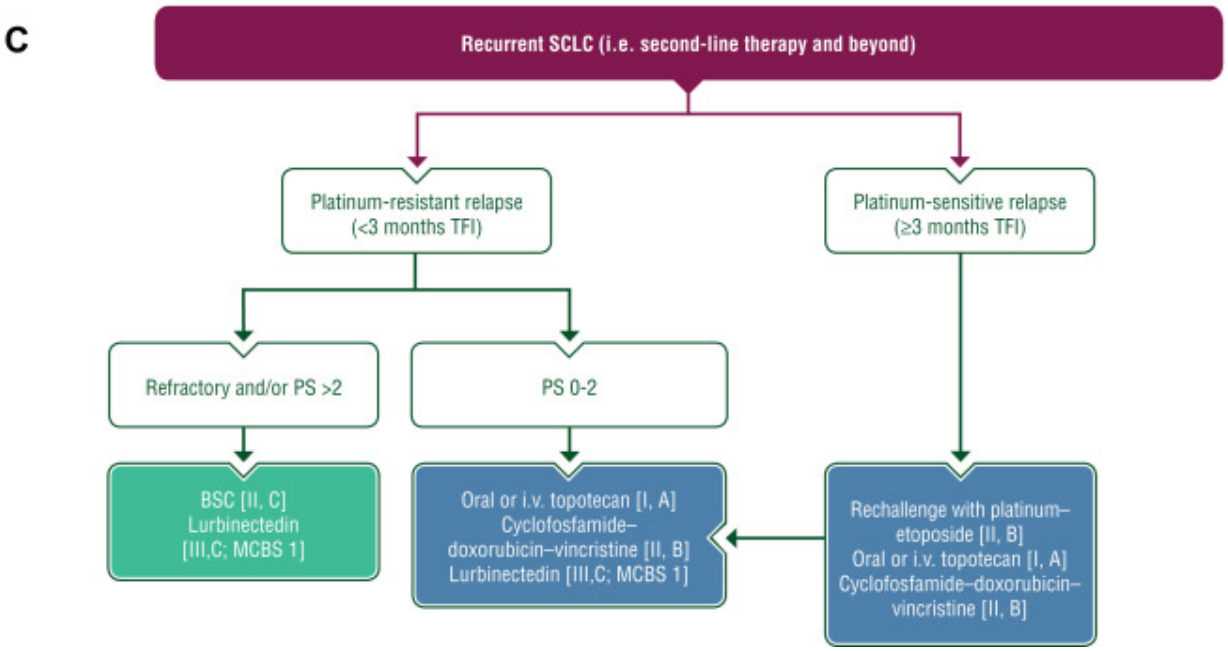
La **PCI disminuye el riesgo de desarrollar metástasis SNC** y aumenta la supervivencia a 3 años en un 5,4 %. El régimen recomendado es **25 Gy en 10 fracciones**.

Se debe **ofrecer PCI a los pacientes con estadio III SCLC con respuesta tras RT/QT y PS 0-1**. Se puede considerar también en pacientes con PS 2. No está definido el papel de

la PCI en pacientes con estadios I-II, paciente frágiles, con deterioro cognitivo o mayores de 70 años.

2. SCLC III (no susceptible tto radical) o IV.





a) Primera línea en enfermedad avanzada.

Quimioterapia. En pacientes no elegibles para IO, el tratamiento estándar en SCLC avanzado (PS 0-1 o PS 2 debido al tumor) es **4-6 ciclos de platino + etopósido** (**EP**).

En SCLC avanzado el cisplatino se puede sustituir por carboplatino (IB) (no diferencias en un metaanálisis; cisplatino podría ser ligeramente mejor en pacientes < 70 años, pero son análisis de subgrupos).

Cisplatino con irinotecan o topotecan oral son alternativas de tratamiento (IIC).

En pacientes con mal pronóstico gemcitabina y carboplatino es una alternativa de tratamiento (IIC).

Inmunoterapia. En los últimos años 2 ensayos fases III aleatorizados han demostrado beneficio con el uso de inmunoterapia en primera línea. En el ensayo doble ciego **IMpower 133**, se aleatorizaron 403 pacientes a recibir atezolizumab más **carboplatino**/etopósido (n = 201) o placebo más carboplatino/etopósido (n = 202). El tratamiento consistió en **4 ciclos** cada 21 días de carboplatino (AUC = 5 día 1) más etopósido (100 mg/m2 días 1-3) más atezolizumab (1.200 mg día 1) o placebo, y se continuó con atezolizumab o placebo de mantenimiento.

En el análisis actualizado de la supervivencia global, la **mediana de la SG fue de 12,3 meses** (IC 95% = 10,8-15,8) en el grupo de atezolizumab **frente a 10,3** meses (IC 95% = 9,3-11,3) en el grupo de control (HR = 0,76, IC del 95% = 0,60-0,95, p = 0,0154), con porcentajes a los 12 y 18 meses del 51,9% vsl 39 % y del 34 % frente al 21 %. En el **IMbrellaA trial** (Liu, Mundial Pulmón 23) se continuó el seguimiento de los pacientes tratados con Atezoliozumab x 2 años en el IMpower133, con un 12% de supervivientes a 5 años (historicamente alcanzaban 5 años un 2%).

En el análisis actualizado en 2021, la mediana de **supervivencia libre de progresión fue de 5,2 meses vs 4,3 meses** (HR = 0,77, IC del 95% = 0,63-0,95) a favor de la IO. No hubo diferencias ni en el porcentaje de respuestas ni en la mediana de duración de las mismas.

Los **acontecimientos adversos** relacionados con la inmunidad (**EAirs**) que requirieron tratamiento con corticosteroides sistémicos se produjeron en el 20,2% frente al 5,6% de los pacientes. Los EAirs más frecuentes fueron la erupción cutánea (20,2% vs 10,7%), el hipotiroidismo (12,6% vs 0,5%), la hepatitis (7,6% vs

4,6%) y las reacciones relacionadas con la infusión (5,6% vs 5,1%); la neumonitis se produjo en el 2,5% frente a 2,6% de los pacientes.

El estudio **CASPIAN** ha demostrado que el tratamiento de primera línea con **Durvalumab + EP** (**tanto cisplatino como carboplatino, en el IMpower solo se aceptaba carbo**) se asocia con una **mejoría clínica y estadísticamente significativa de la SG en comparación con EP** en pacientes con SCLC avanzado, con un **HR de 0,73** (IC del 95%: 0,59-0,91; p = 0,0047), objetivo principal del estudio. Dicho beneficio también se observa en criterios de valoración secundarios como la SLP y la TR. Los datos recientemente publicados con más de 2 años de seguimiento, confirman no sólo el **beneficio** en SG, sino **en supervivencia a 12 meses:** 52,8% para los pacientes tratados con D+PE frente a 39,3% para los pacientes que reciben PE, y **la supervivencia a 24 meses** fue de 22,2% para los que recibieron D + PE frente a 14,4% alcanzado por los pacientes que recibieron PE.

El beneficio es consistente en todos los subgrupos, incluidos pacientes con metástasis cerebrales en el momento basal. Los hallazgos de seguridad fueron consistentes con los perfiles de seguridad establecidos de D y EP, y la mayoría de los EAirs fueron de bajo grado y manejables con las pautas de tratamiento estándar. La combinación de D+PE debe considerarse una opción terapéutica recomendada para pacientes con SCLC avanzado ECOG 0-1 que no han recibido tratamiento previo y sin contraindicaciones para recibir inmunoterapia.

En otros 3 ensayos fase III ni Ipilimumab con EP (**Reck JCO 2016**), ni EP + Pembrolizumab (**ensayo Keynote 604**) ni Nivolumab + Ipilimumab como tratamiento de mantenimiento (**Checkmate 451**) han demostrado beneficio en supervivencia para el brazo experimental.

RT torácica de consolidación en SCLC metastásico.

En base a los resultados de 2 ensayos (Jeremic JCO 99 y el ensayo CREST), se puede considerar la administración de **RT torácica de consolidación en pacientes que responden al tto sistémico y con PS 0-2.**

Irradiación craneal profiláctica en SCLC avanzado.

En pacientes con **PS 0-2, < 75 años, con respuesta tras quimioterapia** y sin RNM SNC de estadificación se puede plantear la administración de **PCI** (20 Gy/5 fracciones o 25/Gy en 10 fracciones) (IIB).

En **pacientes** sin metástasis SNC en la RNM tras QT y **que pueden realizar seguimiento con RNM periódicas se puede omitir PCI** (IIB).

No disponemos de datos suficientes sobre el uso de PCI o radioterapia de consolidación en pacientes SCLC metastásico que hayan recibido inmunoterapia, peor en la clínica hay una tendencia a monitorizar de modo más estrecho y evitarla.

b) Segunda y posteriores líneas.

Tratamiento estándar.

Topotecan IV u oral están aprobados por la EMA como tratamiento de la enfermedad platino resistente (progresión < 3 meses desde fin de EP) o platino sensible (progresión > 3 meses). **CAV** es otra alternativa válida, con eficicacia similar a topotecan, pero mayor toxicidad.

Lurbenictidina es otra opción para paciente en progresión durante o tras terapia basada en platino. En el estudio fase III **ATLANTIS** la combinación de **Lurbenictinida y doxorrubicina** no ha demostrado superioridad respecto a CAV o topotecan. La amrrubicina también fracasó en la comparación frente a Topotecan en un ensayo fase III.

En caso de enfermedad sensible al platino el **rechallenge** con EP también puede valorarse. Otros agentes como paclitaxel, irinotecan o temozolamida han conseguido porcentajes de respuestas en torno al 15-30% en ensayos fases II.

No hay datos sólidos que avalen a día de hoy el uso de **inmunoterapia en segunda o posteriores líneas** en pacientes con SCLC avanzado.

ESMO-MCBS table for new therapies/indications in SCLC

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/ toxicity	ESMO-MCBS score[a]
Atezolizumab + carboplatin and etoposide	First-line treatment of extensive-stage SCLC	A study of carboplatin plus etoposide with or without atezolizumab in participants with untreated extensive-stage SCLC (IMpower133)[25,39,40] Phase III NCT02763579	Placebo + carboplatin and etoposide Median PFS: 4.3 months Median OS: 10.3 months	PFS gain: 0.9 months OS gain: 2.0 months	PFS HR: 0.77 (0.62-0.96) OS HR: 0.76 (0.60-0.95)	Benefit for delayed deterioration in global QoL not significant	3 (Form 2a)
Durvalumab + etoposide and cisplatin or carboplatin	First-line treatment of extensive-stage SCLC	Durvalumab ± tremelimumab in combination with platinum-based ChT in untreated extensive-stage SCLC (CASPIAN)[41-43] Phase III NCT03043872	Platinum + etoposide Median OS: 10.5 months	OS gain: 2.4 months	OS HR: 0.75 (0.62-0.91)	Benefit for delayed deterioration in global QoL not significant	3 (Form 2a)
Lurbinectedin	Metastatic (SCLC) with disease progression on or after platinum-based ChT	Lurbinectedin as second-line treatment for patients with small-cell lung cancer (PM1183-B-005-14)[44] Phase II NCT02454972	Single arm (no control)		ORR: 35.2% DoR: 5.3 months PFS: 3.5 months		1 (Form 3)

SÍNDROMES PARANEOPLÁSICOS ASOCIADOS CON EL SCLC

(Gandhi JNCCN 2006)

Table 1. Paraneoplastic Syndromes Associated With Small Cell Lung Cancer

ECTOPIC HORMONE –ASSOCIATED SYNDROMES

Clinical Syndrome	*Incidence*	*SCLC-Produced Hormone*
Ectopic Cushing syndrome	5%	ACTH
		CRH (rare)
Hyponatremia of malignancy	15%	AVP
		ANP
Hypertension	<1%	Renin
Amenorrhea, galactorrhea	<1%	prolactin, GH
Hyperamylasemia	<1%	salivary amylase

IMMUNE-MEDIATED NEUROLOGIC SYNDROMES

Clinical Syndrome	*Incidence*	*Antibody*	*SCLC-Expressed Gene/Protein*
Lambert-Eaton myasthenic syndrome (LEMS)	1%	anti-VGCC	Synaptotagmin, MysB
Encephalomyelitis	<1%	anti-Hu	HuD, HuC, Hel-N1, N2
Sensory neuronopathy	<1%	anti-Hu	HuD, HuC, Hel-N1, N2
Cerebellar degeneration	<1%	anti-Hu	HuD, HuC, Hel-N1, N2
		anti-VJCC MysB	Synaptotagmin,
		anti-Ri	Nova-1
		anti-Yo	CDR-34
Retinopathy	<1%	anti-CAR	Recoverin
Stiff-person syndrome (encephalitis)	<1%	anti-amphiphysin	Amphiphysin
Opsoclonus, myoclonus	<1%	anti-Hu,	HuD, HuC, Hel-N1, N2
		anti-Ri	Nova-1

Abbreviations: ACTH, adrenocorticotropic hormone; ANP, atrial natriuretic peptides; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; GH, growth hormone; VGCC, voltage-gated calcium channel.

CLASIFICACIÓN TNM 8ª EDICIÓN	
T – primary tumour	
TX	Primary tumour cannot be assessed or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*[a]
T1	Tumour ≤3 cm in the greatest dimension surrounded by lung or visceral pleura and without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)[b] T1mi Minimally invasive adenocarcinoma[c] T1a Tumour ≤1 cm in the greatest dimension[b] T1b Tumour >1 cm but ≤2 cm in the greatest dimension[b] T1c Tumour >2 cm but ≤3 cm in the greatest dimension[b]
T2	Tumour >3 cm but ≤5 cm, or a tumour with any of the following features:[d] ● Involves main bronchus regardless of distance to the carina but without involvement of the carina ● Invades visceral pleura ● Associated with atelectasis or obstructive pneumonitis that extends to the hilar region either involving part of or the entire lung T2a Tumour >3 cm but ≤4 cm in the greatest dimension T2b Tumour >4 cm but ≤5 cm in the greatest dimension

T3	Tumour >5 cm but ≤7 cm in the greatest dimension or one that directly invades any of the following: parietal pleura, chest wall (including superior sulcus tumours) phrenic nerve, parietal pericardium or separate tumour nodule(s) in the same lobe as the primary
T4	Tumour >7 cm or of any size that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina or separate tumour nodule(s) in a different ipsilateral lobe to that of the primary
N – regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peri-bronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)
M – distant metastasis	
M0	No distant metastasis
M1	Distant metastasis M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodules or malignant pleural or pericardial effusion[e] M1b Single extrathoracic metastasis in a single organ[f] M1c Multiple extrathoracic metastasis in a single organ or multiple organs

Occult carcinoma	X	0	0
0	Is	0	0
IA	1	0	0
IA1	1mi 1a	0	0
IA2	1b	0	0
IA3	1c	0	0
IB	2a	0	0
IIA	2b	0	0
IIB	1a-c, 2a,b 3	1 0	0 0
IIIA	1a-c, 2a,b 3 4	2 1 0, 1	0 0 0
IIIB	1a-c, 2a,b 3, 4	3 2	0 0
IIIC	3, 4	3	0
IV	Any	Any	1
IVA	Any	Any	1a, 1b
IVB	Any	Any	1c

EXAMENES OPE. MICROCÍTICO.

1. MURCIA 2014-2016 (3/150 preguntas).

9. En relación al carcinoma microcítico de pulmón, señale la respuesta incorrecta:

A) La supervivencia global es de unos 14 meses en la enfermedad limitada y de unos 9 meses en la enfermedad extendida.
B) La segunda línea aprobada de quimioterapia es topotecan, que obtiene un 20-40% de respuestas.
C) Temozolomida ha mostrado también eficacia en segundas y terceras líneas.
D) El tratamiento en ancianos puede realizarse con etopósido en monoterapia con resultados similares a los obtenidos con dobletes en pacientes jóvenes.

RESPUESTA: D

110. En relación al carcinoma microcítico de pulmón, señale la respuesta incorrecta:

A) Existe en prácticamente todos los casos activación de los genes supresores TP53 y RB-1.
B) Al diagnóstico, aproximadamente el 70% de los pacientes presentan enfermedad extendida.
C) La inmunoterapia con nivolumab con o sin ipilimumab en ensayos fase 1-2 ha promovido el desarrollo de ensayos fases 3.
D) La toxicidad Grado 3-4 en los pacientes tratados en el ensayo fase 1-2 de inmunoterapia (CheckMate 032) varía del 0 al 30%.

RESPUESTA: A

147. En relación al carcinoma de pulmón, señale la respuesta incorrecta:

A) La hipercalcemia paraneoplásica se asocia más frecuentemente al carcinoma epidermoide de pulmón.
B) La osteoartropatía hipertrófica pulmonar es más frecuente en el adenocarcinoma.
C) La acroqueratosis paraneoplásica (síndrome de Bazex) asociada al cáncer de pulmón es más frecuente en el carcinoma de células escamosas.
D) En el cáncer de pulmón, el *eritema gyratum repens* se ha asociado principalmente al carcinoma microcítico de pulmón.

RESPUESTA: D

2. CANARIAS (5/160 preguntas).

34.- ¿Cuál de los siguientes parámetros analíticos es el más importante predictor de mal pronóstico en el cáncer de pulmón microcítico?

A) Cromogranina.
B) LDH
C) CA 15.3
D) Enolasa.

RESPUESTA: B

58.- De las siguientes localizaciones anatómicas, indique la más frecuentemente afectada en el cáncer de pulmón microcítico

A) Tejido subcutáneo.
B) Pulmón contralateral.
C) Médula ósea.
D) Ganglios linfáticos mediastínicos

RESPUESTA: D

79.- El tratamiento quimioterápico de elección del cáncer de pulmón microcítico es, en general, la combinación de cisplatino carboplatino-etopósido. ¿Qué otro fármaco antineoplásico puede asociarse a los platinos en lugar del etopósido con una eficacia similar?

A) Adriamicina.
B) Irinotecán.
C) Ciclofosfamida.
D) Topotecán

RESPUESTA: B

134.- Paciente de 45 años, con un performance status de 1, fue diagnosticado de un cáncer de pulmón microcítico diseminado. Tras tratamiento con etopósido y cisplatino, el paciente presentó una respuesta completa. Actualmente, a los 4 meses, se objetiva una recidiva de su enfermedad diseminada. ¿Cuál de los siguientes fármacos en monoterapia administraría como tratamiento de segunda línea?

A) Cisplatino
B) Topotecán
C) Adriamicina.
D) Gemcitabina

RESPUESTA: B

153.- En el cáncer de pulmón microcítico ¿cuál de las siguientes afirmaciones no es correcta?

A) El tabaco aumenta su incidencia
B) El estado general del paciente es un factor pronóstico importante
C) Las mujeres tienen peor pronóstico que los hombres
D) El síndrome de vena cava superior es una urgencia oncológica

RESPUESTA: C

3. ANDALUCÍA_2015 (3/153 preguntas).

25 En relación al tratamiento del carcinoma microcítico de pulmón enfermedad limitada, señale la que NO corresponda:

A) En pacientes con enfermedad limitada se recomienda tratamiento con quimioterapia y radioterapia concomitante

B) Es necesario el uso de GCSF durante la concomitancia

C) Las mujeres tienen mejor pronóstico

D) El aumento de LDH es un factor pronóstico desfavorable

RESPUESTA: B

54 En un paciente varón de 55 años que presenta una adenopatía supraclavicular derecha, el diagnóstico histológico de la biopsia es tumor de origen desconocido. El estudio inmunohistoquímico aportado por el patólogo es: CD45 negativo, p40 negativo, cromogranina positivo, sinaptofisina positivo, TTF-1 positivo, HMB-45 negativo. ¿cuál crees que sería la orientación diagnóstica mas probable?

A) Carcinoma epidermoide de origen ORL

B) Linfoma de alto grado

C) Melanoma

D) Carcinoma de células pequeñas

RESPUESTA: D

61 En el Tratamiento del Cáncer Microcítico de Pulmón una de las siguientes afirmaciones es Falsa:

A) La Radio-Quimioterapia concurrente aumenta la mielotoxicidad

B) Los esquemas con Carboplatino son más mielotóxicos que con Cisplatino

C) Se deben asociar factores estimuladores de colonias durante el tratamiento concurrente como profilaxis primaria

D) Carboplatino y Cisplatino han demostrado similar eficacia en el tratamiento del cáncer microcítico de pulmón

RESPUESTA: C

4. GALICIA 2016 (4/110 preguntas).

30. El carcinoma de pulmón de célula pequeña (CPCP) se asocia a síndromes paraneoplásicos neurológicos y endocrinos. En relación a la hiponatremia en el CPCP, ¿cuál de las siguientes afirmaciones es falsa?

A) En pacientes con CPCP, el síndrome de secreción inadecuada de ADH (SIADH) es más frecuente que el síndrome de Cushing

B) La hiponatremia puede estar causada por el tratamiento con quimioterapia (p.e. cisplatino) y/o el tratamiento de soporte (p.e. opioides)

C) El tratamiento del SIADH incluye la restricción hídrica y fármacos como la demeclociclina o los inhibidores del receptor de ADH (p.e. tolvaptan)

D) Los niveles séricos de ADH y sodio generalmente empeoran con el tratamiento con quimioterapia del CPCP

RESPUESTA: D

51. ¿Cuál de las siguientes afirmaciones en relación al carcinoma de pulmón de célula pequeña (CPCP) es falsa?:

A) El CPCP representa aproximadamente el 15% de todos los carcinomas de pulmón

B) El CPCP se caracteriza por un tiempo de duplicación rápido, una fracción de crecimiento alta y el desarrollo precoz de metástasis a distancia

C) La cirugía es el tratamiento estándar en pacientes con CPCP enfermedad limitada y diagnóstico anatomopatológico previo confirmado

D) En pacientes con CPCP enfermedad extensa la quimioterapia podría paliar los síntomas ocasionados por la neoplasia y prolongar la supervivencia en la mayoría de los pacientes

RESPUESTA: C

57. Un varón de 65 años, fumador de 80 paquetes-año y sin morbilidad asociada, consulta por un cuadro de tos no productiva y disnea de esfuerzo. La radiografía de tórax muestra una masa mediastínica, y tras completar los estudios, es diagnosticado de un carcinoma de pulmón de célula pequeña (CPCP) con metástasis hepáticas. La RMN de Sistema Nervioso Central (SNC) no evidencia enfermedad intracraneal. En relación a este caso clínico, ¿qué afirmación es verdadera?:

A) Según los resultados de The National Lung Screening Trial (NLST) que demuestran que el cribado con TC torácico anual a baja dosis de radiación es útil en el diagnóstico del CPCP enfermedad limitada, el paciente debería haber participado en un programa de cribado

B) El tratamiento con carboplatino es una alternativa al cisplatino debido a que se asocia un menor riesgo de emesis, nefrotoxicidad y neuropatía, con una eficacia similar

C) El uso de quimioterapia de mantenimiento más allá de 4 o 6 ciclos del tratamiento estándar prolonga la supervivencia

D) El riesgo de desarrollar metástasis en SNC es bajo (inferior al 10%) y por este motivo la irradiación holocraneal profiláctica no está indicada

RESPUESTA: B

93. En relación con el carcinoma de pulmón de célula pequeña (CPCP) y la presencia de metástasis en Sistema Nervioso Central (SNC), ¿qué afirmación es falsa?:

A) Las metástasis en SNC ocurren en menos del 10% de los pacientes con CPCP

B) Ensayos clínicos randomizados han demostrado que la irradiación holocraneal profiláctica disminuye la incidencia de metástasis en el SNC

C) La irradiación holocraneal profiláctica no está recomendada en pacientes con mal performance status (PS-ECOG 3-4)

D) La irradiación holocraneal profiláctica no está recomendada en pacientes con deterioro de las funciones neurocognitivas

RESPUESTA: A

5. ARAGON 2017 (4/110 PREGUNTAS).

43 Una de estas afirmaciones referidas al carcinoma microcítico de pulmón NO es correcta:

A: Su incidencia ha ido disminuyendo progresivamente hasta situarse en el 15% aproximadamente.
B: El 99% de los casos se diagnostican en pacientes con antecedentes de consumo de tabaco.
C: No se estadifican de acuerdo con el sistema TNM.
D: Más del 60% de los casos corresponden a enfermedad diseminada en el momento del diagnóstico.

RESPUESTA: C

50 ¿Cuál de los siguientes tumores se asocia con mayor frecuencia a síndromes paraneoplásicos neurológicos?

A: Carcinoma de mama.
B: Carcinoma'de colon.
C: Carcinoma microcitico de pulmón.
D: Glioblastoma multiforme.

RESPUESTA: C

101 Ante un caso de hiponatremia severa (Na < 120 mmol/L) la primera maniobra terapéutica de urgencia debe ser:

A: Quimioterapia si la enfermedad de base es un cáncer microcítico de pulmón.
B: Tolvaptan.
C: Suero glucosalino.
D: Suero salino hipertónico (3%).

RESPUESTA: D

106 Las metástasis cerebrales son un problema frecuente en el carcinoma microcítico de pulmón. Una de las siguientes afirmaciones NO es correcta.

A: La irradiación craneal profiláctica en enfermedad limitada tras respuesta parcial o completa está indicada salvo mal estado general o deterioro cognitivo.
B: En la enfermedad diseminada el beneficio de la irradiación craneal profiláctica tiene igual evidencia que en la enfermedad limitada.
C: La resonancia magnética es más sensible que el escáner para detectar metástasis cerebrales.
D: En el tratamiento de las metástasis cerebrales sintomáticas la dosis más habitual son 30Gy repartidos en 10 sesiones.

RESPUESTA: B

6. ANDALUCÍA 2017 (1/153 preguntas)

51 La neuropatía autonómica se asocia con frecuencia a otros síntomas paraneoplásicos como la encefalopatía o la neuropatía sensitiva, pero puede ser la única manifestación de un tumor subyacente. El tumor implicado con más frecuencia es:

A) Carcinoma microcítico de pulmón.
B) Cáncer renal.
C) Carcinoma de mama triple negativo.
D) Carcinoma de timo.

RESPUESTA: A

7. EXTREMADURA (2/162 preguntas)

69. De las siguientes qué respuesta es INCORRECTA en lo que se refiere a síndromes paraneoplásicos neurológicos:

a) En la degeneración cerebelosa están implicados varios anticuerpos como anti-Yo, anti-Hu y anti-CV2.
b) La mielopatía necrotizante es una necrosis masiva de predominio de la médula torácica, aunque pueden existir focos necróticos repartidos por toda la médula.
c) El tumor implicado con mayor frecuencia en la neuropatía autonómica es el carcinoma microcítico de pulmón y suele presentar anticuerpos anti-Hu.
d) Cuando ocurre en niños el síndrome opsoclono-mioclono es típica la asociación a meduloblastoma

RESPUESTA: D

122. El diagnostico del cáncer de pulmón de células pequeñas se basa principalmente en el microscopio óptico. En relación a esta afirmación señale la opción INCORRECTA:

a) Hojas densas de células pequeñas con escaso citoplasma.
b) Cromatina nuclear finamente granular.
c) Presenta nucleolos muy visibles y escasas mitosis.
d) La necrosis es común y con frecuencia muestra grandes áreas.

RESPUESTA: C

GALICIA 2021 (/).

45. A Guía clínica ASTRO establece unha serie de recomendacións en canto á Radioterapia para oat cell pulmonar (Simone et al. Pract. Radiat. Oncol. 2020 May–Jun). Cal é certa?

A) Recomendación de radioterapia holocraneal profiláctica (PCI) en estadios II e III en doentes respondedores a quimioradioterapia.

B) En enfermidade extensa: PCI ou seguimento radiolóxico estreito.

C) Consolidación torácica tras cirurxía se afectación ganglionar ou marxes afectos.

D) Todas son certas.

RESPUESTA: D.

56. O estudo deseñado por Turrisi et al. (N. Engl. J. Med. 1999 Jan.) supuxo un antes e un despois no tratamento do cancro microcítico de pulmón, enfermidade limitada tratada concomitantemente con radioterapia e cisplatino–etopósido. Qué é verdade en relación ao mesmo?

A) Os pacientes recibiron catro ciclos de cisplatino e etopósido.

B) Randomizáronse a recibir: 45 Gy de radioterapia torácica concomitante e hiperfraccionada en tres semanas ou a normofraccionamento durante cinco semanas.

C) O hiperfraccionamento mellorou a taxa de supervivencia a dous e cinco anos.

D) Todas son certas.

RESPUESTA D

74. O Atezolizumab en combinación con quimioterapia en primeira liña Cancro de pulmón célula pequena en enfermidade foi estudado no ensaio clínico publicado por Horn et al. (N. engl. J. Med 2018 Dec.). Que é certo en relación a dito estudo?

A) Estudaba a combinaciión de Atezolizumab con Carboplatino e etopósido.

B) Estdaba a combinación de Atexolizumab con Cisplatino e etopósido.

C) A e B.

D) Seis ciclos de indución.

RESPUESTA A.

78. O estudo CONVERT intentou dilucidar a cuestión de Quimioradioterapia concomitante normo vs hiperfraccionada en pacientes con oat cell pulmonar enfermidade localizada (Faivre-Finn et al. LANCET ONCOL. 2017 Aug.). Que resposta é correcta?

A) 45 Gy en fraccionamento dobre (30 fraccións de 1,5 Gy durante 19 días), versus 66 Gy en 33 fraccións de 2 Gy durante 45 días, iniciándose a radioterapia o día 1 de segundo ciclo de quimioterapia (cisplatino-etopósido ata entre catro ou seis ciclos).

B) A supervivencia global a dous anos resultou do 56 % (95 % CI 50-62) no grupo fiperfraccionado fronte ao 51 % (45-57) no de normofraccionamento diario (diferencia absoluta 5·3 % [95 % CI −3·2 % TO 13·7 %]).

C) Non diferencias en toxicidade.

D) Todas son certas.

RESPUESTA D

89. O tratamento con Ipilimumab en combinación con Etopósido e Platino foi analizado vs Placebo con Etopósido e Platino en oat cell pulmonar enfermidade extensa (Reck et al. J. Clin. Oncol. 2016 Nov.). Que é certo en relación a dito estudo fase III?

A) Os pacientes foron randomizados a: etopósito e platino con ipilimumab 10 mg/kg ou placebo cada 3 semanas por catro ciclos nunha primeira fase de indución (ipilimumab ou placebo iniciábanse en ciclo tres a seis), seguido de ipilimumab de mantemento ou placebo cada 12 semanas.

B) Non se obxectivaron diferencias significativas na supervivencia global nin na supervivencia libre de progresión.

C) Taxa de abandonos máis alta no grupo experimental.

D) Todas son certas.

RESPUESTA D

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

Q19 **A.-M. C. Dingemans[1,2], M. Früh[3,4], A. Ardizzoni[5], B. Besse[6,7], C. Faivre-Finn[8], L. E. Hendriks[2], S. Lantuejoul[9], S. Peters[10], N. Reguart[11], C. M. Rudin[12], D. De Ruysscher[13], P. E. Van Schil[14], J. Vansteenkiste[15] & M. Reck[16], on behalf of the ESMO Guidelines Committee***

[1]Department of Pulmonology, Erasmus Medical Center, Rotterdam; [2]Department of Pulmonology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands; [3]Department of Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen; [4]Department of Medical Oncology, University of Bern, Bern, Switzerland; [5]Division of Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [6]Gustave Roussy, Cancer Medicine Department, Villejuif; [7]Paris-Saclay University, Orsay, France; [8]Division of Cancer Sciences, University of Manchester & The Christie, NHS Foundation Q1 Trust, Manchester, UK; [9]Department of Biopathology, Centre Léon Bérard, Grenoble Alpes University, Lyon, France; [10]Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland; [11]Department of Medical Oncology, Hospital Clínic and Translational Genomics and Targeted Therapeutics in Solid Tumors, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [12]Memorial Sloan Kettering Cancer Center, New York, USA; [13]Department of Radiation Oncology (Maastro Clinic), GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands; [14]Department of Thoracic and Vascular Surgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; [15]Department of Respiratory Oncology, University Hospital KU Leuven, Leuven, Belgium; [16]LungenClinic Airway Research Center North (ARCN), German Center for Lung Research, Grosshansdorf, Germany

Available online XXX

Q3 ■■■.

Key words: small-cell lung cancer, Clinical Practice Guidelines, diagnosis, treatment, follow-up

Q4 INCIDENCE AND EPIDEMIOLOGY

Small-cell lung cancer (SCLC) is the most aggressive form of lung cancer. Although SCLC is characterised by rapid responses to chemotherapy (ChT) and sensitivity to radiotherapy (RT), due to early treatment resistance, the 5-year overall survival (OS) is <10%.[1] The incidence of SCLC has decreased in recent decades, and with a prevalence of 1-5 per 10 000 people in the European community, SCLC has an orphan disease designation.[2,3] SCLC is equally prevalent in males and females[2]; however, the proportion of elderly (>70 years) patients with SCLC has increased from 23% in 1975 to 44% in 2010.[4] Computed tomography (CT) screening does not improve survival of SCLC, as demonstrated in three trials [I, E].[5,6] This is possibly related to the aggressiveness of SCLC, reflected both by the occurrence of SCLC as an interval cancer, i.e. diagnosed between two CT screenings, and the primarily late-stage screen-detected SCLC. As SCLC is highly related to tobacco smoking, smoking prevention or cessation are the most effective strategies to decrease the clinical impact of the disease [IV, A].

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

Information regarding the diagnosis and molecular pathology/biology of SCLC can be found in Section 1 (text) of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.03.207.

Recommendations

- SCLC is a high-grade neuroendocrine carcinoma with a typical morphology and should be diagnosed according to the World Health Organization criteria [IV, A].
- For pathological diagnosis, histology is preferred over cytology [V, A].
- Currently, no predictive biomarker is available and programmed death-ligand 1 (PD-L1) and tumour mutational burden (TMB) testing are not recommended in routine clinical practice [I, D].

STAGING AND RISK ASSESSMENT

The TNM (tumour—node—metastasis) staging classification 7th edition was adopted for SCLC, harbouring a higher

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Q2 Ginevra 4, CH-6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

☆Approved by the ESMO Guidelines Committee: February 2002, last update December 2020. This publication supersedes the previously published version—*Ann Oncol.* 2013;24(suppl 6):vi99-vi105.

prognostic value compared with the previously used subdivision in limited and extensive disease [IV, A].[7] The description of disease stages according to the 8th edition TNM, and the median, 1-year and 2-year OS data are depicted in Section 2 (Supplementary Tables S1 and S2) of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.03.207.[8] However, in clinical trials, the terms 'limited disease', defined as tumour being confined to one hemithorax and regional lymph nodes, and 'extensive disease' are used to define eligibility. For this reason, limited and extensive disease are used throughout this guideline.

The staging work-up for patients diagnosed with SCLC is shown in Table 1. A medical history, physical examination and laboratory tests should be carried out [V, A]. Attention should be drawn towards potential autoimmune-mediated paraneoplastic neurological symptoms,[9] with their detection becoming increasingly important with the introduction of immunotherapy [V, C]. In non-metastatic disease, pulmonary function tests are also advised.[10] Imaging consists of a chest and abdomen CT [IV, A]. In case of no metastases on CT scan, imaging should be complemented with a bone scintigraphy {or [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG—PET)—CT if available} [V, B] and a magnetic resonance imaging (MRI) or a less sensitive brain CT scan if MRI is not available/possible [III, A].[11] In patients with stage IV disease who are eligible but do not wish to undergo prophylactic cranial irradiation (PCI), a baseline MRI after ChT is recommended and serial MRIs are then advised as part of the follow-up [III, B].[12] In case of an abnormal blood count or signs of blood—bone marrow infiltration, a bone marrow aspiration and biopsy are recommended in patients without known additional metastases in order to confirm bone marrow involvement [V, C]. The use of FDG—PET is still debated in SCLC; a review of small prospective series showed that 9% of patients were upstaged with FDG—PET and 4% were downstaged.[13] In the majority of these series, pathological confirmation of metastatic sites was not obtained. As false-positive results have been reported using FDG—PET, the presence of a metastasis should be pathologically confirmed if it alters the treatment plan [II, C]. Of note, in the randomised CONVERT trial exploring different RT schedules in limited-stage SCLC, the outcomes of 57% of patients who were staged by PET—CT was not different to those who underwent staging by conventional CT scan.[14] Given the limited evidence for PET—CT in SCLC, its role in the selection of patients for curative treatment remains controversial among those without metastases on CT. However, FDG—PET is recommended to assist in RT volume delineation [III, A]. In case a suspected solitary metastasis cannot be adequately diagnosed, or diagnosis significantly delays the start of treatment, the lesion can be re-evaluated after two cycles of ChT to confirm the diagnosis of metastatic disease. If pleural fluid/pericardial fluid is negative for metastasis, and if it is the only possible site of metastasis, treatment should be according to M0 status.

Poor prognostic factors in SCLC include impaired performance status (PS), weight loss, increased age, male sex, elevated lactate dehydrogenase (LDH) and low sodium [syndrome of inappropriate antidiuretic hormone secretion (SIADH)].[15] In addition, a higher total gross tumour volume predicts a worse outcome in patients with locally advanced SCLC treated with chemoradiotherapy (CRT).[16]

Table 1. Diagnostic and staging work-up of SCLC

History and clinical examination
Medical history (including smoking history and comorbidities)
PS
Physical examination
Assessment of paraneoplastic syndromes (especially when initiating immunotherapy)
Laboratory analysis
CBC, liver enzymes, sodium, potassium, calcium, glucose, LDH and renal functions tests should be carried out
Imaging
CT of the thorax and abdomen should be carried out in all patients; an FDG—PET—CT is optional
In case of a suspicion of bone metastasis and no other metastasis, a bone scintigraphy should be carried out unless FDG—PET is available
Imaging of the brain (preferably MRI) is mandated in patients with stage I-III disease
MRI of the brain is recommended for patients with stage IV disease who are eligible for PCI but who choose not to undergo PCI
Tumour biopsy
A diagnosis of SCLC is preferably assessed based on histological examination of a biopsy
In case of planned surgery, invasive mediastinal staging is required
Functional assessment
Pulmonary function testing (FEV1, VC, DLCO) is required for patients with stage I-III SCLC who are candidates for surgery or RT
VO2 max assessment by cycle ergometry should be carried out if surgery is planned when pulmonary function tests are limited

CBC, complete blood count; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; FDG, [18F]2-fluoro-2-deoxy-D-glucose; FEV1, forced expiratory volume; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCI, prophylactic cranial irradiation; PET, positron emission tomography; PS, performance status; RT, radiotherapy; SCLC, small-cell lung cancer; VC, vital capacity; VO2 max, maximal oxygen uptake.

Recommendations

- Staging of SCLC should be according to the TNM 8th edition [IV, A].
- Initial assessment should include smoking history, physical examination, complete blood count, liver enzymes, sodium, potassium, calcium, glucose, LDH, creatinine and lung function test (if localised disease) [V, A].
- Attention should be drawn towards potential autoimmune-mediated paraneoplastic neurological symptoms [V, C].
- A contrast-enhanced CT of the chest and abdomen is recommended [IV, A].
- Imaging of the brain, preferably MRI, is recommended in localised disease [III, A].
- Brain MRI is also recommended for stage IV patients not undergoing PCI [II, B].
- FDG—PET is optional for staging in limited-stage disease. FDG—PET findings that modify treatment decisions should be pathologically confirmed [II, C]. However, FDG—PET is recommended to assist in RT volume delineation [III, A].

- In limited-stage disease, additional bone scintigraphy is advised when no FDG—PET—CT has been carried out [V, B].
- In limited-stage disease, a bone marrow aspiration and biopsy are advised in the case of abnormal blood counts suggesting bone marrow involvement [V, C].
- In patients eligible for immunotherapy, attention should be paid to the detection of paraneoplastic disorders [V, C].

TREATMENT

Management of limited-stage disease

A proposed treatment algorithm for patients with stage I-III SCLC eligible for treatment of curative intent (selected limited-stage disease) is shown in Figure 1A.

The role of surgery with multimodality treatment. Indications and results of surgical resection for SCLC remain controversial and only a minority of patients with SCLC qualify for surgical resection. In 2017, a Cochrane systematic review concluded that currently available randomised controlled trials (RCTs) do not support a role for surgical resection in the management of stage I-III SCLC.[17] However, the conclusions were of limited value due to the lack of contemporary data and the low quality of available evidence. In a recent retrospective analysis of 205 patients with SCLC who underwent resection, for those with pathological stages I and II, 5-year survival rates were 63.8% and 65.5%, respectively.[18] In another analysis of the National Cancer Database, 507 patients with stage I/II SCLC undergoing lobectomy and adjuvant ChT were matched with patients receiving concurrent CRT.[19] Median OS was 48.6

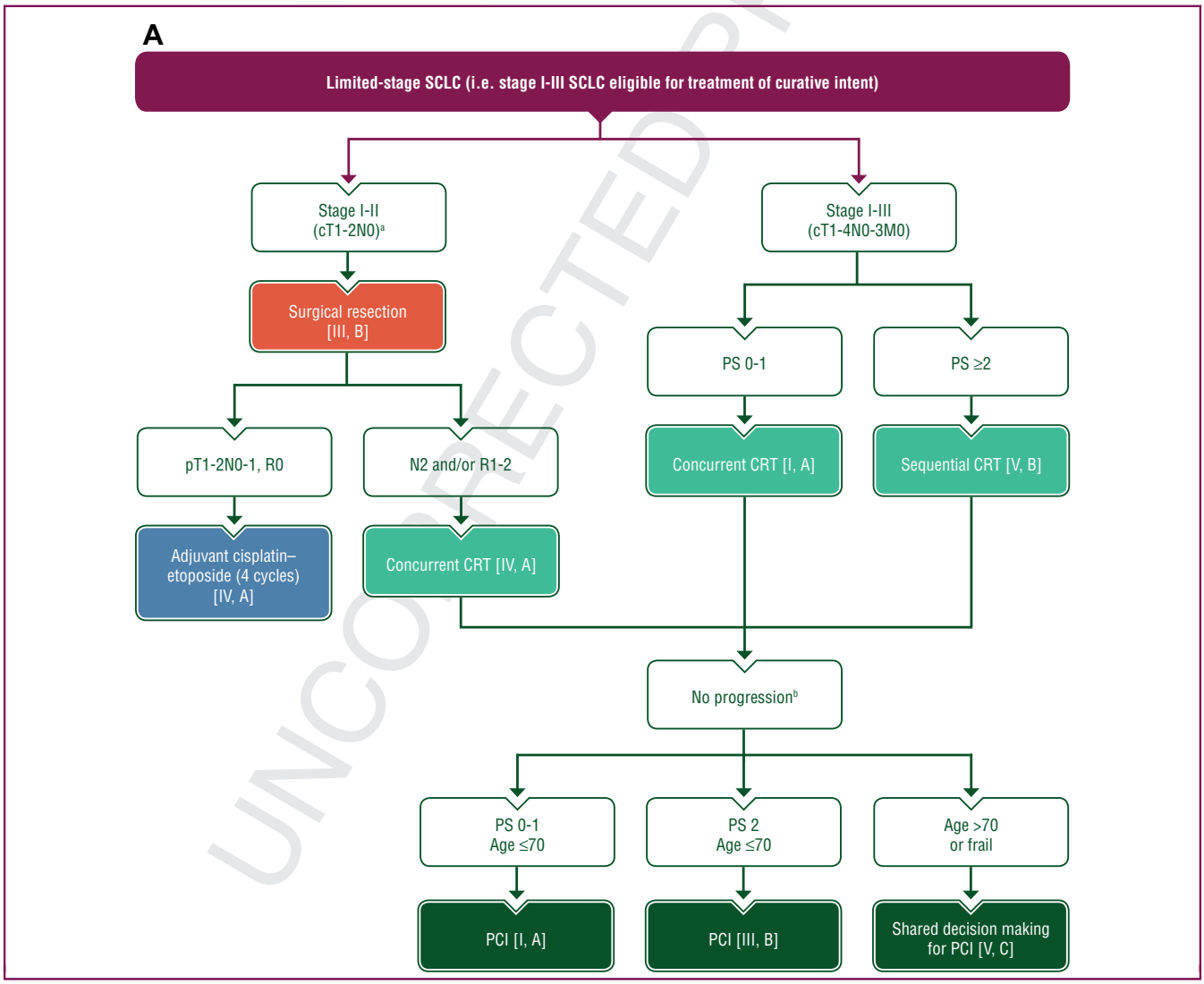


Figure 1. **Treatment algorithm for SCLC in (A) patients with limited-stage disease (i.e. stage I-III SCLC eligible for curative treatment), (B) patients with extensive-stage disease (i.e. stage IV or stage III SCLC not eligible for curative treatment) and (C) patients with recurrent SCLC (i.e. second-line therapy and beyond). BSC, best supportive care; c, clinical; ChT, chemotherapy; CRT, chemoradiotherapy; G-CSF, granulocyte colony-stimulating factor; IO, immunotherapy; i.v., intravenous; M, metastasis; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MRI, magnetic resonance imaging; N, node; PCI, prophylactic cranial irradiation; PS, performance status; R, resection; RT, radiotherapy; SCLC, small-cell lung cancer; T, tumour; TFI, treatment-free interval. [a]After extensive pathological mediastinal staging. [b]The role of PCI is not well defined in patients with stage I-II SCLC, patients >70 years of age and frail patients. In these cases, shared decision-making is recommended, including the option of brain MRI surveillance. [c]Carboplatin may be replaced by cisplatin in patients <70 years of age or based on the toxicity profile [II, C]. [d]No brain metastasis on MRI before PCI. [e]In patients with a PS of ≥2, consider ChT dose reduction and/or G-CSF prophylaxis.**

print & web 4C/FPO

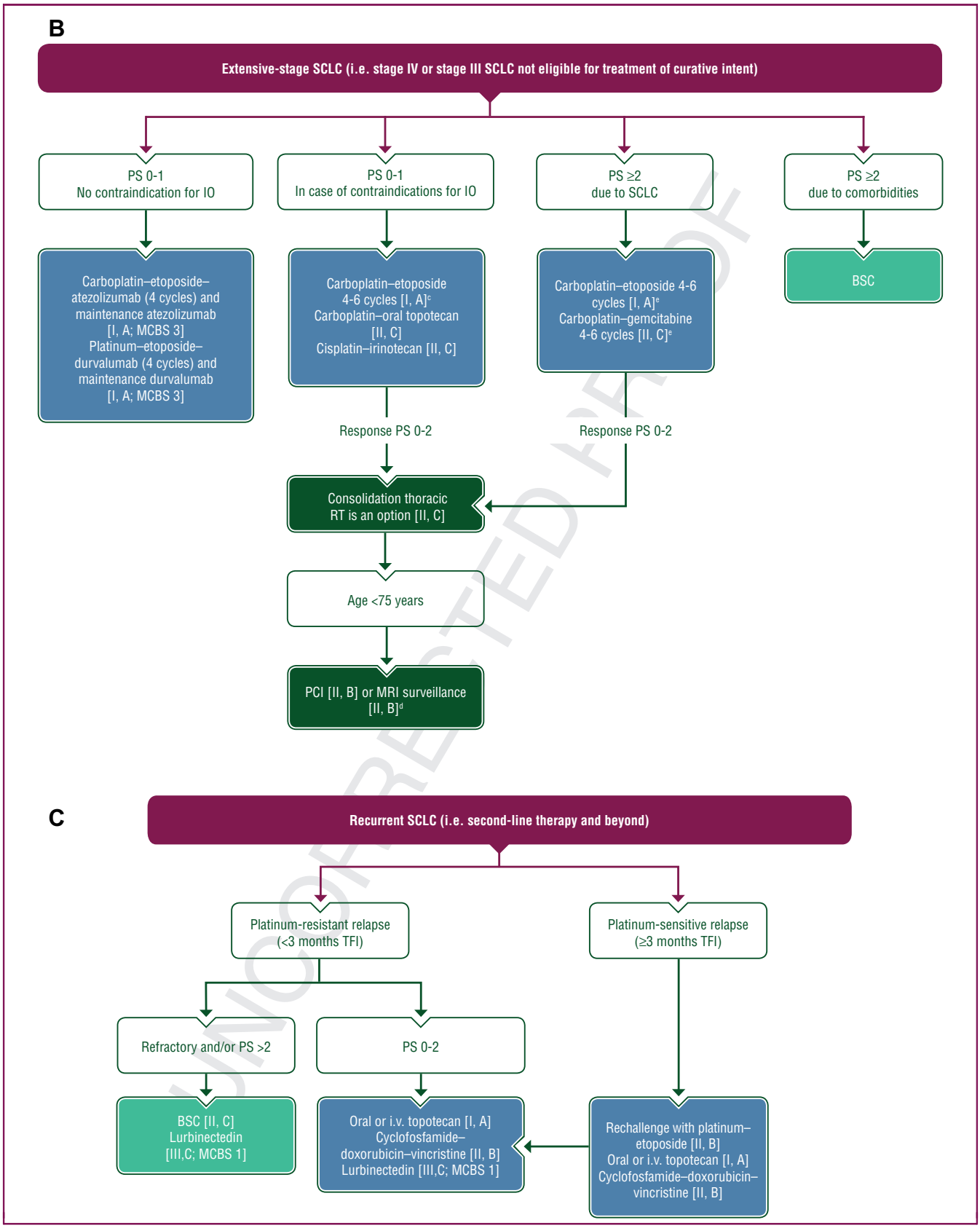


Figure 1. **(Continued)**

and 28.7 months, respectively, favouring the surgical approach ($P < 0.0001$). After extensive work-up, surgery, in the context of a multimodal treatment approach, may be considered in patients with clinical stages I and II disease (cT1-2N0) [III, B] and in those suspected of having a mixed histology of SCLC and non-small-cell lung cancer (NSCLC).[20] SCLC may also be an incidental finding in patients undergoing surgery for a solitary pulmonary nodule, as seen in 4%-12% of cases.[21]

When considering surgical treatment of SCLC, extensive pathological mediastinal staging is required [IV, A].[22,23] As with NSCLC, the aim of surgical treatment should be a complete (R0) resection according to the International Association for the Study of Lung Cancer criteria [III, A].[24] Intraoperatively, a systematic nodal dissection should be carried out [IV, A]. Sublobular resection is not recommended [V, E]. Due to the aggressive nature of SCLC, the risk of progression to unresectable or incurable disease while awaiting surgery should be taken into account.

In an analysis of the National Cancer Database, the 5-year OS rate of 954 patients who underwent R0 resection for pT1-2N0M0 SCLC was 47%.[25] A multivariate analysis showed that adjuvant ChT or ChT with PCI were associated with improved survival compared with no adjuvant therapy. Adjuvant ChT should therefore be administered after surgical resection of SCLC [IV, A]. In patients with unexpected, positive mediastinal lymph nodes (N2) or R1-R2 resection, adjuvant ChT must be combined with RT, preferably concurrently [IV, A].[22]

The role of induction ChT in patients with locally advanced SCLC has not been clearly established and this approach is not indicated for SCLC.[20]

The role of PCI is not well established, as discussed later.

Concurrent CRT: type of ChT and number of cycles. The preferred ChT regimen for patients with limited-stage (stage I-III) SCLC is cisplatin plus etoposide [I, A].[26] When cisplatin is not feasible, carboplatin plus etoposide is a possible alternative, with similar or slightly worse outcomes seen in small comparative studies [II, A].[27] Standard dosing should be used, i.e. cisplatin 60-80 mg/m^2 on day 1 and etoposide 100-120 mg/m^2 on days 1, 2 and 3 of every 3-week cycle, with avoidance of dose reduction, especially during the first two cycles.[28] The dose of cisplatin can also be split over 3 days (etoposide 100 mg/m^2 on days 1-3 and cisplatin 25 mg/m^2 on days 1-3) as this tends to be better tolerated and reduces the need for hydration.[29] The use of granulocyte colony-stimulating factor (G-CSF) or granulocyte–macrophage colony-stimulating factor (GM-CSF) concomitant with CRT has been discouraged based on one randomised study of GM-CSF, but more recent data from the CONVERT trial have shown that these agents can be administered safely when indicated [II, B].[29-31] The number of cycles is usually four; however, only small series have compared four with six cycles in localised SCLC.[32]

The success of introducing immune checkpoint inhibition with durvalumab as consolidation therapy after CRT for NSCLC has fostered interest in this approach in limited-stage SCLC.[33] Consolidation treatment with nivolumab–ipilimumab in patients treated with CRT was investigated in the randomised phase II STIMULI trial.[34] However, no improvement in progression-free survival (PFS) or OS was observed in patients treated with nivolumab–ipilimumab compared with the observational group.

A number of trials addressing the role of immunotherapy in this setting are ongoing (NCT02046733, NCT03540420, NCT03703297, NCT03811002).

RT schedule. With the exception of patients with very early disease, those with T1-4N0-3M0 tumours and a PS of 0-1 should be treated with concurrent ChT and thoracic RT [I, A]. The current standard of care of twice-daily (b.i.d.) RT delivered concurrently with ChT is based on an RCT which demonstrated superiority in terms of survival for RT of 45 Gy b.i.d. in 30 fractions over 3 weeks versus 45 Gy once daily (o.d.) in 25 fractions over 5 weeks, both delivered concurrently with cisplatin plus etoposide.[35] However, there has been a lack of consensus regarding the routine use of b.i.d. RT due to concerns regarding toxicity (one-third of patients developed grade $\geq$3 radiation oesophagitis in an historical study), debate about the RT schedule used in the control arm and practical/logistical issues. The CONVERT trial compared b.i.d. RT (45 Gy/30 fractions over 3 weeks) to a higher dose of o.d. RT (66 Gy/33 fractions over 6.5 weeks), both given concurrently with ChT (starting on cycle two).[29] CONVERT is the first RCT providing outcomes data in patients staged with PET–CT using the TNM classification and treated with modern RT techniques (i.e. three-dimensional conformal RT or intensity-modulated RT without elective nodal irradiation).[14] OS did not significantly differ between the two groups. OS achieved in both arms was higher and the toxicity much lower (>50% reduction) than previously reported in the literature. The 2- and 5-year OS were 56% and 34% in the b.i.d. group and 51% and 31% in the o.d. group, respectively. There was no difference in grade 3-4 oesophagitis or grade 3-4 radiation pneumonitis between the groups (19% versus 19% and 3% versus 2% in the b.i.d. and o.d. groups, respectively). In addition, a Norwegian phase II RCT, comparing 45 Gy/30 fractions b.i.d. with 42 Gy/15 fractions o.d., showed that there was no difference in major toxicity between the schedules and a numerically higher OS for treatment with 45 Gy b.i.d.[36] Since CONVERT was designed to show superiority of o.d. RT and was not powered to show equivalence, the implication is that b.i.d. RT (45 Gy/30 fractions over 3 weeks) should remain as the standard of care in this group of patients [I, A]. When b.i.d. RT is not possible due to logistical reasons, o.d. RT (66 Gy/33 fractions over 6 weeks) is an alternative option. It should, however, be noted that the role of concurrent CRT is not as well defined in patients of age >70 years or in those who are frail.

Regarding the timing of RT and ChT, evidence from clinical trials suggest that thoracic RT should be initiated as early as possible, preferably starting on the first or second cycle of ChT. However, two recent meta-analyses investigating the timing of high-dose thoracic RT with ChT showed

no difference in OS between earlier (≤30 days after starting ChT) and later (>30 days after starting ChT) RT initiation. Furthermore, a higher incidence of toxicity (haematological, oesophagitis and cardiac toxicity) was reported with early versus late thoracic RT.[37,38] However, in the individual patient data meta-analysis, the hazard ratio (HR) was significantly in favour of earlier/shorter RT in trials where patients received ChT without a dose reduction or delay [HR 0.79; 95% confidence interval (CI) 0.69-0.91] [II, A].[37] When the patient PS or dose to the organs at risk do not allow for the early administration of thoracic RT, it may be postponed until the start of the third ChT cycle [II, B]. Sequential CRT is an option for patients who are not considered candidates for concurrent CRT due to poor PS, comorbidities and/or disease volume [V, B].

RT treatment volume. In sequential CRT, the optimal target volume remains an area of debate. An historical Southwest Oncology Group (SWOG) trial without contemporary imaging or RT techniques randomised patients achieving a partial response or stable disease after ChT to either wide-volume RT (pre-ChT tumour volume plus the mediastinum) or reduced-volume RT (post-ChT tumour volume with a margin of 2 cm) followed by further ChT.[39] The local recurrence rate was similar in both arms. Therefore, it is recommended that the post-ChT primary tumour volume should be included in the radiation field [II, B].

No prospective studies are available on the nodal target volume after ChT. Thus, similar to NSCLC, including the involved nodal stations before ChT in the target volume is recommended [V, B].

Omission of elective node irradiation based on CT scans should be used with caution as this strategy may result in nodal failures.[40] Whether selective node irradiation based on pre-treatment PET—CT scans can replace elective node irradiation has been addressed in two small single-arm studies.[41,42] Both studies showed promisingly low nodal recurrence rates. Furthermore, in the CONVERT trial, elective node irradiation was omitted in all patients, with half of them staged using PET—CT.[29] The incidence of isolated nodal failures has not been reported yet but the survival results are the best reported to date. Omission of elective node irradiation is therefore recommended in favour of selective node irradiation (i.e. involved nodes defined as FDG avid on PET—CT, enlarged on CT and/or biopsy-positive) [III, A].

The role of PCI. PCI significantly decreases the risk of symptomatic brain metastases and increases OS in patients with a complete remission (5.4% absolute improvement in 3-year OS).[43] Patients with a PS of 0-1 and a response to CRT should therefore be offered PCI [I, A]. Patients often present with a PS >2 after CRT but very few have been included in PCI clinical trials and meta-analyses. In patients with a PS of 2, PCI can be considered [III, B].[43] The recommended dose is 25 Gy in 10 daily fractions [I, A].[44] However, it should be noted that the role of PCI is not as well defined in patients with stage I-II SCLC, who have a lower risk of developing brain metastases, and in those of age >70 years or who are frail. In such cases, shared decision-making is recommended [V, C]. There was no benefit of hippocampal-sparing PCI in terms of neurocognitive decline in a phase III trial (NCT01780675) which has been presented, but not yet fully published. An additional ongoing trial is addressing this question (NCT01797159).

Management of extensive-stage disease

Patients with SCLC tend to be older (44% >70 years), have more comorbidities and have a poor PS at diagnosis. However, as rapid responses are expected, in many cases, treatment with ChT offers the best palliation.

A proposed treatment algorithm for patients with extensive-stage SCLC is shown in Figure 1B.

First-line ChT. For decades, a platinum plus etoposide has been the preferred first-line treatment for extensive-stage SCLC, with a median OS of 9-10 months, PFS of 5-6 months and 1-year OS of ∼35% [I, A].[26] A meta-analysis of individual patient data showed no difference in OS between cisplatin and carboplatin.[45] From this meta-analysis, it seems that in younger patients (<70 years), the outcome might be moderately better with cisplatin, although these subgroup analyses were exploratory. The toxicity profiles should also be considered in treatment decision-making: cisplatin is associated with more non-haematological toxicity, such as nausea, vomiting and renal toxicity, whereas carboplatin leads to more myelosuppression. Therefore, in extensive-stage SCLC, cisplatin can be substituted by carboplatin [I, B]. However, for some patients, cisplatin might be preferred when taking age (<70 years), PS and toxicity profile into account [II, C]. Many RCTs have explored maintenance or continuation treatment in SCLC but none have shown improved outcomes compared with four to six cycles of a platinum plus etoposide [I, A].[46]

A study from the Japanese Cooperative Oncology Group (JCOG 9511) showed improved outcomes with the combination of cisplatin and irinotecan compared with cisplatin and etoposide (median OS: 12.8 versus 9.4 months).[47] However, this could not be confirmed in a large, non-Asian study.[48] A recent meta-analysis of 12 RCTs (7 written in Chinese) showed no difference in outcomes between cisplatin plus etoposide and cisplatin plus irinotecan in patients with ChT-naive, stage IV SCLC.[49] Non-inferiority to platinum plus etoposide has been shown for platinum plus oral topotecan and for carboplatin plus gemcitabine in patients with a poor PS [II, C].[50,51]

First-line systemic treatment: the role of immunotherapy. Immunotherapy has dramatically modified cancer treatment across several malignancies and has been an active area of investigation in SCLC.

Despite initial promising phase II trial results, the use of ipilimumab in combination with first-line platinum plus etoposide did not improve clinical outcomes compared with ChT in a phase III RCT.[52]

Recently, new standards of care were established in first-line therapy of extensive-stage SCLC based on two double-blind, phase III RCTs: IMpower133 and CASPIAN.[53,54] IMpower133 evaluated the efficacy and safety of first-line atezolizumab (1200 mg, day 1) or placebo in combination with carboplatin [area under the curve (AUC) 5, day 1] and etoposide (100 mg/m^2, days 1-3) every 3 weeks for four cycles followed by atezolizumab or placebo maintenance in treatment-naive patients with extensive-stage SCLC. PCI was permitted but consolidation thoracic RT was not. It met its co-primary endpoints of OS and investigator-assessed PFS at the first interim analysis. Median OS was 12.3 months (95% CI 10.8-15.9 months) for atezolizumab versus 10.3 months (95% CI 9.3-11.3 months) for placebo (HR 0.70; 95% CI 0.54-0.91; $P = 0.0069$). In the atezolizumab group, 34% of patients were alive at 18 months compared with 21% in the placebo group.[55] Median PFS was 5.2 months (95% CI 4.4-5.6 months) for atezolizumab versus 4.3 months (95% CI 4.2-4.5 months) for placebo (HR 0.77; 95% CI 0.62-0.96; $P = 0.017$). Benefits were consistent across patient subgroups. Of importance, the modest PFS and OS benefits clearly emphasise the need for the identification of new predictive biomarkers, with exploratory analyses showing no predictive ability of blood TMB for this specific combination. CASPIAN is a three-arm trial evaluating durvalumab in patients with previously untreated, extensive-stage SCLC. Patients were randomised 1 : 1 : 1 to receive either platinum (carboplatin AUC 5-6 or cisplatin 75-80 mg/m^2, day 1) plus etoposide (80-100 mg/m^2, days 1-3) and durvalumab (1500 mg, day 1), with or without tremelimumab (75 mg, day 1), every 3 weeks for four cycles followed by durvalumab maintenance on day 1 every 4 weeks, or up to six cycles of platinum plus etoposide alone (control arm). PCI (used at the investigator's discretion) was only allowed in the control arm. A statistically significant improvement in OS was reported with the addition of durvalumab to ChT, with a median OS of 12.9 months (95% CI 11.3-14.7 months) for durvalumab plus ChT versus 10.5 months (95% CI 9.3-11.2 months) for platinum plus etoposide alone (HR 0.75; 95% CI 0.62-0.91; $P = 0.0032$).[56] OS at 18 months was 32.0% (95% CI 26.5% to 37.7%) for durvalumab versus 24.8% (95% CI 19.7% to 30.1%) in the ChT-only group. Benefits were consistent across patient subgroups and quality of life (QoL) was maintained.[57] The addition of tremelimumab to durvalumab and the platinum doublet did not show any improvement in outcomes compared with ChT. With very similar results, and in the context of a severe unmet need, both trials justify the need for immunotherapy in the frontline setting. However, it is important to stress that in both trials, only patients with a good clinical condition were enrolled (i.e. PS 0-1 and asymptomatic or treated brain metastases). Additionally, the median age of enrolled patients was relatively low (62-64 years). In stage IV SCLC, atezolizumab or durvalumab in combination with a platinum plus etoposide should be offered to all eligible ChT-naive patients with stage IV SCLC and a PS of 0-1 [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 3 for atezolizumab and 3 for durvalumab]. In the recently reported KEYNOTE-604 trial, patients with extensive stage IV SCLC were randomised to receive platinum (carboplatin AUC 5 or cisplatin 75 mg/m^2, day 1) and etoposide (100 mg/m^2, days 1-3) with either pembrolizumab 200 mg or placebo for four cycles followed by pembrolizumab or placebo as maintenance therapy.[58] PCI was optional in both arms. The study met its co-primary PFS endpoint (HR 0.75; 95% CI 0.61-0.91; $P = 0.0023$); however, the prespecified significance threshold for OS was not met (HR 0.80; 95% CI 0.64-0.98; $P = 0.0164$). The 2-year OS in the pembrolizumab group was 22.5% versus 11.2% in the ChT-only group.

The CheckMate 451 study showed no OS improvement of maintenance therapy with nivolumab plus ipilimumab or nivolumab alone compared with placebo (HR 0.92; 95% CI 0.75-1.12; $P = 0.37$ and HR 0.84; 95% CI 0.69-1.02).[59]

Thoracic RT in extensive-stage SCLC. Two phase III RCTs have investigated the role of thoracic RT in extensive-stage SCLC. In the trial of Jeremic et al., a total of 210 patients were treated with three cycles of cisplatin plus etoposide.[60] Patients with a complete response (CR) in distant metastases received either thoracic RT with concurrent daily carboplatin plus etoposide followed by two cycles of cisplatin plus etoposide or an additional four cycles of cisplatin plus etoposide. All patients with a CR in distant metastases also received PCI. Patients who received thoracic RT had significantly better survival rates than those who received only ChT (median OS 17 versus 11 months; 5-year survival 9.1% versus 3.7%, respectively; $P = 0.041$). Acute high-grade toxicity was higher in the RT group.

In the CREST trial, 495 patients with extensive-stage SCLC Q13 and a response to ChT were randomised to receive either PCI alone or PCI with thoracic RT (30 Gy/10-15 fractions).[61] No significant improvement in 1-year OS (primary endpoint) was observed: 33% versus 28% for thoracic RT versus no thoracic RT. In a pre-planned secondary analysis, the 2-year OS was 13% versus 3% favouring thoracic RT ($P = 0.004$). An additional exploratory analysis showed that in patients with residual intrathoracic disease (a stratification factor), the OS was significantly longer in the thoracic RT group (HR 0.81; 95% CI 0.66-1.00; $P = 0.044$).[62] No significant differences in toxicity were seen between the treatment arms. Thus, in patients with a PS of 0-2 who achieve a response after ChT, RT to the residual primary tumour and lymph nodes (30 Gy/10 fractions) is a treatment option [II, C]. There is a paucity of data on the integration of thoracic RT and immunotherapy; this should be explored in future research.

PCI in extensive-stage SCLC. PCI is a standard treatment for patients with stage IV SCLC who are <75 years old, PS 0-2 and who have no progression after first-line ChT [II, B]. PCI reduces the occurrence of symptomatic brain metastases compared with observation and leads to a longer median survival. In the studies showing that PCI confers a survival benefit in patients with extensive-stage SCLC, patients were not pre-screened for brain metastases.[43,63] A Japanese phase III RCT investigated the effectiveness of PCI in

patients with extensive-stage SCLC.[12] Overall, 224 patients without brain metastases on MRI after platinum-containing ChT were randomised to receive either PCI (25 Gy/10 fractions) and MRI follow-up or MRI follow-up only (every 3 months for 1 year and then at 18 and 24 months). The study was stopped early because of futility; no significant differences in OS or PFS were observed. The most common grade ≥3 adverse events after 3 months were loss of appetite (6% in the PCI group versus 2% in the observation group), malaise (3% versus 1%) and muscle weakness in the lower extremities (<1% versus 5%). No difference in the mini mental state examination score was observed between the two groups.

There are important differences between these studies, including the fact that brain MRI was not carried out for staging or follow-up in the trial reported by Slotman et al. RCTs comparing PCI and brain MRI surveillance versus MRI surveillance alone are in development. Thus, PCI (20 Gy/5 fractions and 25 Gy/10 fractions) is justified in the absence of staging or follow-up brain MRI assessments in patients of age <75 years and a PS of 0-2 who achieved a response after ChT [II, B]. There is a paucity of data on the integration of PCI and immunotherapy. In the IMpower133 study, PCI was allowed in the maintenance phase and 22 patients in each arm received PCI.[53] In KEYNOTE-604, PCI was optional in both arms and 11.8% and 14.2% of patients in the pembrolizumab and placebo arms, respectively, received PCI.[58] However, no details of the toxicity data for patients treated with PCI were provided. Additional research is therefore required regarding both the safety and efficacy of this approach.

Second-line therapy and beyond. A proposed treatment algorithm for second-line therapy and beyond in patients with recurrent SCLC is shown in Figure 1C.

Standard treatment. Although SCLC is remarkably sensitive to ChT, most patients relapse within 6 months. Response rates to second-line treatment depend on the treatment-free interval (TFI) and response to first-line platinum-based induction therapy.[64] Response rates to second-line ChT are usually around 20%-30% in platinum-sensitive patients (i.e. TFI ≥ 3 months) and 15% in platinum-resistant patients (i.e. TFI < 3 months). In platinum-refractory (i.e. patients not responding or progressing during ChT) and -resistant patients, outcomes are very poor and the clinical benefit of further systemic therapy is uncertain. For these patients, participation in a clinical trial or best supportive care (BSC) is recommended [II, C].

Topotecan is the only drug licensed in the European Union for use as second-line therapy in SCLC. Before topotecan development, anthracycline-based regimes were commonly used, including cyclophosphamide plus doxorubicin and vincristine (CAV). The first randomised trial with topotecan versus CAV showed similar objective response rates (ORRs), time to progression and OS between the two treatment arms and better tolerability with intravenous (i.v.) topotecan versus CAV.[65] Subsequently, a phase III trial of oral topotecan demonstrated an improvement in OS versus BSC (median 25.9 versus 13.9 weeks for topotecan versus BSC, respectively; $P = 0.0104$), a slower decline in QoL and greater symptom control in patients with relapsed SCLC, of whom half had resistant disease.[66] Oral and i.v. topotecan demonstrated similar efficacy in another phase III trial but with differing toxicity profiles.[67] Either oral or i.v. topotecan is recommended for patients with platinum-resistant or -sensitive relapse, with CAV as an alternative option [II, B]. Another valid option in platinum-sensitive patients is rechallenge with first-line platinum plus etoposide [II, B].[68] A phase III RCT recently showed comparable outcomes in patients with sensitive relapse when treated with either topotecan or rechallenge with carboplatin plus etoposide.[69]

Immunotherapy. The efficacy of nivolumab and pembrolizumab as third-line monotherapies in stage IV SCLC was assessed in small phase I/II studies.[70,71] In CheckMate 032, a single-arm, phase I/II study, 109 patients were treated with nivolumab (3 mg/kg) as third-line or later therapy. The ORR (primary outcome measure) was 11.9% (95% CI 6.5% to 19.5%).[70] The median duration of response was 17.9 months (95% CI 3.0-42.1 months). In KEYNOTE-028, a single-arm, phase Ib study, 24 patients who had failed standard treatment were treated with pembrolizumab 10 mg/kg every 2 weeks.[71] ORR was 33.3% (95% CI 15.6% to 55.3%). In addition, in KEYNOTE-158, an open-label, single-arm phase II study in advanced solid tumours, 76 SCLC patients who had failed standard first-line treatment (cohort G) were treated with pembrolizumab 200 mg every 3 weeks.[72] ORR was 18.4%. These results led to the Food and Drug Administration (FDA) approvals of both nivolumab and pembrolizumab as monotherapies for the treatment of patients with stage IV SCLC who have progressed after platinum-based ChT and at least one other line of therapy. However, in late 2020/early 2021, the manufacturers of nivolumab and pembrolizumab both voluntarily withdrew the SCLC indication for their product following discussions with the FDA as both drugs failed to reach the OS endpoint in their phase III confirmatory trials (KEYNOTE-604, CheckMate 451 and CheckMate 331), a post-marketing requirement following accelerated approval by the FDA.[73,74] In addition, the phase III RCT, CheckMate 331, comparing nivolumab to topotecan (or amrubicin) as second-line treatment in unselected (platinum-sensitive and -resistant) patients with stage IV SCLC and a PS of 0-1 failed to demonstrate an improvement in OS, PFS or ORR for nivolumab versus ChT.[75] Limited efficacy was also seen in the phase II French Cooperative Thoracic Intergroup 16-03 trial evaluating atezolizumab in relapsed SCLC ($N = 73$); the Q14 disappointing ORR (2.3%) and median PFS (1.4 months) following immunotherapy precluded activation of the phase III part of the study.[76]

The combination of cytotoxic T-lymphocyte-associated protein 4 and PD-L1 blockade is being evaluated in several ongoing trials. CheckMate 032 investigated nivolumab plus ipilimumab in patients with SCLC who progressed after one

or more prior regimens. Although a modest ORR of 19%-23% was reported, this increased to 46.2% in the highest tertile of tumours classified by TMB, with a median OS of 22 months.[77,78] Preliminary results from the phase II BALTIC study evaluating the combination of durvalumab and tremelimumab in platinum-refractory or -resistant stage IV SCLC showed similar results with an ORR of 9.5% and a median OS of 6 months.[79] These data require prospective validation and comparison with second-line ChT. In addition, the studies were carried out before the routine use of immune checkpoint inhibitors as first-line therapy. No data are available regarding rechallenge with immunotherapy in this setting.

Other systemic therapies in relapsed SCLC. Paclitaxel, irinotecan and temozolomide have all shown a degree of activity, with ORRs in the order of 15%-29% in small phase II studies.[80-83] In a phase III trial (JCOG 0605) comparing triplet ChT (cisplatin, etoposide and irinotecan) with topotecan as second-line treatment in highly selected, fit patients with SCLC who had relapsed ≥90 days after first-line therapy, the triplet regimen demonstrated superiority in terms of OS (median 18.2 versus 12.5 months, respectively; HR 0.67; $P = 0.0079$). However, the regimen has never been adopted because of the high proportion of grade ≥3 adverse events.[84]

Amrubicin failed to show a survival benefit versus topotecan in a phase III RCT, although a non-significant and modest improvement in OS was seen in a subset of platinum-refractory patients (HR 0.77; $P = 0.047$).[85] Amrubicin is currently not available in Western countries.

Lurbinectedin, a selective inhibitor of RNA polymerase II, has recently been granted orphan drug status by the European Medicines Agency (EMA) as well as accelerated FDA approval for the treatment of SCLC. In a recent single-arm, phase II trial (PM1183-B-005-14, NCT02454972) of 105 patients with relapsed SCLC, single-agent lurbinectedin 3.2 mg/m^2 given every 3 weeks showed promising activity as second-line therapy, with an ORR of 35.2% (22.2% in platinum-resistant and 45% in platinum-sensitive patients), median duration of response of 5.3 months and a manageable safety profile.[86] Median OS was 9.3 months (95% CI 6.3-11.8 months). A randomised phase III trial (ATLANTIS, NCT02566993) of lurbinectedin at a dose of 2.0 mg/m^2 plus doxorubicin versus investigator's choice of CAV or topotecan has completed recruitment, and a recent press release reported that the trial failed to meet the prespecified superiority endpoint of OS.[87] Lurbinectedin is a treatment option for patients progressing on or after first-line platinum-based ChT [III, C; ESMO-MCBS v1.1 score: 1].

Rovalpituzumab tesirine (Rova-T) is an antibody—drug conjugate targeting delta-like ligand 3 protein (DLL3). DLL3 is expressed in the majority of SCLCs whereas there is no or very limited expression in normal tissue, making it an interesting therapeutic target. However, a phase II study was not promising, with an ORR of 13.2% and an OS of 5.6 months in patients with DLL3-high SCLC.[88] Enrolment of two phase III studies (NCT03061812, NCT03033511) was ceased after an interim analysis and development of Rova-T was halted. Drugs using bispecific T-cell engager (BiTE®) and chimeric antigen receptor T-cell approaches are in development and phase I trials are recruiting. Thus, although DLL3 is an interesting potential target, the efficacy of agents targeting DLL3 needs to be demonstrated.

Transformed SCLC

SCLC transformation is a known resistance mechanism in patients with epidermal growth factor receptor (EGFR)-mutated NSCLC who are treated with EGFR tyrosine kinase inhibitors.[89] It occurs in 3%-5% of patients, especially in the presence of co-occurring *RB1* and *TP53* mutations.[90] A retrospective analysis of 67 patients with EGFR-mutated SCLC showed a response rate of 54% to platinum—etoposide, with a median PFS of 3.4 months.[91] Of 20 patients who were treated with a taxane, 10 (50%) had a response. However, none of the 17 patients who were treated with immunotherapy had a response. Thus, although responses appear inferior compared with those seen in *de novo* SCLC, both platinum—etoposide and taxanes are treatment options in patients with EGFR-mutated SCLC transformation [IV, B].

Recommendations

- Surgery may be considered in patients with clinical stages I and II (cT1-2N0) SCLC in the context of a multimodal treatment concept and following a multidisciplinary board decision [III, B].
- When considering surgical treatment for SCLC, pathological mediastinal staging is required [IV, A].
- The aim of surgical treatment is to achieve an R0 resection [III, A].
- Sublobular resection is not recommended for SCLC [V, E].
- During surgery for SCLC, a systematic nodal dissection should be carried out [IV, A].
- Adjuvant ChT should be given after surgical resection of SCLC [IV, A].
- In patient with an R1-R2 resection or positive mediastinal lymph nodes (N2), adjuvant ChT should be combined with RT, preferably concurrently [IV, A].
- The preferred ChT for patients with limited-stage (stage I-III) SCLC is cisplatin plus etoposide [I, A].
- When cisplatin is contraindicated because of comorbidities, carboplatin plus etoposide is an alternative [II, A].
- G-CSF is a treatment option to prevent haematological toxicity [II, B].
- Patients with T1-4N0-3M0 tumours and a good PS (0-1) should be treated with concurrent ChT and thoracic RT [I, A].
- The recommended dose fractionation schedule is 45 Gy b.i.d. in 30 fractions [I, A].
- Thoracic RT should be initiated as early as possible, starting on the first or second cycle of ChT [II, A].
- When the patient PS or dose to the organs at risk do not allow for the early administration of thoracic RT, it may

be postponed until the start of the third cycle of ChT [II, B].
- Sequential CRT is an option for patients who are not candidates for concurrent CRT due to poor PS, comorbidities and/or disease volume [V, B].
- In case of response to ChT, the post-ChT primary tumour should be included in the radiation field [II, B].
- In case of response to ChT, the pre-ChT nodal stations should be included in the radiation field [V, B].
- Omission of elective node irradiation is recommended, in favour of selective node irradiation (i.e. involved nodes defined as FDG avid on PET—CT, enlarged on CT and/or biopsy-positive) [III, A].
- Patients with stage III SCLC with a response after treatment (CRT) and a PS of 0-1 should be offered PCI [I, A]. PCI can be considered in patients with a PS of 2 [III, B].
- The role of PCI is not as well defined in patients with stage I-II SCLC or in those of age >70 years or who are frail. In such cases, shared decision-making is recommended [V, C].
- The role of PCI or consolidation thoracic RT in combination with immunotherapy is not well defined in patients with extensive-stage SCLC due to a paucity of data. Treatment may be considered following a shared decision-making process [IV, C].
- The recommended PCI regimen is 25 Gy/10 fractions [I, A].
- An anti-PD-L1 inhibitor (atezolizumab [I, A; ESMO-MCBS v1.1 score: 3] or durvalumab [I, A; ESMO-MCBS v1.1 score: 3]) in combination with four to six cycles of a platinum and etoposide can be offered to all patients with treatment-naive extensive-stage SCLC, a PS of 0-1 and no contraindications for immunotherapy [I, A].
- For immunotherapy-ineligible patients, the preferred first-line treatment of extensive-stage SCLC (PS 0-1 and PS 2 due to SCLC) is four to six cycles of a platinum plus etoposide [I, A].
- In extensive-stage SCLC, cisplatin can be substituted with carboplatin [I, B].
- For selected patients, considering age and toxicity profile, cisplatin might be preferred [II, C].
- Cisplatin with irinotecan or oral topotecan are alternative treatment options [II, C].
- In poor prognosis patients, gemcitabine plus carboplatin is an alternative treatment option [II, C].
- In patients achieving a response after ChT and a PS of 0-2, RT to the residual primary tumour and lymph nodes (30 Gy/10 fractions) is a treatment option [II, C].
- PCI (20 Gy/5 fractions and 25 Gy/10 fractions) is justified without prior MRI staging or follow-up in patients of age <75 years and a PS of 0-2 who achieved a response after ChT [II, B].
- In patients with extensive-stage SCLC without brain metastases on brain MRI after ChT and who can be followed-up with regular brain MRI, PCI may be omitted [II, B].
- Patients with platinum-refractory SCLC have a poor prognosis and participation in a clinical trial or BSC is recommended [II, C].
- Either oral or i.v. topotecan is recommended for patients with platinum-resistant or -sensitive relapse; CAV is an alternative option [II, B].
- Lurbinectedin [III, C; ESMO-MCBS v1.1 score: 1] is a treatment option for patients progressing on or after first-line platinum-based ChT [III, C].
- In patients with platinum-sensitive SCLC, rechallenge with first-line platinum plus etoposide can be considered [II, B].
- Both platinum—etoposide and taxanes are treatment options in patients with EGFR-mutated SCLC transformation [IV, B].

PERSONALISED MEDICINE

There are still no validated biomarkers that can be used for disease classification that have prognostic or predictive relevance or that can be used to inform medical treatment decisions. In addition, no targeted treatment has demonstrated activity in SCLC.

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Interval and duration of follow-up

Although no prospective trials are available regarding regular follow-up and its effect on survival, asymptomatic recurrences might be detected early with regular follow-up, with available treatments offered while the patient still has a good PS.[92] CT scans every 2-3 months are recommended in patients with extensive-stage disease potentially qualifying for further treatments [V, C]. Patients with limited-stage disease who have received potentially curative treatment should undergo 3-6-monthly CT scans for 2 years with lengthening of intervals thereafter [V, C]. Regular brain MRIs (every 3 months in the first year and then every 6 months) are advised in patients who did not undergo PCI [II, C].[12]

Another reason for regular (long-term) follow-up is the early detection of second primaries. In one series, the cumulative relative risk for developing a second primary was 3.73 and was 6.83 for developing a secondary NSCLC.[93] Yearly follow-up with a low-dose CT scan starting at the end of regular follow-up may be considered [V, C].

PCI: long-term toxicity

The long-term effects of PCI were studied in several randomised trials.[94-96] In the PCI intergroup trial of 720 patients with non-metastatic SCLC, clinical neurological outcome and QoL were evaluated.[95] There was no significant difference between the two groups over 3 years in any of the 17 selected items assessing QoL and neurological and cognitive functions. There was a mild deterioration over time of communication deficit, fatigue, intellectual deficit and memory. Age was a significant cofactor of neurocognitive decline and chronic neurotoxicity.[96]

In a recently reported Dutch-Flemish randomised phase III trial comparing standard PCI with hippocampus-sparing PCI, no differences in memory were observed.[97]

Neurocognitive decline after PCI may also be caused by other disorders, such as dementia and depression.[98] In addition, some nutritional deficiencies, which may be exacerbated by systemic ChT (e.g. vitamin B and folate deficiency), may lead to cognitive impairment, dementia and depression. Thus, a thorough evaluation is needed before a diagnosis of post-RT cognitive decline can be made, especially in elderly patients with multiple comorbidities. PCI results in a mild decline in neurocognitive functioning in ~30% of patients. Severe deterioration requires an in-depth analysis looking for other treatable causes [IV, A].

Comorbidities and influence on long-term toxicity

Three-quarters of patients with SCLC have comorbidities, with half having two or more comorbidities. Cardiovascular and pulmonary diseases occur most frequently.[99] Regular follow-up, paying attention to these comorbidities, could therefore be an option as this may improve survival. Pre-existing comorbidities, smoking habits and RT to the heart can all result in cardiac problems. Approximately 10% of patients with stage I-III SCLC experience cardiac problems and 3% die as a result.[100]

Smoking cessation

Continued smoking is associated with a higher risk of tumour recurrences, the development of second primaries, cardiovascular and cerebrovascular disease and all-cause mortality compared with those who stop smoking.[101] Moreover, continued smoking is associated with a decreased QoL among survivors.[102] Smoking cessation in patients already diagnosed with lung cancer improves PS and health-related QoL and may also improve survival.[103] Therefore, smoking cessation is highly encouraged [IV, B].

Recommendations

- Two- to three-monthly CT scans are recommended in patients with extensive-stage disease potentially qualifying for further treatments [V, C].
- Six-monthly CT scans for 2 years with lengthening of intervals thereafter are recommended for patients with non-metastatic disease who have received potentially curative treatment [V, C].
- Regular brain MRIs (every 3 months for the first year, then every 6 months) are advised in patients who have not undergone PCI [II, C].
- As patients with a history of lung cancer are at high risk of developing a second primary, yearly follow-up with a low-dose CT starting from the end of regular follow-up may be considered [V, C].
- Severe neurocognitive deterioration after PCI requires an in-depth analysis looking for other treatable causes [IV, A].
- The occurrence of second malignancies, particularly if smoking is continued, is of concern in survivors and smoking cessation counselling is essential [IV, B].

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. An ESMO-MCBS table with ESMO-MCBS scores is included in Section 3 (Supplementary Table S3) of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.03.207. ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the EMA and the FDA (https://www.esmo.org/Guidelines/ESMO-MCBS).[104] The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. Levels of evidence and grades of recommendation have been applied using the system shown in Section 4 (Supplementary Table S4) of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.03.207.[105] Statements without grading were considered justified standard clinical practice by the authors.

ACKNOWLEDGEMENTS

Corinne Faivre-Finn is supported by a grant from the NIHR Manchester Biomedical Research Centre. Manuscript editing support was provided by Angela Corstorphine of Kstorfin Medical Communications Ltd; this support was funded by ESMO.

FUNDING

No external funding has been received for the preparation of these guidelines. Production costs have been covered by ESMO from central funds.

DISCLOSURE

A-MCD reports receipt of honoraria for participation in advisory boards and/or lectures from Roche, Eli Lilly, Boehringer Ingelheim, AstraZeneca, Pfizer, BMS, Amgen, Novartis, MSD, Takeda and Pharmamar; research funding from BMS, AbbVie and Amgen. **MF** reports receipt of advisory board honoraria to institution from BMS, Takeda, AstraZeneca, Boehringer Ingelheim, MSD and Roche. **AA** reports receipt of honoraria for participation in advisory boards from AstraZeneca, Roche, MSD, BMS, Lilly, Takeda and Bayer; research grant from BMS. **BB** reports receipt of grants/research support to institute from AbbVie, Amgen, AstraZeneca, BeiGene, Blueprint Medicines, BMS, Boehringer Ingelheim, Celgene, Cristal Therapeutics, Daiichi Sankyo, Eli Lilly, GSK, Ignyta, IPSEN, Inivata, Janssen, Merck KGaA, MSD, Nektar, Onxeo, OSE Immunotherapeutics, Pfizer, Pharma Mar, Roche-Genentech, Sanofi, Servier, Spectrum Pharmaceuticals, Takeda, Tiziana Pharma and

Tolero Pharmaceuticals. **CF-F** reports participation in advisory boards for AstraZeneca; research funding from MSD and AstraZeneca. **LEH** reports research funding to institution from Roche, Boehringer Ingelheim and AstraZeneca; advisory board honoraria to institution from BMS, Lilly, Roche, Pfizer, Takeda, MSD, Amgen and Boehringer Ingelheim; speaker fees from MSD; travel/conference reimbursement from Roche and BMS; participation in mentorship program funded by AstraZeneca; fees for educational webinars from Quadia; fees to institution for interview sessions from Roche. **SL** reports consulting activities for MSD, AstraZeneca, BMS, Bayer and Eli Lilly. **SP** reports receipt of honoraria to institute for consultancy, advisory boards and/or lectures from AbbVie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer Ingelheim, BMS, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, Roche, Foundation Medicine, Illumina, Janssen, MSD, Merck Serono, Merrimack, Mirati, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics, Takeda and Vaccibody; institutional financial support for clinical trials from Amgen, AstraZeneca, Biodesix, Boehringer Ingelheim, BMS, Clovis, Roche, Illumina, MSD, Merck Serono, Novartis and Pfizer. **NR** reports receipt of speaker honoraria from MSD, BMS, Roche, Boehringer Ingelheim, Guardant Health, Pfizer, AbbVie, Ipsen, Novartis, AstraZeneca, Lilly, Takeda and Amgen; fees for organising educational events from Amgen and Roche; advisory panel honoraria from MSD, BMS, Roche, Boehringer Ingelheim, Guardant Health, Pfizer, AbbVie, Ipsen, Novartis, AstraZeneca, Lilly, Takeda and Amgen; sponsorship to attend scientific meetings from Boehringer Ingelheim, MSD and Roche; research grants from Novartis and Pfizer. **CMR** reports consultancy for AbbVie, Amgen, Ascentage, AstraZeneca, Bicycle, Celgene, Daiichi Sankyo, Genentech/Roche, Ipsen, Jazz, Lilly, Pfizer, PharmaMar, Syros and Vavotek; serves on scientific advisory boards for Bridge Medicines and Harpoon Therapeutics. **DDR** reports receipt of research grants to institute from BMS, AstraZeneca and Boehringer Ingelheim; advisory board honoraria to institute from BMS, AstraZeneca, Boehringer Ingelheim and Philips; funding to institute for investigator-initiated study from Olink. **PEVS** reports board membership of IASLC; treasurer of BACTS; fees to institution for serving as an external expert for AstraZeneca, MSD and National Cancer Institute, France. **JV** reports receipt of advisory board honoraria and/or lecture fees from Boehringer Ingelheim, AstraZeneca, MSD, Novartis, Roche, Pfizer and BMS; research grant to institute from MSD. **MR** reports receipt of honoraria for lectures and consultancy from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Lilly, Merck, MSD, Novartis, Pfizer, Roche and Samsung; funding for academic research from BMS and Boehringer Ingelheim.

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures 2019*. Atlanta: American Cancer Society. 2019. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed October 20, 2020.
2. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol* 2006;24(28):4539-4544.
3. Breitling LP, Rinke A, Gress TM. Recent survival trends in high-grade neuroendocrine neoplasms and lung cancer. *Neuroendocrinology* 2020;110(3-4):225-233.
4. Abdel-Rahman O. Changing epidemiology of elderly small cell lung cancer patients over the last 40 years; a SEER database analysis. *Clin Respir J* 2018;12(3):1093-1099.
5. Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. *N Engl J Med* 2013;369(10):920-931.
6. Silva M, Galeone C, Sverzellati N, et al. Screening with low-dose computed tomography does not improve survival of small cell lung cancer. *J Thorac Oncol* 2016;11(2):187-193.
7. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol* 2007;2(12):1067-1077.
8. Nicholson AG, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016;11(3):300-311.
9. Gozzard P, Woodhall M, Chapman C, et al. Paraneoplastic neurologic disorders in small cell lung carcinoma: a prospective study. *Neurology* 2015;85(3):235-239.
10. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;28(suppl 4):iv1-iv21.
11. Seute T, Leffers P, ten Velde GP, et al. Detection of brain metastases from small cell lung cancer: consequences of changing imaging techniques (CT versus MRI). *Cancer* 2008;112(8):1827-1834.
12. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2017;18(5):663-671.
13. Martucci F, Pascale M, Valli MC, et al. Impact of (18)F-FDG PET/CT in staging patients with small cell lung cancer: a systematic review and meta-analysis. *Front Med (Lausanne)* 2019;6:336.
14. Manoharan P, Salem A, Mistry H, et al. (18)F-Fludeoxyglucose PET/CT in SCLC: analysis of the CONVERT randomized controlled trial. *J Thorac Oncol* 2019;14(7):1296-1305.
15. Foster NR, Mandrekar SJ, Schild SE, et al. Prognostic factors differ by tumor stage for small cell lung cancer: a pooled analysis of North Central Cancer Treatment Group trials. *Cancer* 2009;115(12):2721-2731.
16. Reymen B, Van Loon J, van Baardwijk A, et al. Total gross tumor volume is an independent prognostic factor in patients treated with selective nodal irradiation for stage I to III small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013;85(5):1319-1324.
17. Barnes H, See K, Barnett S, et al. Surgery for limited-stage small-cell lung cancer. *Cochrane Database Syst Rev* 2017;4(4):Cd011917.
18. Zhao X, Kallakury B, Chahine JJ, et al. Surgical resection of SCLC: prognostic factors and the tumor microenvironment. *J Thorac Oncol* 2019;14(5):914-923.
19. Wakeam E, Acuna SA, Leighl NB, et al. Surgery versus chemotherapy and radiotherapy for early and locally advanced small cell lung cancer: a propensity-matched analysis of survival. *Lung Cancer* 2017;109:78-88.
20. Villaruz L, Karlovits BJ, Burns TF, et al. Small-cell lung cancer. In: LoCicero III J, Colson YL, Feins RH, et al., editors. *Shields' General Thoracic Surgery*. Philadelphia, PA: Wolters Kluwer; 2019. p. 1308-1319.

21. Kreisman H, Wolkove N, Quoix E. Small cell lung cancer presenting as a solitary pulmonary nodule. *Chest* 1992;101(1):225-231.
22. Ernani V, Ganti AK. Surgery for limited-stage small cell lung cancer: ready for prime-time? *J Thorac Dis* 2017;9(10):3576-3578.
23. Stinchcombe TE. Current treatments for surgically resectable, limited-stage, and extensive-stage small cell lung cancer. *Oncologist* 2017;22(12):1510-1517.
24. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer* 2005;49(1):25-33.
25. Yang CF, Chan DY, Speicher PJ, et al. Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. *J Clin Oncol* 2016;34(10):1057-1064.
26. Mascaux C, Paesmans M, Berghmans T, et al. A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis. *Lung Cancer* 2000;30(1):23-36.
27. Karam I, Jiang SY, Khaira M, et al. Outcomes of small cell lung cancer patients treated with cisplatin-etoposide versus carboplatin-etoposide. *Am J Clin Oncol* 2015;38(1):51-54.
28. Arriagada R, Pignon JP, Le Chevalier T. Initial chemotherapeutic doses and long-term survival in limited small-cell lung cancer. *N Engl J Med* 2001;345(17):1281-1282.
29. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol* 2017;18(8):1116-1125.
30. Gomes F, Faivre-Finn C, Mistry H, et al. Safety of G-CSF with concurrent chemo-radiotherapy in limited-stage small cell lung cancer—secondary analysis of the randomised phase 3 CONVERT tria. *Lung Cancer* 2021;153:165-170.
31. Bunn PA Jr, Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. *J Clin Oncol* 1995;13(7):1632-1641.
32. Veslemes M, Polyzos A, Latsi P, et al. Optimal duration of chemotherapy in small cell lung cancer: a randomized study of 4 versus 6 cycles of cisplatin-etoposide. *J Chemother* 1998;10(2):136-140.
33. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 2018;379(24):2342-2350.
34. Peters S, Pujol JL, Dafni U, et al. LBA84 consolidation ipilimumab and nivolumab vs observation in limited stage SCLC after chemoradiotherapy: results from the ETOP/IFCT 4-12 STIMULI trial. *Ann Oncol* 2020;31:S1211.
35. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340(4):265-271.
36. Grønberg BH, Halvorsen TO, Fløtten Ø, et al. Randomized phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer. *Acta Oncol* 2016;55(5):591-597.
37. De Ruysscher D, Lueza B, Le Péchoux C, et al. Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis. *Ann Oncol* 2016;27(10):1818-1828.
38. Lu H, Fang L, Wang X, et al. A meta-analysis of randomized controlled trials comparing early and late concurrent thoracic radiotherapy with etoposide and cisplatin/carboplatin chemotherapy for limited-disease small-cell lung cancer. *Mol Clin Oncol* 2014;2(5):805-810.
39. Kies MS, Mira JG, Crowley JJ, et al. Multimodal therapy for limited small-cell lung cancer: a randomized study of induction combination chemotherapy with or without thoracic radiation in complete responders; and with wide-field versus reduced-field radiation in partial responders: a Southwest Oncology Group Study. *J Clin Oncol* 1987;5(4):592-600.
40. De Ruysscher D, Bremer RH, Koppe F, et al. Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: a phase II trial. *Radiother Oncol* 2006;80(3):307-312.
41. van Loon J, De Ruysscher D, Wanders R, et al. Selective nodal irradiation on basis of (18)FDG-PET scans in limited-disease small-cell lung cancer: a prospective study. *Int J Radiat Oncol Biol Phys* 2010;77(2):329-336.
42. Shirvani SM, Komaki R, Heymach JV, et al. Positron emission tomography/computed tomography-guided intensity-modulated radiotherapy for limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012;82(1):e91-e97.
43. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999;341(7):476-484.
44. Le Péchoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol* 2009;10(5):467-474.
45. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. *J Clin Oncol* 2012;30(14):1692-1698.
46. Rossi A, Garassino MC, Cinquini M, et al. Maintenance or consolidation therapy in small-cell lung cancer: a systematic review and meta-analysis. *Lung Cancer* 2010;70(2):119-128.
47. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346(2):85-91.
48. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006;24(13):2038-2043.
49. Liu ZL, Wang B, Liu JZ, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin in patients with previously untreated extensive-stage small cell lung cancer: a meta-analysis. *J Cancer Res Ther* 2018;14(supplement):S1076-S1083.
50. Eckardt JR, von Pawel J, Papai Z, et al. Open-label, multicenter, randomized, phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naive patients with extensive-disease small-cell lung cancer. *J Clin Oncol* 2006;24(13):2044-2051.
51. Lee SM, James LE, Qian W, et al. Comparison of gemcitabine and carboplatin versus cisplatin and etoposide for patients with poor-prognosis small cell lung cancer. *Thorax* 2009;64(1):75-80.
52. Reck M, Luft A, Szczesna A, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. *J Clin Oncol* 2016;34(31):3740-3748.
53. Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 2018;379(23):2220-2229.
54. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2019;394(10212):1929-1939.
55. Liu SV, Reck M, Mansfield AS, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). *J Clin Oncol* 2021;39(6):619-630. Q16
56. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* 2021;22(1):51-65.

57. Goldman JW, Garassino MC, Chen Y, et al. Patient-reported outcomes with first-line durvalumab plus platinum-etoposide versus platinum-etoposide in extensive-stage small-cell lung cancer (CASPIAN): a randomized, controlled, open-label, phase III study. *Lung Cancer* 2020;149:46-52.
58. Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol* 2020;38(21):2369-2379.
59. Owonikoko TK, Kim HR, Govindan R, et al. LBA1_PR—Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): results from the double-blind, randomized phase III CheckMate 451 study. *Ann Oncol* 2019;30:ii77.
60. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. *J Clin Oncol* 1999;17(7):2092-2099.
61. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet* 2015;385(9962):36-42.
62. Slotman BJ, van Tinteren H, Praag JO, et al. Radiotherapy for extensive stage small-cell lung cancer—authors' reply. *Lancet* 2015;385(9975):1292-1293.
63. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007;357(7):664-672.
64. Owonikoko TK, Behera M, Chen Z, et al. A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. *J Thorac Oncol* 2012;7(5):866-872.
65. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999;17(2):658-667.
66. O'Brien ME, Ciuleanu TE, Tsekov H, 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(34):5441-5447.
67. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol* 2007;25(15):2086-2092.
68. Postmus PE, Berendsen HH, van Zandwijk N, et al. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. *Eur J Cancer Clin Oncol* 1987;23(9):1409-1411.
69. Baize N, Monnet I, Greillier L, 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(9):1224-1233.
70. Ready N, Farago AF, de Braud F, et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. *J Thorac Oncol* 2019;14(2):237-244.
71. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. *J Clin Oncol* 2017;35(34):3823-3829.
72. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 2020;21(10):1353-1365.
73. Merck. Merck provides update on KEYTRUDA® (pembrolizumab) indication in metastatic small cell lung cancer in the US. 2021. Available at: https://www.merck.com/news/merck-provides-update-on-keytruda-pembrolizumab-indication-in-metastatic-small-cell-lung-cancer-in-the-us/. Accessed March 19, 2021.
74. BMS. Bristol Myers Squibb statement on Opdivo (nivolumab) small cell lung cancer U.S. indication. 2020. Available at: https://news.bms.com/news/details/2020/Bristol-Myers-Squibb-Statement-on-Opdivo-nivolumab-Small-Cell-Lung-Cancer-US-Indication/default.aspx. Accessed March 19, 2021.
75. Spigel DR, Vicente D, Ciuleanu TE, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331☆. *Ann Oncol* 2021. https://doi.org/10.1016/j.annonc.2021.01.071. Q17
76. Pujol JL, Greillier L, Audigier-Valette C, et al. A randomized non-comparative phase II study of anti-programmed cell death-ligand 1 atezolizumab or chemotherapy as second-line therapy in patients with small cell lung cancer: results from the IFCT-1603 trial. *J Thorac Oncol* 2019;14(5):903-913.
77. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol* 2016;17(7):883-895.
78. Hellmann MD, Callahan MK, Awad MM, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. *Cancer Cell* 2019;35(2):329.
79. Bondarenko I, Juan-Vidal O, Pajkos G, et al. 1665PD—Preliminary efficacy of durvalumab plus tremelimumab in platinum-refractory/resistant ED-SCLC from arm A of the phase II BALTIC study. *Ann Oncol* 2018;29:viii596.
80. Smit EF, Fokkema E, Biesma B, et al. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. *Br J Cancer* 1998;77(2):347-351.
81. Yamamoto N, Tsurutani J, Yoshimura N, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. *Anticancer Res* 2006;26(1b):777-781.
82. Pietanza MC, Kadota K, Huberman K, et al. Phase II trial of temozolomide in patients with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. *Clin Cancer Res* 2012;18(4):1138-1145.
83. Zauderer MG, Drilon A, Kadota K, et al. Trial of a 5-day dosing regimen of temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase. *Lung Cancer* 2014;86(2):237-240.
84. Goto K, Ohe Y, Shibata T, et al. Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer (JCOG0605): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2016;17(8):1147-1157.
85. von Pawel J, Jotte R, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol* 2014;32(35):4012-4019.
86. Trigo J, Subbiah V, Besse B, 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(5):645-654.
87. Jazz Pharmaceuticals. Jazz Pharmaceuticals and PharmaMar announce results of ATLANTIS phase 3 study evaluating Zepzelca™ in combination with doxorubicin for patients with small cell lung cancer following one prior platinum-containing line. 2020. Available at: https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-and-pharmamar-announce-results-atlantis. Accessed February 2, 2021.
88. Morgensztern D, Besse B, Greillier L, et al. Efficacy and safety of rovalpituzumab tesirine in third-line and beyond patients with DLL3-expressing, relapsed/refractory small-cell lung cancer: results from the phase II TRINITY study. *Clin Cancer Res* 2019;25(23):6958-6966.
89. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013;19(8):2240-2247.
90. Offin M, Chan JM, Tenet M, et al. Concurrent RB1 and TP53 alterations define a subset of EGFR-mutant lung cancers at risk for histologic transformation and inferior clinical outcomes. *J Thorac Oncol* 2019;14(10):1784-1793.
91. Marcoux N, Gettinger SN, O'Kane G, et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: clinical outcomes. *J Clin Oncol* 2019;37(4):278-285.

92. Sugiyama T, Hirose T, Hosaka T, et al. Effectiveness of intensive follow-up after response in patients with small cell lung cancer. *Lung Cancer* 2008;59(2):255-261.
93. Sagman U, Lishner M, Maki E, et al. Second primary malignancies following diagnosis of small-cell lung cancer. *J Clin Oncol* 1992;10(10): 1525-1533.
94. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer* 1997;33(11):1752-1758.
95. Le Péchoux C, Laplanche A, Faivre-Finn C, et al. Clinical neurological outcome and quality of life among patients with limited small-cell cancer treated with two different doses of prophylactic cranial irradiation in the intergroup phase III trial (PCI99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01). *Ann Oncol* 2011;22(5): 1154-1163.
96. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;81(1):77-84.
97. Belderbos J, Ruysscher D, Jaeger K, et al. OC-0503 phase III trial of prophylactic cranial irradiation with or without hippocampus avoidance in SCLC. *Radiother Oncol* 2019;133:S259.
98. De Ruysscher D, Niedermann G, Burnet NG, et al. Radiotherapy toxicity. *Nat Rev Dis Primers* 2019;5(1):13.
99. Aarts MJ, Aerts JG, van den Borne BE, et al. Comorbidity in patients with small-cell lung cancer: trends and prognostic impact. *Clin Lung Cancer* 2015;16(4):282-291.
100. Ferris MJ, Jiang R, Behera M, et al. Radiation therapy is associated with an increased incidence of cardiac events in patients with small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2018;102(2):383-390.
101. Parsons A, Daley A, Begh R, et al. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *BMJ* 2010;340:b5569.
102. Chen J, Qi Y, Wampfler JA, et al. Effect of cigarette smoking on quality of life in small cell lung cancer patients. *Eur J Cancer* 2012;48(11):1593-1601.
103. Dobson Amato KA, Hyland A, Reed R, et al. Tobacco cessation may improve lung cancer patient survival. *J Thorac Oncol* 2015;10(7):1014-1019.
104. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol* 2017;28(10):2340-2366.
105. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001;33(2):139-144 (adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. Clin Infect Dis.1994;1918:1421).

Systemic Therapy for Small-Cell Lung Cancer: ASCO-Ontario Health (Cancer Care Ontario) Guideline

Humera Khurshid, MD[1]; Nofisat Ismaila, MD[2]; Jessica Bian, MD[3]; Raetasha Dabney, MD[4]; Millie Das, MD[5]; Peter Ellis, MD[6]; Jill Feldman, BS, MA[7]; Christine Hann, MD, PhD[8]; Swati Kulkarni, MD[9]; Janessa Laskin, MD, PhD[10]; Rami Manochakian, MD[11]; Deebya Raj Mishra, MD[12]; Isabel Preeshagul, DO[13]; Pavan Reddy, MD[14]; Ashish Saxena, MD, PhD[15]; Frank Weinberg, MD, PhD[16]; and Gregory P. Kalemkerian, MD[17]

DOI https://doi.org/10.1200/JCO.23.01435

ABSTRACT

PURPOSE To provide evidence-based recommendations to practicing clinicians on the management of patients with small-cell lung cancer.

METHODS An Expert Panel of medical oncology, thoracic surgery, radiation oncology, pulmonary, community oncology, research methodology, and advocacy experts were convened to conduct a literature search, which included systematic reviews, meta-analyses, and randomized controlled trials published from 1990 through 2022. Outcomes of interest included response rates, overall survival, disease-free survival or recurrence-free survival, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS The literature search identified 95 relevant studies to inform the evidence base for this guideline.

RECOMMENDATIONS Evidence-based recommendations were developed to address systemic therapy options, timing of therapy, treatment in patients who are older or with poor performance status, role of biomarkers, and use of myeloid-supporting agents in patients with small-cell lung cancer.
Additional information is available at www.asco.org/thoracic-cancer-guidelines.

ACCOMPANYING CONTENT

Listen to the podcast by Dr Kalemkerian at guideline.libsyn.com

Appendix

Data Supplement

Accepted July 20, 2023
Published October 11, 2023

Evidence Based Medicine Committee approval:
June 26, 2023

J Clin Oncol 41:5448-5472

View Online Article

INTRODUCTION

Small-cell lung cancer (SCLC) is an aggressive, poorly differentiated, neuroendocrine carcinoma with more than 150,000 people diagnosed worldwide each year.[1,2] Nearly all patients with SCLC have a history of cigarette use. In the United States, SCLC accounts for approximately 15% of all new lung cancer cases and its incidence is declining because of decreased rates of cigarette smoking.[3]

SCLC is usually staged using the Veterans Administration Lung Study Group staging system, which defines limited-stage (LS-SCLC) as disease confined to one hemithorax within a tolerable radiation field, and extensive-stage (ES-SCLC) as disease extending beyond LS-SCLC, including malignant pleural effusion, contralateral lung involvement, and hematogenous metastases.[4] Over two thirds of patients present with extensive-stage disease at diagnosis.

LS-SCLC is potentially curable when treated with concurrent chemoradiotherapy, with 5-year overall survival (OS) rates reported as up to 34%.[5] ES-SCLC remains an incurable disease with a 5-year OS rate of <5%.[2,3] Until recently, the major improvements in outcomes achieved for patients with SCLC were due to advances in radiotherapy, particularly in those with limited-stage disease.[6,7] Since the last ASCO update in SCLC management in 2015,[8] there have now been significant advances in the systemic treatment of ES-SCLC with the incorporation of immune checkpoint inhibitors (ICIs) into first-line therapy,[9,10] and additional options for subsequent treatment of recurrent disease.[11,12]

Importantly, any discussion of the management of patients with SCLC would be incomplete without a strong recommendation for smoking cessation, not only to decrease the risk of developing lung cancer, but also to improve the outcomes of people already diagnosed with lung cancer. Numerous studies have reported that smoking cessation results in superior outcomes in terms of cancer recurrence, tolerance of and response to treatment, and OS for patients with both early-stage and advanced lung cancer.[13-17] The purpose of this ASCO and Ontario Health (Cancer Care Ontario) updated guideline is to summarize recommendations for systemic therapy in the management of patients with SCLC in light of recent advances.

THE BOTTOM LINE

Systemic Therapy for Small-Cell Lung Cancer: ASCO-Ontario Health (Cancer Care Ontario) Guideline

Guideline Questions

What is the optimal systemic therapy for patients with small-cell lung cancer (SCLC)?

Target Population

Patients with SCLC.

Target Audience

Medical oncologists, radiation oncologists, thoracic surgeons, pulmonologists, pathologists, radiologists, primary care physicians, nurse practitioners, physician assistants, pharmacists, nurses, and other providers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Recommendation 1.1

Adjuvant chemotherapy should be offered to patients with resected limited-stage SCLC who have adequate performance status (PS) (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Recommendation 1.2

Adjuvant chemotherapy should consist of four cycles of cisplatin (PE) or carboplatin plus etoposide (CE) (Type: Informal consensus, benefits outweigh harms; Evidence quality: Not applicable; Strength of recommendation: Weak).

Recommendation 1.3

Adjuvant chemotherapy should be initiated within 8 weeks from resection (Type: Informal consensus, benefits outweigh harms; Evidence quality: Not applicable; Strength of recommendation: Weak).

Recommendation 2.1

Cisplatin and etoposide should be administered with concurrent radiotherapy in patients with limited-stage small-cell lung cancer (LS-SCLC) (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 2.2

Carboplatin and etoposide may be offered as systemic therapy concurrent with radiation for patients with LS-SCLC and contraindications to the use of cisplatin (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Recommendation 2.3

Chemotherapy should be commenced as soon as possible in patients with LS-SCLC and not deferred until radiation therapy can be started (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Recommendation 3.1

First-line systemic therapy with CE or PE plus immunotherapy (atezolizumab or durvalumab) followed by maintenance immunotherapy should be offered to patients with extensive-stage small-cell lung cancer (ES-SCLC) if there are no contraindications to immunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 4.1

In patients with relapsed SCLC with a chemotherapy-free interval of <90 days, single-agent chemotherapy may be offered. Preferred agents are topotecan or lurbinectedin (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statement. Single-agent chemotherapy is preferred over multi-agent chemotherapy due to concerns regarding the balance of risks versus benefits.

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Recommendation 4.2

In patients with relapsed SCLC with a chemotherapy-free interval of at least 90 days, rechallenge with a platinum-based regimen or single-agent chemotherapy (preferred agents are topotecan or lurbinectedin) may be offered (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 4.3

In patients with relapsed SCLC who had progression while on maintenance immunotherapy, there is no evidence to support continuation of immunotherapy (Type: Informal consensus, benefit to harm ratio not assessable; Evidence quality: Not applicable; Strength of recommendations: Strong).

Recommendation 4.4

In an immunotherapy-naïve patient, second-line immunotherapy alone is not recommended outside of the clinical trial setting. Participation in clinical trials to better identify predictive biomarkers is encouraged (Type: Evidence based, no net benefit; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 5.1

Older patients with LS-SCLC and Eastern Cooperative Oncology Group (ECOG) PS 0-1 may be offered standard treatment with concurrent chemoradiotherapy with curative intent (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 5.2

Patients with LS-SCLC and ECOG PS 2 due to SCLC may be offered standard treatment with concurrent chemoradiotherapy with curative intent (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 5.3

Patients with LS-SCLC and ECOG PS 3-4 due to SCLC may be offered initial chemotherapy followed by sequential radiotherapy if there is improvement in PS (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 5.4

Older patients with ES-SCLC and ECOG PS 0-1 may be offered standard treatment with carboplatin and etoposide plus immunotherapy (atezolizumab or durvalumab) followed by maintenance immunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 5.5

Patients with ES-SCLC and ECOG PS 2 may be offered carboplatin and etoposide plus immunotherapy (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 5.6

Patients with ES-SCLC and ECOG PS 3-4 due to SCLC may be offered chemotherapy (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 6.1

Patients with non–small-cell lung cancer (NSCLC) harboring an *EGFR* mutation that has transformed to SCLC should be managed with CE or PE (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statement. There is insufficient evidence to support the use of immunotherapy in this setting. Clinical trial enrollment should be offered whenever possible.

Recommendation 6.2

EGFR inhibitor may be continued with chemotherapy in patients with NSCLC harboring an *EGFR* mutation that has transformed to SCLC (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Recommendation 7.1

There is no evidence to support the use of molecular profiling and biomarker analysis to guide standard treatment in patients with de novo SCLC (Type: Evidence based, benefit to harm ratio not assessable; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 8.1

Trilaciclib or granulocyte colony-stimulating factor (G-CSF) may be offered as a myeloid supportive agent for patients with untreated or previously treated ES-SCLC who are undergoing treatment with chemotherapy or chemoimmunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Recommendation 8.2

G-CSF may be offered in patients with LS-SCLC who are undergoing chemoradiotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

In addition, ASCO has appraised and endorses the American Society for Radiation Oncology guidelines on radiotherapy for patients with SCLC.[18]

GUIDELINE QUESTIONS

This clinical practice guideline addresses eight overarching clinical questions: (1) What is the optimal treatment regimen for adjuvant systemic therapy in patients with resected SCLC? (2) What is the optimal systemic therapy for use with concurrent radiotherapy in patients with LS-SCLC? (3) What is the optimal first-line systemic therapy for patients with ES-SCLC? (4) What systemic therapy options are available for treating relapsed SCLC? (5) What is the best management approach for treatment-naïve patients who are older or who have poor performance status (PS)? (6) What is the optimal systemic therapy for patients with non–small-cell lung cancer (NSCLC) harboring an epidermal growth factor receptor (*EGFR*) mutation that has transformed to SCLC? (7) What is the role of biomarkers, including molecular profiling in guiding therapy for patients with SCLC? (8) Which myeloid supportive agents may be considered for use in patients with SCLC?

METHODS

Guideline Development Process

This systematic review (SR)–based joint guideline product was developed by a multidisciplinary Expert Panel with representatives from OH (CCO), a patient representative, and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1). Four full panel and several subgroup panel meetings were held and members were asked to provide ongoing input on the quality and assessment of the evidence, generation of recommendations, draft content, as well as review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the expert panel co-chairs and corresponded with the panel via e-mail to coordinate the process to completion. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee (EBMC) before publication. In addition to the ASCO approval process, OH (CCO) provided approval through its Program in Evidence-Based Care approval internal and external processes. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a SR of evidence identified through online searches of PubMed (January 1990-December 2022) and Cochrane Library (January 2010-August 2022) of phase II and III randomized clinical trials (RCTs), and clinical experience. Articles were selected for inclusion in the SR based on the following criteria.

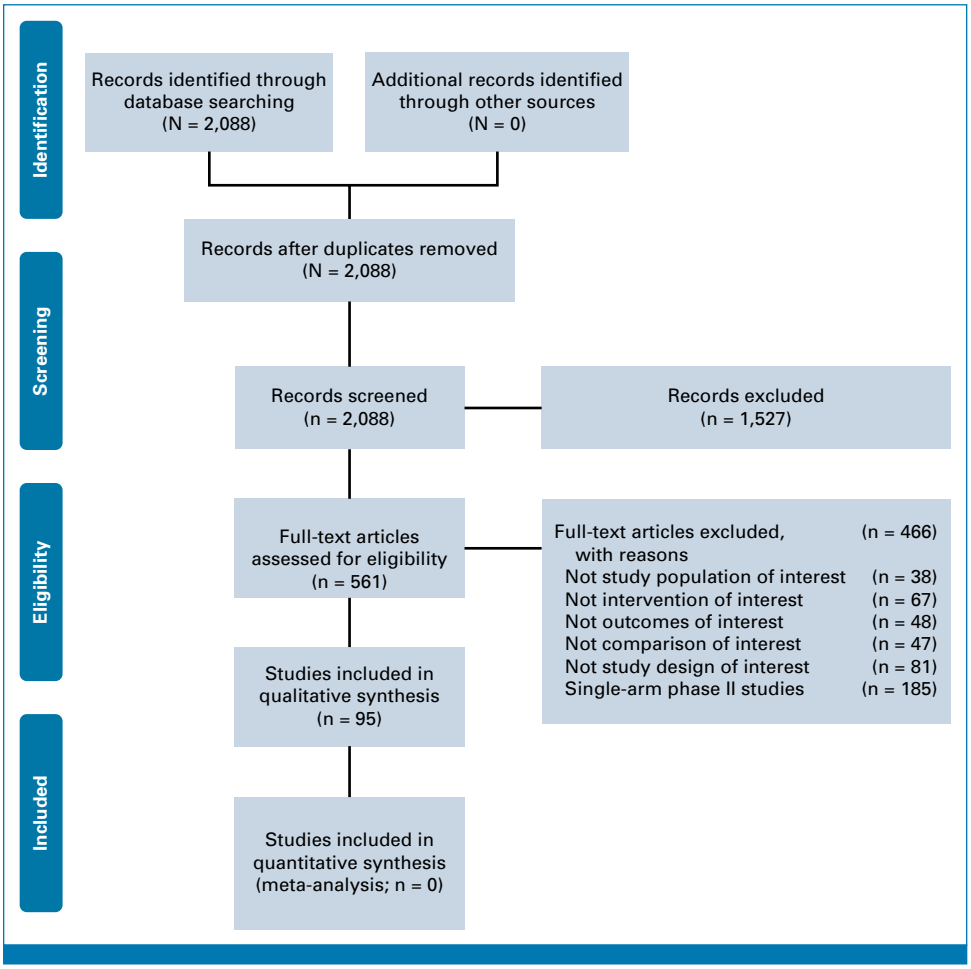


FIG 1. PRISMA flow diagram. From Moher et al.[117]

- Population: Patients with SCLC
- Interventions and comparisons: Systemic therapies, biomarkers, and myeloid supportive agents
- Outcomes: Survival, response rates (RRs), quality of life (QoL), and toxicity
- Study designs: SRs, meta-analyses (MAs), phase III RCTs, and phase II RCTs for some specific research questions.

Articles were excluded from the SR if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software.[19] In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for type and strength of the recommendation, and evidence quality are provided with each recommendation. The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[20,21] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The

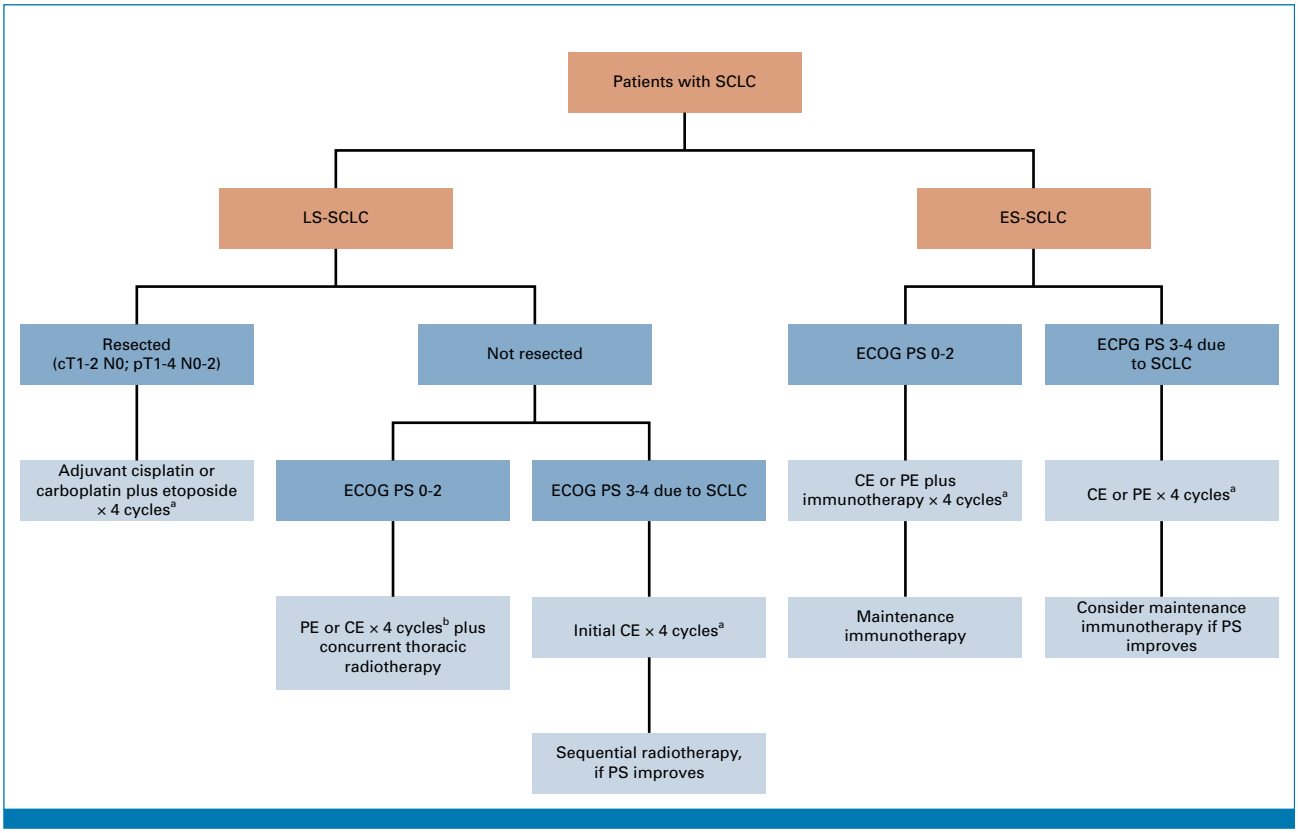


FIG 2. Systemic therapy for SCLC algorithm. [a]May use trilaciclib or G-CSF if clinically indicated. [b]May use G-CSF if clinically indicated. CE, carboplatin plus etoposide; cT, clinical TNM classification; ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small-cell lung cancer; G-CSF, granulocyte colony-stimulating factor; LS-SCLC, limited-stage small-cell lung cancer; PE, cisplatin plus etoposide; PS, performance status; pT, pathologic TNM classification; SCLC, small-cell lung cancer.

information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third-party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions. OH (CCO) makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of

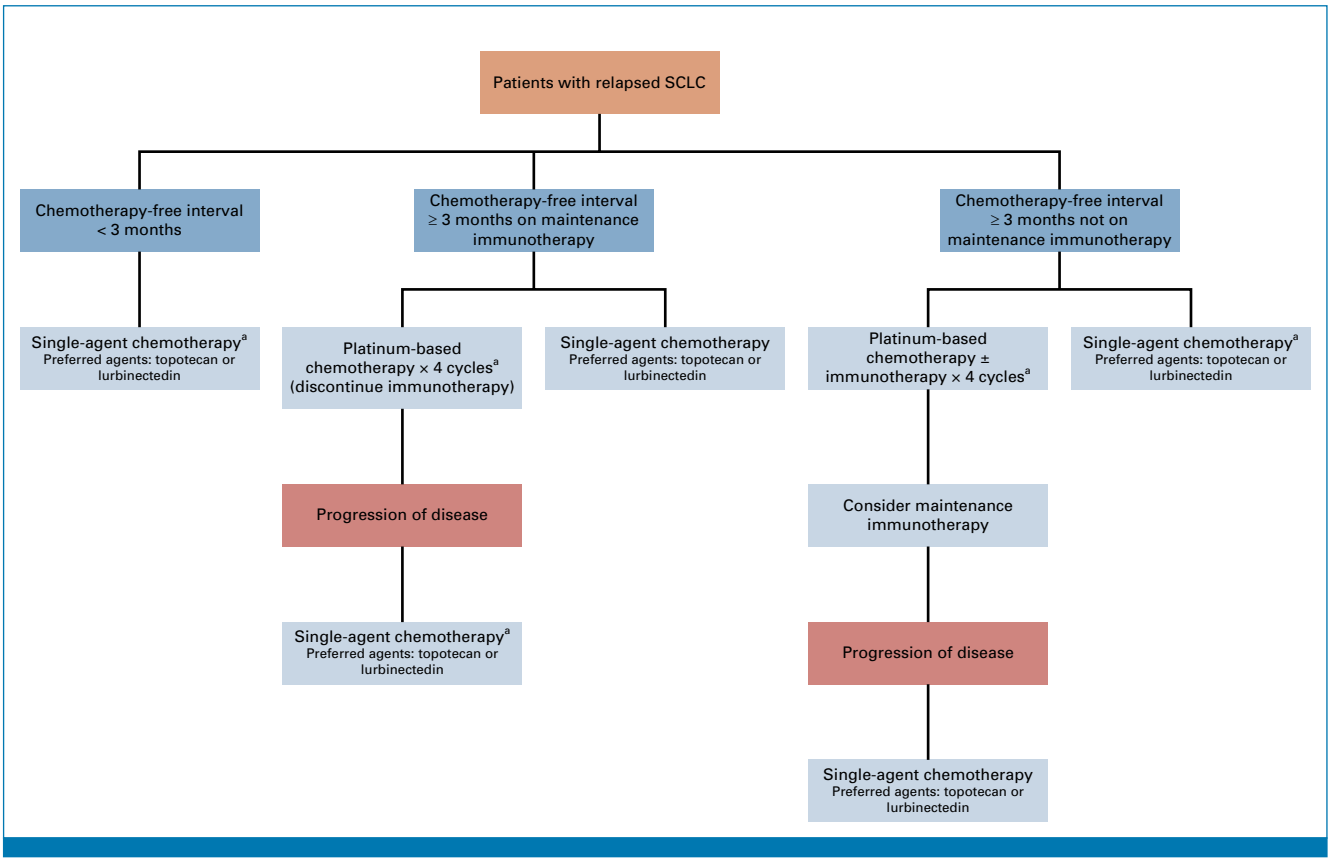


FIG 3. Systemic therapy for relapsed SCLC algorithm. [a]May use trilaciclib or granulocyte colony-stimulating factor if clinically indicated. SCLC, small-cell lung cancer.

the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 2,088 articles were identified in the literature search. After applying the eligibility criteria, 95 remained, forming the evidentiary basis for the guideline recommendations. These include 19 SRs and MAs,[22-40] three pooled analyses,[41-43] 34 phase III RCTs,[44-77] 26 phase II studies,[78-103] and four prospective[104-107] and nine retrospective cohort studies.[108-116] Primary studies already included in the SRs and MA are not included in this total.

The identified trials were published between 1990 and 2022. The studies compared different systemic therapy treatments, timing of therapy, therapy in patients who are older or with poor PS, biomarker testing, and use of myeloid supportive agents. The outcomes included OS, disease-free survival, progression-free survival (PFS), RR, QoL, toxicity, and febrile neutropenia. Figure 1 presents the SR flow diagram. Evidence summary tables for all included studies are available in the Data Supplement (online only).

Evidence Quality Assessment

Study quality was formally assessed for the RCTs identified. Design aspects related to the individual study quality were assessed by the research methodologist, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc, generally indicating an unclear to high overall risk-of-bias assessment for most of the identified evidence. Details of the assessment can be found in the GRADE tables included in the Data Supplement. Refer to Methodology Manual for definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

Clinical Question 1

What is the optimal treatment regimen for adjuvant systemic therapy in patients with resected SCLC? (1) Who should be offered adjuvant systemic therapy for resected SCLC? (2) What is the optimal timing for receiving adjuvant systemic therapy?

Recommendation 1.1

Adjuvant chemotherapy should be offered to patients with resected limited-stage SCLC who have adequate PS (Type:

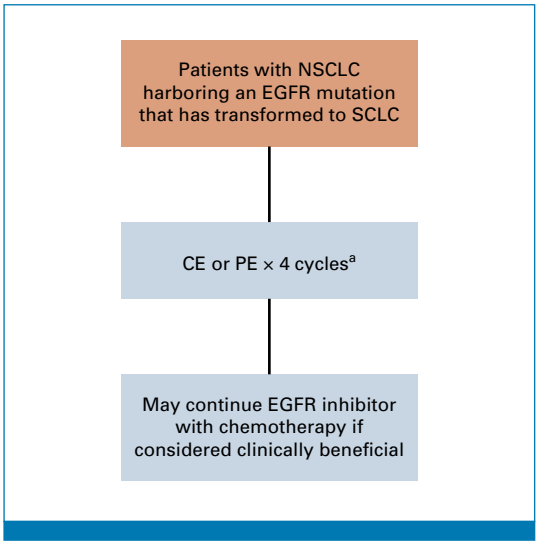


FIG 4. Systemic therapy for *EGFR*-mutant NSCLC transformed to SCLC algorithm. [a]May use trilaciclib or granulocyte colony-stimulating factor if clinically indicated. CE, carboplatin plus etoposide; NSCLC, non–small-cell lung cancer; PE, cisplatin plus etoposide; SCLC, small-cell lung cancer.

Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Literature review and clinical interpretation. Surgery is performed in fewer than 5% of patients with SCLC, primarily in those with clinical stage I-IIA (T1a-2b N0) disease. There are no randomized trials of adjuvant systemic therapy in SCLC, so the evidence base for adjuvant therapy is of lower quality than that for NSCLC in which there are multiple randomized trials of adjuvant systemic therapy.

The literature review identified only one population-based cohort study of patients with early-stage SCLC.[114] This study includes patients from the National Cancer Database with T1-2 N0 M0 SCLC who had surgical resection from 2003 to 2011. Patients with a prior malignancy, neoadjuvant therapy, incomplete resection, missing data, or treated outside the reporting facility were excluded. Of 1,574 patients who underwent surgical resection, 954 were included in the analysis. Patients were treated with surgery alone, surgery plus chemotherapy, surgery plus chemotherapy and radiation, or radiation alone. Patients treated with surgery and chemotherapy ± radiation had a significantly longer median OS than those who had surgery alone (66 months *v* 42.1 months), with a significant improvement in 5-year OS rate (52.7% *v* 40.4%; $P < .01$). In a multivariate analysis, the use of adjuvant chemotherapy alone (hazard ratio [HR], 0.78; 95% CI, 0.63 to 0.95) and the use of adjuvant chemotherapy plus radiation to the brain (HR, 0.52; 95% CI, 0.36 to 0.75) were associated with significant improvements in OS. Interestingly, the use of chemotherapy plus radiation to the chest was not associated with a significant improvement in OS (HR, 0.88; 95% CI, 0.63 to 1.23). The design of this study is subject to potential selection bias, hence the quality of the evidence is considered low. However, the committee agreed with a strong recommendation for the use of adjuvant chemotherapy for patients who have undergone complete resection of limited-stage SCLC.

Recommendation 1.2

Adjuvant chemotherapy should consist of four cycles of cisplatin (PE) or carboplatin plus etoposide (CE) (Type: Informal consensus, benefits outweigh harms; Evidence quality: Not applicable; Strength of recommendation: Weak).

Literature review and clinical interpretation. There were no data identified comparing different types of adjuvant chemotherapy in patients with resected SCLC. The committee felt that it was reasonable to extrapolate from data in other clinical scenarios in SCLC in which platinum plus etoposide is the preferred regimen.

Recommendation 1.3

Adjuvant chemotherapy should be initiated within 8 weeks from resection (Type: Informal consensus, benefits outweigh harms; Evidence quality: Not applicable; Strength of recommendation: Weak).

Literature review and clinical interpretation. There were no data identified examining the appropriate time frame in which to initiate adjuvant chemotherapy in patients with resected SCLC. The committee felt it was reasonable to extrapolate from data in patients with NSCLC where it is recommended that adjuvant chemotherapy should ideally be initiated within 8 weeks of resection.

Clinical Question 2

What is the optimal systemic therapy for use with concurrent thoracic radiotherapy in patients with LS-SCLC? (1) What is the optimal timing for starting systemic therapy in LS-SCLC?

Recommendation 2.1

Cisplatin and etoposide should be administered with concurrent radiotherapy in patients with LS-SCLC (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Literature review and clinical interpretation. The combination of cisplatin and etoposide has been the standard chemotherapy regimen used in the majority of trials evaluating concurrent chemoradiotherapy in patients with limited-stage SCLC.[39] Standard dosing should be used, that is, cisplatin 60-80 mg/m² once on day 1 and etoposide 100-120 mg/m² once on days 1, 2, and 3 of an every 3-week cycle with attempts to minimize dose reductions, especially during the first two cycles.[118] Given that there is no evidence

of a survival benefit for extending chemotherapy to six cycles, chemotherapy is usually limited to four cycles.[119]

The updated SR identified only one RCT where cisplatin and etoposide were compared to cisplatin and irinotecan in patients with limited-stage SCLC.[120] In this Japanese trial, patients with previously untreated limited-stage SCLC initially received one cycle of PE with concurrent radiotherapy before randomization to three more cycles of either cisplatin and etoposide or cisplatin and irinotecan. OS was not significantly different between the two arms (median, PE = 3.2 years [95% CI, 2.4 to 4.1] *v* cisplatin plus irinotecan = 2.8 years [95% CI, 2.4 to 3.6]; HR, 1.09; 95% CI, 0.80 to 1.46). Thus, PE has remained the preferred regimen.[53]

Recommendation 2.2

Carboplatin and etoposide may be offered as systemic therapy concurrent with radiation for patients with LS-SCLC and contraindications to the use of cisplatin (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Literature review and clinical interpretation. Clinically, carboplatin is often substituted for cisplatin in patients with contraindications or intolerance to cisplatin across tumor types. The sole contraindication to cisplatin listed in its US Food and Drug Administration (FDA) label is hypersensitivity to cisplatin; however, other, often irreversible, toxicities of cisplatin, including nephrotoxicity, neuropathy, and ototoxicity, are listed as black box warnings.

One randomized trial has directly compared PE to CE in patients with both LS-SCLC (n = 82) and ES-SCLC (n = 61).[121] Patients were randomly assigned to receive six cycles of either PE or CE. Most of those with LS-SCLC also underwent concurrent thoracic radiotherapy and prophylactic cranial irradiation. For LS-SCLC, RRs were 76% for PE and 86% for CE. Comparative survival data were only reported for patients with all stages combined, with no clinically relevant differences between PE and CE: time to progression (8.4 *v* 8.6 months, respectively); OS (12.5 *v* 11.8 months, respectively). The COCIS MA of 663 patients from four trials compared cisplatin- to carboplatin-based therapy for first-line treatment of SCLC with 33% of patients having LS-SCLC.[36] Overall, there were no significant differences between cisplatin and carboplatin in any efficacy endpoint: RR (67% *v* 66%; *P* = .83), median PFS (5.5 *v* 5.3 months; *P* = .25), and median OS (9.6 *v* 9.4 months; *P* = .37). Subset analyses did not demonstrate any significant survival difference in patients with LS-SCLC. Carboplatin-based regimens resulted in more myelosuppression, while cisplatin caused more nausea, vomiting, neurotoxicity, and nephrotoxicity.

Review of the literature identified one cohort study of 4,408 patients with SCLC who were enrolled in the National Veterans Affairs Central Cancer Registry and had received either cisplatin-based or carboplatin-based chemotherapy.[122] Of these, 1,756 patients were identified with LS-SCLC treated with concurrent chemoradiotherapy: 801 received carboplatin-based therapy, 1,018 received cisplatin-based therapy, and 62 were exposed to both cisplatin and carboplatin. No significant difference was observed for the primary endpoint of OS (median, cisplatin 26.9 months *v* carboplatin 25.6 months; HR, 1.04; 95% CI, 0.94 to 1.16; *P* = .46). The quality of evidence is considered low as this was a retrospective study and 95% of the cohort was male. Based on the broad use of carboplatin in patients with lung cancer and intolerance or contraindication to cisplatin, and lack of data suggesting worse outcomes with the use of carboplatin, the panel agreed with a strong recommendation for the use of carboplatin in patients with LS-SCLC who are intolerant or have contraindications to cisplatin.

Recommendation 2.3

Chemotherapy should be commenced as soon as possible in patients with LS-SCLC and not deferred until radiation therapy (RT) can be started (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Literature review and clinical interpretation. While there are ample data regarding the need to start radiotherapy early in the treatment course (ie, within the first two cycles of chemotherapy), there were no data identified examining the most appropriate time to start chemotherapy. The committee felt it was most reasonable to recommend initiation of chemotherapy as soon as possible, given the aggressiveness of SCLC, the usually high symptom burden caused by the disease, and the high degree of responsiveness of SCLC to chemotherapy. Frequently, the initiation of radiotherapy is delayed due to the need for complex treatment planning, whereas chemotherapy can usually be started in a more timely manner. The timing of radiation initiation with respect to chemotherapy in patients with LS-SCLC is addressed in the American Society for Radiation Oncology guidelines.[18,123]

Clinical Question 3

What is the optimal first-line systemic therapy for patients with ES-SCLC?

Recommendation 3.1

First-line systemic therapy with CE or PE plus immunotherapy (atezolizumab or durvalumab) followed by maintenance immunotherapy should be offered to patients with ES-SCLC if there are no contraindications to immunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Literature review and clinical interpretation. The current recommendation for first-line chemoimmunotherapy in patients with ES-SCLC is derived primarily from two,

large, randomized, phase III clinical trials, IMpower133 and CASPIAN. IMpower133 was a multinational, phase III trial in which 403 patients were randomly assigned to receive four cycles of carboplatin and etoposide with either atezolizumab or placebo followed by continuation maintenance therapy with atezolizumab or placebo.[124] While the RR was similar in both arms (60% *v* 64%), both PFS (1-year, 12.6% *v* 5.4%; HR, 0.77; $P = .02$) and OS (1-year, 52% *v* 38%; HR, 0.70; $P = .007$) were significantly improved by the addition of atezolizumab. In subset analyses, patients with brain metastases had no apparent benefit (though the analysis is limited by enrollment of only 35 patients with brain metastases) and those younger than 65 had greater benefit than older patients. An update continued to support an improvement in OS with chemoimmunotherapy (18-month, 34% *v* 21%, HR, 0.76; $P = .015$).[10] Grade 3-4 adverse events (AEs; 56.6% *v* 56.1%) and treatment-related deaths (1.5% in both arms) were similar in both arms, though immune-related AEs (39.9% *v* 24.5%) were more common with immunotherapy. Patient-reported quality-of-life outcomes were also similar in both arms.[125]

CASPIAN was an international, phase III, open-label trial in which 805 patients with previously untreated ES-SCLC were randomly assigned to one of three arms: chemotherapy alone (PE or CE × 6 cycles); chemotherapy plus durvalumab × 4 cycles followed by maintenance durvalumab; or chemotherapy plus durvalumab and tremelimumab × 4 cycles followed by maintenance durvalumab.[126] The addition of durvalumab to chemotherapy improved RR (68% *v* 58%), PFS (1-year, 18% *v* 5%, HR, 0.78), and OS (1-year, 54% *v* 40%, HR, 0.73; $P = .005$). A recent update reported 18-month OS of 32% with durvalumab plus chemotherapy and 25% with chemotherapy alone.[127] Overall toxicity was similar in both arms, with 62% of patients having grade 3-4 AEs and treatment-related mortality of 5%-6%, while immune-related AEs were more common with durvalumab (20% *v* 3%).[126] The addition of both durvalumab and tremelimumab to chemotherapy failed to significantly improve RR, PFS, or OS when compared to chemotherapy alone.[127]

ASTRUM-005 was a phase III trial performed in China in which 585 patients with untreated ES-SCLC were randomly assigned in a 2:1 manner to receive carboplatin and etoposide × 4 cycles plus either serplulimab (an anti–PD-1 monoclonal antibody) or placebo followed by maintenance with serplulimab or placebo. All efficacy endpoints favored serplulimab: RR (80.2% *v* 70.4%), PFS (median, 5.7 *v* 4.3 months; HR, 0.48, 95% CI, 0.38 to 0.59), and OS (median, 15.4 *v* 10.9 months; 1-year, 61% *v* 48%; $P < .001$).[128]

A similar phase III study, KEYNOTE-604, allocated 453 patients with previously untreated ES-SCLC to receive CE or PE plus either pembrolizumab or placebo followed by maintenance with pembrolizumab or placebo.[129] The addition of pembrolizumab significantly improved PFS (1-year, 13.6% *v* 3.1%, HR, 0.75; $P = .002$), but the improvement in OS did not reach statistical significance (2-year, 22.5% *v* 11.2%, HR, 0.80; $P = .16$). EA5161, a randomized phase II trial of chemotherapy with CE or PE alone versus chemotherapy plus nivolumab followed by maintenance nivolumab, enrolled 160 patients with previously untreated ES-SCLC, and found that both PFS and OS were significantly better in patients who received nivolumab.[130]

Several MAs have further confirmed the overall benefit of chemoimmunotherapy over chemotherapy alone for patients with ES-SCLC.[25,28-31,131] For example, the MA by Yu et al[25] included four randomized trials of chemoimmunotherapy versus chemotherapy alone (Impower133, CASPIAN, KEYNOTE-604, and EA5161) with a total of 1,553 patients, and found strong evidence for an improvement in both PFS and OS with the addition of immunotherapy, with no significant difference between anti–PD-L1 and anti–PD-1 agents. Based on the available evidence, the panel suggests that patients with ES-SCLC should be treated with first-line platinum and etoposide plus either durvalumab or atezolizumab for four cycles followed by maintenance immunotherapy.

Platinum plus etoposide is the preferred first-line chemotherapy option either in combination with immunotherapy or alone in patients with contraindications to immunotherapy. Only one trial has directly compared PE to CE, randomizing 147 patients with LS- or ES-SCLC to six cycles of PE or CE with concurrent thoracic RT for those with LS-SCLC.[121] There was no difference in RR (57% *v* 58%), time to progression (8.4 *v* 8.6 months), or OS (12.5 *v* 11.8 months) between PE and CE, respectively. The COCIS MA of 663 patients from four trials compared cisplatin- to carboplatin-based therapy for first-line treatment of SCLC with 67% of patients having extensive-stage disease, and reported no significant difference between cisplatin and carboplatin in any efficacy endpoint: RR (67% *v* 66%; $P = .83$), median PFS (5.5 *v* 5.3 months; $P = .25$), and median OS (9.6 *v* 9.4 months; $P = .37$).[36] Carboplatin-based regimens resulted in more myelosuppression, while cisplatin caused more nausea, vomiting, neurotoxicity, and nephrotoxicity. Given the available data and the palliative nature of therapy for patients with ES-SCLC, CE appears to be a favorable treatment option, though the choice of chemotherapy should be based on individual patient characteristics.

For patients who are not candidates for immunotherapy, chemotherapy with platinum plus etoposide for 4-6 cycles remains the recommended therapy, though cisplatin or carboplatin plus irinotecan is another reasonable alternative based on RCT data and MAs.[32,33,120,132-135] The optimal duration of chemotherapy for ES-SCLC is not clearly defined; however, 4-6 cycles of chemotherapy should be given based on patient tolerance and response to therapy.

Numerous chemotherapy-based strategies have been studied in randomized trials, including dose intensification,[65,66] three-drug cytotoxic regimens,[63,73,136,137] alkylator-anthracycline–based regimens,[68,69,75] platinum-based

nonetoposide regimens,[71,72,74] alternating non–cross-resistant regimens,[69,75] maintenance therapy,[61,62,87] and consolidation therapy.[76] All have failed to yield convincing improvements in survival and/or resulted in unacceptable toxicity. A wide variety of molecularly targeted agents, including anti-angiogenics and poly (ADP-ribose) polymerase (PARP) inhibitors, used either concurrently with chemotherapy[30,64,92,93,95-99] or as maintenance therapy[38,59,60,86,88-91] have also not demonstrated a significant improvement in outcomes.

Clinical Question 4

What systemic therapy options are available for treating patients with relapsed SCLC? (1) Which systemic therapy options should be given based on treatment-free interval?

Recommendation 4.1

In patients with relapsed SCLC with a chemotherapy-free interval of <90 days, single-agent chemotherapy may be offered. Preferred agents are topotecan or lurbinectedin (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statement. Single-agent chemotherapy is preferred over multi-agent chemotherapy due to concerns regarding the balance of risks versus benefits.

Literature review and clinical interpretation. Patients who initially had either LS-SCLC or ES-SCLC and develop a recurrence of SCLC within 90 days of completion of first-line chemotherapy (ie, chemotherapy-free interval of <90 days) are generally considered to be resistant or refractory to combination, platinum-based therapy. In such patients, single-agent chemotherapy is recommended as second-line treatment, preferably with topotecan or lurbinectedin.

Data supporting topotecan come from two randomized studies that predated the use of immunotherapy in the first-line setting.[50,84] In the first trial, 211 patients with relapsed SCLC who had recurred at least 60 days after completion of first-line chemotherapy were randomly assigned to receive either topotecan or combination therapy with cyclophosphamide, doxorubicin, and vincristine (CAV).[84] While the overall response rates observed with topotecan and CAV were 24% *v* 18%, respectively ($P = .28$), there was no significant difference in OS (median, 25 *v* 24.7 weeks; $P = .79$). Patients receiving topotecan were significantly less likely to have neutropenia and more likely to have improvement in symptoms. In the second trial, 141 patients with relapsed SCLC who were not deemed to be candidates for intravenous (IV) chemotherapy were randomly assigned to receive oral topotecan versus best supportive care (BSC).[50] Despite a RR of only 7%, topotecan resulted in an improvement in OS (25.9 *v* 13.9 weeks; $P = .0104$). Topotecan also resulted in greater symptom control and slower deterioration of QoL. Other trials have reported no difference in efficacy or safety between the oral and IV formulations of topotecan.[138]

Recent data have shown that the novel transcriptional inhibitor, lurbinectedin, has substantial activity against relapsed SCLC. In a phase II study of 105 patients with relapsed SCLC and no brain metastases whose disease had progressed on or after platinum-based chemotherapy with or without immunotherapy, single-agent lurbinectedin yielded a RR of 33% with a median duration of response of 5.1 months and with 25% of patients responding for at least 6 months. Among patients with a chemotherapy-free interval of <90 days, the RR was 22%, while in those with a chemotherapy-free interval of at least 90 days, the RR was 45%.[11]

ATLANTIS, a randomized phase III trial evaluating lurbinectedin 2.0 mg/m^2 plus doxorubicin 40 mg/m^2 once on a 21 day cycle versus investigator's choice of CAV or topotecan in 613 patients with relapsed SCLC, failed to find any significant difference in efficacy between the two arms: RR (32% *v* 29%); PFS (median, 4 months in both arms); and OS (median, 8.6 *v* 7.6 months; HR, 0.97; $P = .70$).[139] Single-agent lurbinectedin remains a reasonable choice for second-line treatment of patients with relapsed SCLC with appreciable activity and tolerability.

Other options for treatment of patients with relapsed SCLC are based on phase II studies demonstrating RRs of 10%-25% and include single-agent irinotecan, paclitaxel, docetaxel, temozolomide, gemcitabine, or vinorelbine.[140-143] All subsequent treatments should be based on individual patient's PS and clinical trial eligibility.

Amrubicin is a synthetic anthracycline that is not approved for use in the United States, but is an option in Japan. A phase III trial comparing amrubicin to topotecan in 637 patients with relapsed SCLC demonstrated improved RR with amrubicin (31% *v* 17%; $P < .001$), but no difference in OS (median, 7.5 *v* 7.8 months; $P = .17$). In a subset analysis, patients with a chemotherapy-free interval of < 90 days had a significant improvement in OS with amrubicin (median, 6.2 *v* 5.7 months; $P = .047$). Amrubicin did result in higher rates of infection and febrile neutropenia, but less overall myelosuppression.[144]

Recommendation 4.2

In patients with relapsed SCLC with a chemotherapy-free interval of at least 90 days, rechallenge with a platinum-based regimen or single-agent chemotherapy (preferred agents are topotecan or lurbinectedin) may be offered (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and clinical interpretation. Two recent phase III trials have compared rechallenge with a platinum-based chemotherapy regimen to topotecan in patients with relapsed SCLC and a chemotherapy-free interval of

at least 90 days. A phase III study from France compared CE to oral topotecan in 164 patients who had previously responded to first-line platinum plus etoposide, but had disease progression at least 90 days after completion of first-line treatment.[47] Combination therapy improved both RR (49% *v* 25%; *P* = .002) and PFS (4.7 *v* 2.7 months; *P* = .004), though there was no significant difference in OS (median, 7.5 *v* 7.4 months; *P* = .94). The lack of survival benefit may be secondary to a large crossover, particularly in the topotecan group with almost 40% of patients receiving CE as third-line treatment. Toxicity favored platinum rechallenge with higher rates of grade 3-4 myelosuppression and febrile neutropenia in patients receiving topotecan. The results from this study also confirm the findings of a multi-institutional retrospective analysis that reported a median PFS of 5.5 months in patients with sensitive-relapsed SCLC who were rechallenged with platinum plus etoposide.[145]

The phase III JCOG0605 trial from Japan compared the combination of cisplatin, etoposide, and irinotecan to topotecan in 180 patients with sensitive-relapsed SCLC.[48] RR (84% *v* 27%; *P* < .0001), PFS (5.7 *v* 3.6 months; *P* < .0001), and OS (18.2 *v* 12.5 months; *P* = .008) all favored combination therapy, though combination therapy also resulted in much higher rates of myelosuppression and febrile neutropenia as well as high rates of dose reduction and delay. These data support combination platinum-based therapy as a second-line treatment option for patients with good PS and sensitive-relapsed SCLC.

In patients who were initially treated for LS-SCLC without immunotherapy and have had a chemotherapy-free interval of at least 90 days, treatment with platinum-based chemotherapy plus immunotherapy followed by maintenance immunotherapy may be offered.

Recommendation 4.3

In patients with relapsed SCLC who had progression while on maintenance immunotherapy, there is no evidence to support continuation of immunotherapy (Type: Informal consensus, benefit to harm ratio not assessable; Evidence quality: Not applicable; Strength of recommendation: Strong).

Literature review and clinical interpretation. There are no RCTs in patients who develop disease progression while on maintenance immunotherapy comparing continuation of immunotherapy in combination with second-line therapy versus second-line therapy alone. There are also no reported clinical trials evaluating switching to a different immunotherapy agent or a combination of immunotherapy agents after disease progression on maintenance immunotherapy. Due to limited data in this clinical setting and lack of oncological rationale, the general consensus is to recommend against continuing immunotherapy in patients with disease progression while on maintenance immunotherapy.

Recommendation 4.4

In an immunotherapy-naïve patient, second-line immunotherapy alone is not recommended outside of the clinical trial setting. Participation in clinical trials to better identify predictive biomarkers is encouraged (Type: Evidence based, no net benefit; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and clinical interpretation. Promising data from early trials of immunotherapy in patients with relapsed SCLC who had not received prior immunotherapy led to the accelerated FDA approval of both single-agent nivolumab and pembrolizumab for these patients. However, the disappointing results of subsequent randomized trials led to the voluntary withdrawal of both nivolumab and pembrolizumab in the relapsed setting. In the phase III CheckMate-331 trial, nivolumab did not improve OS when compared to chemotherapy (topotecan or amrubicin) in patients with relapsed SCLC.[46] The KEYNOTE-604 phase III trial of platinum and etoposide plus either pembrolizumab or placebo as first-line treatment in untreated patients was also a negative trial as the difference in OS did not reach statistical significance.[129] Even though this study was not done in the relapsed setting, the results dimmed enthusiasm for pembrolizumab in SCLC. Finally, in the randomized phase II IFCT-1603 trial, which compared atezolizumab to chemotherapy (topotecan plus etoposide or CE) as second-line therapy in people with relapsed SCLC, both RR and PFS were better in the chemotherapy arm while OS was similar in both arms.[82] Taken together, these data do not support the use of immunotherapy alone as subsequent treatment in immunotherapy-naïve SCLC patients.

Clinical Question 5

What is the best management approach for treatment-naïve patients who are older or with poor PS?

A large proportion of people with SCLC do not fit within the standard inclusion criteria for clinical trials, specifically, those who are older and/or have a poor Eastern Cooperative Oncology Group (ECOG) PS. Historically, these two often unrelated categories of patients have frequently been combined in studies and individual trials have used varying definitions of "older patient," further complicating the development of clear guidance on how to manage and treat these challenging patients. Most studies have defined "older patient" as ≥70 years of age, but some have used ≥65 years, which aligns with the WHO definition. There is little data on which to base treatment decisions in people over 80 years of age.

Approximately 40% of patients with SCLC are older than 70 years of age. In these older patients, treatment of SCLC is more challenging, given the decline in physiological reserve, increased comorbidities, polypharmacy, cognitive

decline, and other age-related medical and social issues. Most of the data on the treatment of older patients comes from retrospective studies. However, limited prospective data are available to guide treatment decisions in this special population. Based on available data, standard approaches are feasible in carefully selected, "fit" older patients.[146]

Comprehensive geriatric assessment (CGA), which includes essential domains such as evaluations of function (Activities of Daily Living scales, Instrumental Activities of Daily Living scales), comorbidity, nutritional status, social support, medications, and psychological and cognitive status, has been shown to be a better predictor of fitness, vulnerabilities, and impairments in cancer patients over 65 years of age than routine oncologic assessment tools. While there are no published trials evaluating CGA in older patients with SCLC, studies on patients with other cancers have demonstrated that CGA-based interventions, including modification of systemic therapy and referrals to physical therapy, nutritional counseling, and psychological evaluation, result in better treatment completion, compliance, and tolerance without compromising survival.[147,148]

The Expert Panel endorses ASCO guidelines for CGA prior to systemic anticancer treatment in order to better identify "fit" older patient who may qualify for standard SCLC therapy.[149]

Recommendation 5.1

Older patients with LS-SCLC and ECOG PS 0-1 may be offered standard treatment with concurrent chemoradiotherapy with curative intent (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and clinical interpretation. Most of the data to support this recommendation come from subset analyses of trials that included patients of all ages. Schild et al[52] compared the outcomes of patients ≥70 years of age to those of their younger counterparts enrolled in a phase III trial of combined-modality therapy with hyperfractionated versus once-daily radiotherapy for LS-SCLC. All patients received six cycles of PE with radiation given concurrently during cycles 4-5. Of 263 total patients, 54 (21%) were ≥70 years of age. The older cohort did lose more weight and had a higher rate of pneumonitis (6% *v* 0%), but the rates of other common toxicities were comparable and there was no significant difference in OS (5-year, 17% *v* 22%; $P = .14$).

In a similar study, Yuen et al[112] compared the outcomes of 50 (13%) patients ≥70 years of age to younger patients enrolled in the Intergroup 0096 study, which randomly assigned patients with LS-SCLC to receive either once-daily or twice-daily radiotherapy concurrently with four cycles of PE. The older cohort had more grade 4-5 hematological toxicity (84% *v* 61%; $P < .01$), and more fatalities (10% *v* 1%; $P = .01$), but the RR was similar for both age categories. However, the 5-year OS rate did favor the younger cohort (22% *v* 16%; $P = .05$) primarily due to deaths within first 6 months, likely from treatment toxicity.

The toxicity profile of cisplatin can be a barrier to treatment in older patients and there is evidence to support the preferred use of carboplatin. Kim et al[113] reported on a large cohort of 565 people abstracted from the SEER database between 1992 and 2007 who were ≥65 years of age (median, 72 years) and received concurrent chemoradiotherapy with either PE or CE. The reported outcomes were virtually identical, with median (13.8 *v* 13.7 months) and 5-year OS (10.2% *v* 10.9%) for those receiving cisplatin versus carboplatin, respectively.

These studies echo previous findings from earlier trials of combined-modality therapy and support the recommendation that patients ≥70 years of age with good PS should be offered concurrent chemoradiation with a detailed discussion of the risks and benefits that will allow them to make rational treatment decisions, given the inherent side effects of these intensive treatment regimens.

Recommendation 5.2

Patients with LS-SCLC and ECOG PS 2 due to SCLC may be offered standard treatment with concurrent chemoradiotherapy with curative intent (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. People are often diagnosed with SCLC based on cancer-related symptoms, and an individual's medical fitness and comorbidities play a significant role in the therapeutic decision-making process. Historically, there has been reluctance to include patients with poor PS in clinical trials, because of concerns regarding tolerability and toxicity, which might dilute the potential benefit of new therapies. Many SCLC trials do include patients with ECOG PS 2, so there is sufficient data to support the recommendation for potentially curative, concurrent chemoradiotherapy for this patient subgroup. For example, in the concurrent National Cancer Institute-Canada trials (BR3 and BR6), 12%-16% of patients had ECOG PS 2-3.[150]

As PS can be subjective and multifactorial, a practical approach to inclusion of ECOG PS 2 patients has been demonstrated in recent trials, such as the CONVERT study.[5] In this multicenter randomized phase III study of concurrent chemoradiotherapy with radiotherapy given either once daily or twice daily, the inclusion criteria specified that patients with PS 2 could be included if their debility was due to disease-related symptoms and not comorbidities. Although only 3% of the 547 patients enrolled had PS 2, the wording of the inclusion criterion aligns with this panel's

recommended approach for considering more intensive treatment for this subgroup of patients.

Recommendation 5.3

Patients with LS-SCLC and ECOG PS 3-4 due to SCLC may be offered initial chemotherapy followed by sequential radiotherapy if there is improvement in PS (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. There is little published data to guide therapeutic decision-making for patients who present with LS-SCLC and very poor PS. As previously noted, although a very small number of patients with ECOG PS 3 have been included in concurrent chemoradiotherapy trials,[150] it is difficult to draw generalizable conclusions.

As with people who present with LS-SCLC and ECOG PS 2, those who are even more debilitated by symptoms that are related to their SCLC may derive benefit from an aggressive treatment approach. SCLC tends to exhibit a robust response to initial chemotherapy, so symptoms due to disease, such as pain, cough, or dyspnea may improve rapidly enough to reconsider concurrent treatment with subsequent cycles. Therefore, a step-wise approach to treatment may be considered on a case-by-case basis, starting with systemic therapy and then introducing radiotherapy, either concurrently or sequentially, for those patients who improve with initial treatment. Consideration of palliative care, including palliative radiotherapy, is also an option for this diverse patient cohort.

Recommendation 5.4

Older patients with ES-SCLC and ECOG PS 0-1 may be offered standard treatment with carboplatin and etoposide plus immunotherapy (atezolizumab or durvalumab) followed by maintenance immunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and clinical interpretation. As yet, there are no studies that specifically address the safety and efficacy of chemoimmunotherapy in older patients with ES-SCLC. The best evidence comes from the subset analyses of older patients enrolled in the CASPIAN and IMpower133 trials (referenced previously in section 4). In the CASPIAN trial, 113 of 537 patients with ES-SCLC and ECOG PS 0-1 were defined as older, and in the IMpower133 trial, 186 of 403 patients were ≥65 years of age. Neither study was powered to evaluate the impact of age on outcomes, but there appeared to be no difference in the benefit of chemoimmunotherapy in older versus younger patients.

As real-world evidence accumulates and new trials are developed for this population, more informative data should become available. Currently, there is sufficient evidence to support the use of combination chemoimmunotherapy in carefully selected patients ≥65 years of age with ES-SCLC and ECOG PS 0-1.

Recommendation 5.5

Patients with ES-SCLC and ECOG PS 2 may be offered carboplatin and etoposide plus immunotherapy (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. Despite the fact that many patients with ES-SCLC present with ECOG PS ≥ 2, few such patients are enrolled in randomized clinical trials. As with LS-SCLC, the distinction between a poor PS driven by SCLC rather than underlying comorbidities should be the primary consideration when contemplating the addition of systemic therapy to BSC.

Support for the use of CE for patients with ECOG PS 2 can be deduced from the inclusion of such patients in prior randomized trials. For example, a MA comparing cisplatin- versus carboplatin-containing regimens for first-line treatment of SCLC included four randomized trials that included 663 patients with ECOG PS 0-2 (or 0-3 in one trial), most of whom had ES-SCLC.[36] Overall, there was no significant difference in the efficacy between cisplatin- and carboplatin-containing regimens, though there were differences in the toxicity profiles. In addition, outcomes appeared to be similar in the PS 0-1 and PS ≥ 2 cohorts.

The JOG 9702 study[151] was a randomized phase III study that compared CE to divided-dose PE in patients with PS 3 and age <70, or PS 0-2 and age 70 or older. Although there were more frequent AEs in patients with poor PS, both groups demonstrated promising OS rates. This trial provides the rationale for the JOG's ongoing phase II study of carboplatin, etoposide, and durvalumab in patients with ES-SCLC and poor PS.[152]

In 2004, Treat et al reported the results of a retrospective analysis of five topotecan registration trials in patients with relapsed SCLC. Of 480 patients, 98 had ECOG PS 2.[153] RRs were similar for those with PS 0-1 versus PS 2, but toxicity was greater and OS was shorter in the PS 2 population. PS is a strong prognostic indictor in SCLC, and the balance of treatment risks and benefits must be carefully considered for each patient.

Recommendation 5.6

Patients with ES-SCLC and ECOG PS 3-4 due to SCLC may be offered chemotherapy (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. There is a true paucity of data for patients with ES-SCLC with an ECOG PS 3-4, highlighting an area of much-needed research. There is anecdotal evidence of response and benefit for patients whose poor PS is directly due to SCLC, for example,

patients with abrupt respiratory compromise who respond quickly to chemotherapy, but this cannot be considered a general recommendation.

As noted previously, the COCIS MA did not demonstrate any significant differences in efficacy between cisplatin- versus carboplatin-containing regimens, though only one of the included studies allowed patients with PS 3.[36] Similar results have been reported in a more contemporary Japanese trial comparing carboplatin-based with cisplatin-based regimens.[143] Given the more favorable toxicity profile of carboplatin, it would appear to be more reasonable to offer carboplatin-based rather than cisplatin-based treatment for people with poor PS. As is the case for all patients with ES-SCLC, an emphasis should be placed on palliative and supportive care, which may include palliative radiotherapy.

Clinical Question 6

What is optimal systemic therapy for patients with NSCLC harboring an EGFR mutation that has transformed to SCLC?

Recommendation 6.1

Patients with NSCLC harboring an *EGFR* mutation that has transformed to SCLC should be managed with CE or PE (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statement. There is insufficient evidence to support the use of immunotherapy in this setting. Clinical trial enrollment should be offered whenever possible.

Literature review and clinical interpretation. Transformation to SCLC has been reported to occur in 3%-14% of people with *EGFR*-mutant lung adenocarcinoma as a mechanism of resistance at the time of progression on EGFR tyrosine-kinase inhibitor (TKI) therapy. *EGFR* mutations have also rarely been identified in de novo SCLC.[154-156] Several pooled analyses and case series have reported that progression with transformed SCLC occurs after a median of 16-19 months on EGFR TKI therapy and that the OS after transformation is poor (median of 6-11 months).[154-156] Frequency of small cell transformation in *ROS1* and *ALK* fusion-positive lung cancers appears relatively low (2% and 0.8%, respectively).[157]

Thus far, there are no prospective studies evaluating the appropriate treatment of transformed SCLC. The majority of reported patients with transformed SCLC have received treatment with platinum plus etoposide. In one pooled analysis of 46 such patients treated with platinum plus etoposide, the RR was 54% and the median PFS was 3.4 months.[155] Another pooled analysis of 48 patients treated with platinum plus etoposide reported a RR of 45%.[154]

Only one case series has evaluated the efficacy of ICIs in transformed SCLC, reporting no responses in 17 patients treated with either single-agent or combination immunotherapy.[155] Thus, there is no evidence to support the use of immunotherapy in the treatment of *EGFR*-mutant, transformed SCLC.

Recommendation 6.2

EGFR inhibitor may be continued with chemotherapy in patients with NSCLC harboring an *EGFR* mutation that has transformed to SCLC (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. Case series and pooled analyses have shown that although the majority of transformed SCLCs retain the original *EGFR* mutation, EGFR protein expression is suppressed, resulting in resistance to further EGFR TKI therapy. However, in some patients, there is co-occurring persistence of an *EGFR*-mutant adenocarcinoma component, which may retain sensitivity to an EGFR TKI, providing rationale for continuation of EGFR TKI therapy. Overall, there is inadequate data to recommend for or against continuation or reintroduction of EGFR TKI therapy and the decision should be made on an individual patient basis.

Clinical Question 7

What is the role of biomarkers, including molecular profiling in guiding therapy for patients with de novo SCLC?

Recommendation 7.1

There is no evidence to support the use of molecular profiling and biomarker analysis to guide standard treatment in patients with de novo SCLC (Type: Evidence based, benefit to harm ratio not assessable; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. There are few prospective studies investigating the utility of biomarker analysis to guide therapy in patients with SCLC. In a phase II study, 14 patients with ES-SCLC expressing c-Kit were treated with imatinib maintenance therapy after four cycles of cisplatin plus irinotecan with a 4-month PFS rate of only 1.3 months (95% CI, 1 to 5.7 months) after initiation of imatinib, leading to early study closure as it did not meet the predetermined threshold.[78] A more recent phase II umbrella study enrolled 286 patients with relapsed ES-SCLC who received either biomarker-directed or non–biomarker-directed therapy. Patients with *CDKN2A* and *TP53* mutations or *MYC* amplification were treated with adavosertib, a WEE1 inhibitor, and those with *RICTOR* amplification were treated with vistusertib, a mTORC1/2 inhibitor. Patients with tumors lacking these biomarkers were randomly assigned to treatment with adavosertib or vistusertib. Neither objective response nor PFS was improved by the biomarker-driven interventions.[104] Another study of 51 patients with LS- or ES-SCLC who were receiving chemotherapy with or without radiotherapy

investigated circulating tumor cells (CTCs) as a predictive and prognostic biomarker. Patients with ≥8 CTCs detected on pretreatment samples had worse OS than those with <8 CTCs (HR, 3.5; 95% CI, 1.45 to 8.60; $P = .0014$). The worst outcomes overall were noted in patients with ≥8 CTCs on post-treatment samples or samples obtained at relapse.[105]

Most of the data on the potential clinical utility of predictive and prognostic biomarkers in SCLC comes from retrospective studies. Liu et al performed an exploratory analysis of PD-L1 expression in patients enrolled on IMpower133, the randomized, phase III study of first-line atezolizumab plus chemotherapy in patients with ES-SCLC. An OS benefit was found across all PD-L1 subgroups and PD-L1 expression did not appear to be a predictive biomarker for chemo-immunotherapy in patients with ES-SCLC. This analysis was limited, since only 34% of the study population had undergone PD-1 analysis.[10] This study also found that blood tumor mutational burden (TMB) was not predictive of benefit with chemoimmunotherapy. The lack of predictive utility for PD-L1 expression has been echoed in similar analyses of the CASPIAN and KEYNOTE 604 trials.[129,158]

Hellmann et al[106] analyzed the predictive value of TMB in a nonrandomized cohort of patients with ES-SCLC from the CheckMate 032 study, which evaluated nivolumab or nivolumab plus ipilimumab in patients with advanced solid tumors. While the efficacy of immunotherapy was better in patients in the highest tertile of TMB (≥248 total somatic missense mutations) as compared to those with medium (143-247 mutations) or low (0-143 mutations) TMB, subsequent studies have not confirmed the predictive power of TMB for immunotherapy response in SCLC. Larger, prospective studies are needed to define the potential role of TMB in treatment decision making in SCLC.

Multiple retrospective studies have focused on understanding the genomic landscape of SCLC as both a predictive and prognostic biomarker. Several studies seeking to identify genetic alterations which might serve as candidates for therapeutic intervention have found nonrandom aberrations in several key pathways, including cell cycle regulation, receptor kinase or PI3K signaling, transcriptional regulation, Notch signaling, and neuroendocrine differentiation.[159] A subsequent retrospective study of tumors from patients with SCLC found that alterations in six genes (*MCM2*, *EXH2*, *CDKN2A*, *CEMPK*, *CHEK1*, and *EXOSC2*) correlated with OS. Some of these alterations also predicted response to anti–PD-1 therapy and cisplatin.[111] In another study that assessed tumors from 231 patients with LS-SCLC who were treated with chemoradiotherapy, *CDK4* and *GATA6* expression as well as EGFR-activating mutations were prognostic for poorer OS (HR, 2.18; HR, 2.39; HR, 2.26).[160] Additionally, Zhang et al[109] created a prognostic signature based on N^6-methyladenosine (m^6A), an epigenetic modification involved in tumorigenesis and immune function. Among 265 patients with LS-SCLC, those with a high m6A score had decreased OS (HR, 5.19; 95% CI, 2.75 to 9.77; $P < .001$), a finding that was validated in two independent cohorts. In addition, a low m^6A score was predictive of benefit from chemotherapy and immunotherapy.[109]

Recently, there has been a concerted effort to differentiate the genomic landscape of SCLC by characterizing subtypes that may predict outcomes with specific therapies. Gay et al proposed four distinct subtypes of SCLC based on expression of specific transcription factors: SCLC-A (high ASCLC1), SCLC-N (high NEUROD1), SCLC-P (high POUF2F3), and SCLC-I (low ASCLC1, NEUROD1, and POUF2F3). The SCLC-I subtype appeared to be most responsive to chemo-immunotherapy.[161] Further studies are needed to fully determine whether these subtypes are predictive of benefit for rationally designed targeted therapies.[162,163] To date, there is no validated role for any predictive biomarker to guide treatment of patients with SCLC.

Clinical Question 8

Which myeloid supportive agents may be considered for use in patients with SCLC? (1) What is the role of trilaciclib or granulocyte colony-stimulating factor (G-CSF) in patients with ES-SCLC? (2) What is the role of G-CSF in patients undergoing chemoradiotherapy?

Recommendation 8.1

Trilaciclib or G-CSF may be offered as a myeloid supportive agent for patients with untreated or previously treated ES-SCLC who are undergoing treatment with chemotherapy or chemoimmunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Literature review and clinical interpretation. In February 2021, the FDA approved trilaciclib, a CDK 4/6 inhibitor, to reduce the frequency of chemotherapy-induced bone marrow suppression in adults receiving certain types of chemotherapy for ES-SCLC. A phase Ib, randomized phase II trial of trilaciclib in patients with SCLC receiving first-line chemotherapy with CE showed a significant reduction of both the occurrence and duration of severe neutropenia and a reduction in the percentage of patients receiving red blood cell transfusions and the rate of transfusions.[80]

A randomized, placebo-controlled phase II trial showed that, compared with placebo, trilaciclib administered prior to first-line carboplatin, etoposide, and atezolizumab in patients with ES-SCLC resulted in significant decreases in the mean duration of severe neutropenia in cycle 1 (0 *v* 4 days; $P < .0001$) and the occurrence of severe neutropenia (1.9% *v* 49.1%; $P < .0001$), with additional improvements in red blood cell and platelet measures and health-related QoL. Patients receiving trilaciclib had fewer grade ≥3 AEs than those receiving placebo.[164]

Another randomized, placebo-controlled, phase II trial reported that the administration of trilaciclib prior to

topotecan in previously treated patients with ES-SCLC resulted in statistically significant decreases in duration of severe neutropenia in cycle 1 (mean, 2 *v* 7 days; $P < .0001$) and occurrence of severe neutropenia (40.6% *v* 75.9%; $P = .016$), with numerical improvements in red blood cell and platelet measures. Myelopreservation benefits extended to improvements in patient-reported outcomes.[79]

Two separate pooled analyses of the previously mentioned studies confirmed that trilaciclib led to a statistically significant improvement in multilineage chemotherapy-induced myelosuppression, thereby reducing the need for supportive care and improving QoL. Trilaciclib had no effect on antitumor efficacy.[41,43] Another exploratory pooled analysis assessed five major adverse hematological events, including all-cause hospitalizations, all-cause chemotherapy dose reductions, febrile neutropenia, prolonged severe neutropenia, and RBC transfusions, and demonstrated that, compared to placebo, trilaciclib resulted in statistically significant reductions in all of these endpoints except all-cause hospitalizations.

Recommendation 8.2

G-CSF may be offered in patients with LS-SCLC who are undergoing chemoradiotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Literature review and clinical interpretation. Historically, the use of G-CSF has been discouraged in patients with LS-SCLC undergoing chemoradiotherapy. In the early 1990s, SWOG 8812, a prospective randomized phase III study, evaluated the effect of granulocyte-macrophage colony-stimulating factor (GM-CSF) in LS-SCLC[45] in patients treated with six cycles of PE and concurrent thoracic radiotherapy of 45 Gy in 25 fractions. Patients receiving GM-CSF had a significantly increased frequency and duration of grade 3-4 thrombocytopenia, nonhematologic toxicity, and treatment-related deaths. Subsequently, ASCO guidelines for use of white blood cell growth factors in 2006 and 2015 recommended avoiding GM-CSF and G-CSF in patients receiving concurrent chemoradiotherapy, particularly involving the mediastinum.[165,166]

Two subsequent studies reported less toxicity with G-CSF administration during concurrent chemoradiotherapy in the era of modern 3D-conformal RT techniques. In a phase II study of concurrent chemotherapy and once-daily versus twice-daily thoracic radiation in LS-SCLC, 20 patients received G-CSF according to local policy for treatment of febrile neutropenia, or as primary or secondary prophylaxis.[81] This showed an increased risk of clinically significant thrombocytopenia without increased risk of pneumonitis. No episodes of bleeding were observed, and no treatment-related deaths occurred. The authors noted that G-CSF was given to patients already at elevated risk of hematologic toxicity, which may have confounded interpretation of results. This was followed by the phase III, open-label, randomized CONVERT trial evaluating once-daily versus twice-daily radiotherapy with concurrent chemotherapy in 487 patients with LS-SCLC.[44] G-CSF administration was allowed per investigator choice for primary or secondary prophylaxis. In a secondary analysis, 180 patients who received G-CSF had a higher incidence of severe thrombocytopenia and rate of blood transfusions without observed differences in RT-related toxicity, treatment-related mortality, or survival outcomes. More patients who received G-CSF achieved an optimal dose intensity of chemotherapy. The higher incidence of severe thrombocytopenia and blood transfusions was attributed to selection bias, as those patients selected for G-CSF had higher risks of myelotoxicity. However, it is worth noting this was an unplanned secondary analysis and the study lacked strict criteria for G-CSF administration.

Based on these more recent studies, the panel concludes that G-CSF may be offered in patients with LS-SCLC who undergo chemoradiotherapy if there is an appropriate clinical indication. The use of GM-CSF is not recommended. Potential higher risks of thrombocytopenia and need for blood transfusions should be noted and may reflect baseline increased hematologic risk in those patients selected for G-CSF administration during chemoradiotherapy.

Please refer to the treatment algorithm in Figures 2-4 for the visual representation of these recommendations.

DISCUSSION

It is clear to all clinicians caring for people with SCLC that all patients are not the same. Future advances will require the identification of subsets of patients with specific predictive biomarkers and molecular vulnerabilities. Along these lines, several molecular subtypes of SCLC have now been defined based on gene expression profiling[161,162] and molecular genetic analysis.[167] Current and future research now aims to identify and therapeutically target the molecular drivers of cell survival, proliferation, and metastasis that are unique to each of these SCLC subtypes.

Although ICIs are only FDA-approved as first-line therapy in combination with chemotherapy for ES-SCLC, about 10%-15% of patients with SCLC have demonstrated some benefit from ICIs regardless of clinical scenario, be it first-line therapy, maintenance therapy, or relapsed disease. Even in the negative maintenance trials of pembrolizumab[168] and nivolumab,[169] about 10% of patients had long-term disease control, and third-line pembrolizumab yielded a 2-year OS rate of 21%.[170] Recent studies have presumptively identified an inflammatory subtype in about 10% of SCLC samples that may predict response to immunotherapy.[161]

Clinically useful predictive biomarkers have not yet been defined for immunotherapy. In addition to identifying positive predictive biomarkers to select patients most likely to benefit from treatment, it is equally important to identify negative biomarkers that identify those who will not benefit in order to spare them from the potential toxicity of ICIs.

The identification of negative predictive biomarkers also may aid in the detection of potential targets for novel strategies to overcome therapeutic resistance. Due to the complexity of immunoregulatory pathways, indices incorporating multiple tumor and host characteristics, rather than a single marker, may hold the most promise as clinically useful predictive factor.

In LS-SCLC, the addition of ICIs to chemoradiotherapy, either concurrently or as consolidation therapy, may offer hope for improving long-term outcomes, as consolidation durvalumab has in stage III NSCLC, and the results from several ongoing clinical trials are eagerly awaited (ClinicalTrials.gov identifiers: NCT03811002, NCT02402920, NCT03540420 [ACHILES], NCT02046733 [STIMULI], NCT03585998).

Up to 60% of patients with SCLC develop brain metastases during the course of their disease.[171] In the IMpower133 trial, the presence of brain metastases was associated with lack of benefit from atezolizumab.[124] Studies exploring combinations of ICIs with other agents to improve CNS activity may overcome this limitation. One such trial is investigating nivolumab plus temozolomide, an oral cytotoxic agent with blood-brain barrier penetrance (ClinicalTrials.gov identifier: NCT03728361).

Many studies evaluating novel combinations of ICIs with molecularly targeted drugs or other immunomodulatory agents are underway. Combinations of ICIs with CHK1 and PARP inhibitors have reported dramatic effects in preclinical models of SCLC.[172] Thus far, clinical trials of ICIs plus PARP inhibition in SCLC have been disappointing[173,174] but have suggested potential biomarkers for enhanced patient selection.

SCLC causes substantial morbidity and debility in most patients with the disease and the restriction of clinical trials to people with good PS limits the generalizability of trial results. Expanding clinical trial eligibility to patients with marginal PS (ie, ECOG PS 2) would allow better assessment of the risk-benefit ratio for ICIs and other novel therapies in a broader range of patients.

While empiric chemotherapy and radiotherapy have had a major impact on the survival of patients with SCLC, it is doubtful that these modalities will provide further significant improvements in outcomes. The addition of ICIs to the SCLC armamentarium has offered patients new therapeutic options and hope for the first time in over 30 years, but the number of patients benefitting from treatment remains small. Recently, advances in our knowledge of SCLC biology, molecular subtypes, and therapeutic vulnerabilities have created a buzz in the field for the first time in several decades. Ongoing efforts to translate these findings to the clinic will hopefully launch a golden age of SCLC research and improvements in survival.

PATIENT AND CLINICIAN COMMUNICATION

In the era of precision medicine, the evolution of biomarkers has become an accelerating revolution in the treatment of NSCLC, but small-cell lung cancer advancements have only been incremental. There are some promising studies in the pipeline, but managing the disease continues to be complicated. Furthermore, the cancer symptoms and side effects from treatment can significantly impact a person's QoL.

At a time when patients and families are faced with making difficult treatment decisions, distress and anxiety cloud their ability to comprehend clearly, so you can expect an emotional reaction. However, it is how you communicate that will make a difference. Beyond words, the simple yet complex art of conversation is the heart of a patient's experience.

- Get to know your patients. Leave all assumptions at the door, step out of the scientific box, and ask relational, not technical, questions. Patients want to know that the doctor caring for them also cares about them.
- Treating small-cell lung cancer is more complicated than ever, and with scientific evidence often incomplete and/or conflicting, there often are no concrete rights or wrongs. The right thing is to know the medical data and apply it in the context of the patient and their family.
- OS is not the only important endpoint for patients and families. It is not enough to just survive; patients want life! What that means is unique to each patient and can only be answered by the patient and their family.
- The most important conversations with patients are not the data-driven ones. Have those difficult conversations about goals of care, what is important and meaningful in their life besides living longer, what they are afraid of, and what tradeoffs they are willing to make. These discussions need to happen before talking about treatment.
- You are the experts in the science, but patients also have their PhD—person with history of disease. Patients are the experts in the lived experience and the only reliable source for symptoms, side effects, severity, and how they impact QoL.
- Words matter. Smoking-related stigma is an important issue. Taking a person's smoking history is important for cancer treatment, but it must be addressed as an addiction, a disease, not a behavior or moral failing.
- The IASLC Language Guide was created to provide best practices when talking or writing about lung cancer. There are four main principles: person first, stigma-free, blame-free, and equitable and inclusive language. The guide is not meant to call people out but instead to call people in as an essential step in increasing respect and unity throughout the lung cancer community.
- Provide hope, with reality—hope may need to be redefined at times, but it is a vital emotion no matter where someone is in their phase of care.

Every person is different, but there is one thing we all share—a common goal of survival. How that goal is reached

will be different for each patient, but achieving that goal absolutely requires good communication: an open, honest, and respectful relationship between physicians and patients. You may not save every life, but if you help your patients find their hope, you will make a difference in their lives and their families.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care and/or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation, geographic location, and insurance access are known to affect cancer care outcomes.[175] Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[176-178] Studies have found that Black race, lack of insurance or having nonprivate insurance, lower education, and older age were factors associated with lower odds of receiving systemic treatment for ES-SCLC. In addition to racial disparities in the delivery of chemotherapy for patients with ES-SCLC, other studies have reported that Black patients are less likely to receive prophylactic cranial irradiation and effective doses of consolidative thoracic radiotherapy. Socioeconomic factors such as type of health insurance may also affect receipt of chemotherapy and survival. Higher education was associated with an increased likelihood of receiving chemotherapy. Older patients have a higher incidence of comorbidities and tend to have worse outcomes in general. The poorer OS in older patients with SCLC could be related to decreased tolerance or dose limitations of chemotherapy or RT, in addition to non–cancer-related causes of death.[179] Studies also show that older patients and non-Hispanic Black patients are less likely to receive guidelines-concordant treatment across most clinical subgroups of lung cancer.[180]

Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations. Achieving health equity requires efforts that inform, educate, and empower all individuals. Stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer and research, and addressing the structural barriers that preserve health inequities.[175]

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions—a situation in which the patient may have two or more such conditions, referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients in order to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

All treatment plans need to take into account the complexity and uncertainty created by the presence of MCC, and patients with MCC highlight the importance of shared decision-making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[181,182] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[183,184]

Discussion of cost can be an important part of shared decision making.[185] Clinicians should discuss with patients the use of less-expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[185]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different

products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[185]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data; agents that are not currently available in either the United States or Canada; or are industry-sponsored. Four cost-effectiveness analyses were identified to inform some of the topics discussed in this guideline.[186-189]

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from January 17 through 31, 2023. There were 15 respondents in total and were all medical oncologists. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation with 53 written comments received. A total of 80%-92% of the responses either agreed or agreed with slight modifications to the recommendations and 8% of the responses disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to EBMC review and approval.

The draft was submitted to OH external reviewers with content expertise in medical oncology. It was rated as high quality, and it was agreed it would be useful in practice. Comments were reviewed by the Expert Panel and integrated into the final manuscript before approval by the EBMC.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is not only to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Radiation Therapy for Small Cell Lung Cancer[18] (http://ascopubs.org/doi/10.1200/JCO.20.03364)
- Integration of Palliative Care into Standard Oncology Care[190] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[191] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[192] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.[193-196] With the acknowledgment that ASCO guidelines may impact the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data based on gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

AFFILIATIONS

[1]Brown University, Providence, RI
[2]American Society of Clinical Oncology (ASCO), Alexandria, VA
[3]Maine Health, South Portland, ME
[4]Texas Oncology, Grapevine, TX
[5]Stanford University, Stanford, CA
[6]Juravinski Cancer Center, Hamilton Health Sciences, Hamilton, Ontario, Canada

[7]EGFR Resisters Patient Advocacy Group, Deerfield, IL
[8]Johns Hopkins University, Baltimore, MD
[9]Western University, Windsor Regional Cancer Program, Windsor, Ontario, Canada
[10]University of British Columbia, Vancouver, British Columbia, Canada
[11]Mayo Clinic, Jacksonville, FL
[12]Janata Clinic, Aloknagar, Kathmandu, Nepal
[13]Memorial Sloan Kettering Cancer Center, Montvale, NJ
[14]Cancer Center of Kansas, Wichita, KS
[15]Weill Cornell Medicine, New York, NY
[16]University of Illinois, Chicago, IL
[17]University of Michigan, Ann Arbor, MI

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Ste 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/thoracic-cancer-guidelines.

EQUAL CONTRIBUTION

H.K. and G.K. were expert panel co-chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.01435.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The Expert Panel wishes to thank Drs Christina Annunziata, Michael Mullane, and the Ontario Health reviewers, Drs Jonathan Sussman, Bill Evans, Muriel Brackstone, and the Evidence Based Medicine Committee for their thoughtful reviews and insightful comments on this guideline.

REFERENCES

1. Wang S, Tang J, Sun T, et al: Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. Sci Rep 7:1339, 2017
2. Oronsky B, Reid TR, Oronsky A, et al: What's new in SCLC? A review. Neoplasia 19:842-847, 2017
3. Siegel RL, Miller KD, Fuchs HE, et al: Cancer statistics, 2022. CA Cancer J Clin 72:7-33, 2022
4. Zelen M: Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 3:31-42, 1973
5. Faivre-Finn C, Snee M, Ashcroft L, et al: Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): An open-label, phase 3, randomised, superiority trial. Lancet Oncol 18:1116-1125, 2017
6. Govindan R, Page N, Morgensztern D, et al: Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 24:4539-4544, 2006
7. Gaspar LE, Gay EG, Crawford J, et al: Limited-stage small-cell lung cancer (stages I-III): Observations from the National Cancer Data Base. Clin Lung Cancer 6:355-360, 2005
8. Rudin CM, Ismaila N, Hann CL, et al: Treatment of small-cell lung cancer: American Society of Clinical Oncology endorsement of the American College of Chest Physicians guideline. J Clin Oncol 33:4106-4111, 2015
9. Paz-Ares L, Chen Y, Reinmuth N, et al: Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO Open 7:100408, 2022
10. Liu SV, Reck M, Mansfield AS, et al: Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). J Clin Oncol 39:619-630, 2021
11. Trigo J, Subbiah V, Besse B, 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 21:645-654, 2020
12. Navarro A, Aix SP, Aranda ICB, et al: Analysis of patients with relapsed small cell lung cancer (SCLC) receiving single-agent lurbinectedin in the phase 3 ATLANTIS trial. J Clin Oncol 40, 2022 (suppl 16; abstr 8524)
13. Parsons A, Daley A, Begh R, et al: Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: Systematic review of observational studies with meta-analysis. BMJ 340: b5569, 2010
14. Warren GW, Sobus S, Gritz ER: The biological and clinical effects of smoking by patients with cancer and strategies to implement evidence-based tobacco cessation support. Lancet Oncol 15: e568-e580, 2014
15. Caini S, Del Riccio M, Vettori V, et al: Quitting smoking at or around diagnosis improves the overall survival of lung cancer patients: A systematic review and meta-analysis. J Thorac Oncol 17: 623-636, 2022
16. Jassem J: Tobacco smoking after diagnosis of cancer: Clinical aspects. Transl Lung Cancer Res 8:S50-S58, 2019
17. Tsao AS, Liu D, Lee JJ, et al: Smoking affects treatment outcome in patients with advanced nonsmall cell lung cancer. Cancer 106:2428-2436, 2006
18. Daly ME, Ismaila N, Decker RH, et al: Radiation therapy for small-cell lung cancer: ASCO guideline endorsement of an ASTRO guideline. J Clin Oncol 39:931-939, 2021
19. Shiffman RN, Michel G, Rosenfeld RM, et al: Building better guidelines with BRIDGE-Wiz: Development and evaluation of a software assistant to promote clarity, transparency, and implementability. J Am Med Inform Assoc 19:94-101, 2012
20. Higgins JPT, Thomas J, Chandler J, et al (eds): Cochrane Handbook for Systematic Reviews of Interventions (ed 2). Chichester, United Kingdom, Wiley, 2019
21. Balshem H, Helfand M, Schünemann HJ, et al: GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64:401-406, 2011
22. Horita N, Yamamoto M, Sato T, et al: Amrubicin for relapsed small-cell lung cancer: A systematic review and meta-analysis of 803 patients. Sci Rep 6:18999, 2016
23. Horita N, Yamamoto M, Sato T, et al: Topotecan for relapsed small-cell lung cancer: Systematic review and meta-analysis of 1347 patients. Sci Rep 5:15437, 2015
24. Owonikoko TK, Behera M, Chen Z, et al: A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. J Thorac Oncol 7:866-872, 2012
25. Yu H, Chen P, Cai X, et al: Efficacy and safety of PD-L1 inhibitors versus PD-1 inhibitors in first-line treatment with chemotherapy for extensive-stage small-cell lung cancer. Cancer Immunol Immunother 71:637-644, 2022
26. Chen CY, Chen WC, Hung CM, et al: Chemotherapy or chemo-immunotherapy as first-line treatment for extensive-stage small-cell lung cancer: A meta-analysis. Immunotherapy 13:1165-1177, 2021
27. Liu X, Xing H, Zhang H, et al: Immunotherapy versus standard chemotherapy for treatment of extensive-stage small-cell lung cancer: A systematic review. Immunotherapy 13:989-1000, 2021
28. Zhang S, Bi M: The efficiency and safety of immune checkpoint inhibitors in the treatment of small cell lung cancer: A meta-analysis. Ann Palliat Med 9:4081-4088, 2020
29. Zhang S, Li S, Cheng Y: Efficacy and safety of PD-1/PD-L1 inhibitor plus chemotherapy versus chemotherapy alone as first-line treatment for extensive-stage small cell lung cancer: A systematic review and meta-analysis. Thorac Cancer 11:3536-3546, 2020
30. Zhou T, Zhang Z, Luo F, et al: Comparison of first-line treatments for patients with extensive-stage small cell lung cancer: A systematic review and network meta-analysis. JAMA Netw Open 3:e2015748, 2020

31. Zhou F, Zhao W, Gong X, et al: Immune-checkpoint inhibitors plus chemotherapy versus chemotherapy as first-line treatment for patients with extensive-stage small cell lung cancer. J Immunother Cancer 8:e001300, 2020
32. Xu F, Ren X, Chen Y, et al: Irinotecan-platinum combination therapy for previously untreated extensive-stage small cell lung cancer patients: A meta-analysis. BMC Cancer 18:808, 2018
33. Han D, Wang G, Sun L, et al: Comparison of irinotecan/platinum versus etoposide/platinum chemotherapy for extensive-stage small cell lung cancer: A meta-analysis. Eur J Cancer Care (Engl) 26, 2017
34. Jiang L, Yang KH, Guan QL, et al: Cisplatin plus etoposide versus other platin-based regimens for patients with extensive small-cell lung cancer: A systematic review and meta-analysis of randomised, controlled trials. Intern Med J 42:1297-1309, 2012
35. Lima JP, Santos LVD, Sasse EC, et al: Camptothecins compared with etoposide in combination with platinum analog in extensive stage small cell lung cancer: Systematic review with meta-analysis. J Thorac Oncol 5:1986-1993, 2010
36. Rossi A, Di Maio M, Chiodini P, et al: Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: The COCIS meta-analysis of individual patient data. J Clin Oncol 30:1692-1698, 2012
37. Jiang S, Huang L, Zhen H, et al: Carboplatin versus cisplatin in combination with etoposide in the first-line treatment of small cell lung cancer: A pooled analysis. BMC Cancer 21:1308, 2021
38. Roviello G, Zanotti L, Cappelletti MR, et al: No advantage in survival with targeted therapies as maintenance in patients with limited and extensive-stage small cell lung cancer: A literature-based meta-analysis of randomized trials. Clin Lung Cancer 17:334-340, 2016
39. Mascaux C, Paesmans M, Berghmans T, et al: A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis. Lung Cancer 30:23-36, 2000
40. Rossi A, Garassino MC, Cinquini M, et al: Maintenance or consolidation therapy in small-cell lung cancer: A systematic review and meta-analysis. Lung Cancer 70:119-128, 2010
41. Ferrarotto R, Anderson I, Medgyasszay B, et al: Trilaciclib prior to chemotherapy reduces the usage of supportive care interventions for chemotherapy-induced myelosuppression in patients with small cell lung cancer: Pooled analysis of three randomized phase 2 trials. Cancer Med 10:5748-5756, 2021
42. Gómez MD, Csőszi T, Jaal J, et al: Exploratory composite endpoint demonstrates benefit of trilaciclib across multiple clinically meaningful components of myeloprotection in patients with small cell lung cancer. Int J Cancer 149:1463-1472, 2021
43. Weiss J, Goldschmidt J, Andric Z, et al: Effects of trilaciclib on chemotherapy-induced myelosuppression and patient-reported outcomes in patients with extensive-stage small cell lung cancer: Pooled results from three phase II randomized, double-blind, placebo-controlled studies. Clin Lung Cancer 22:449-460, 2021
44. Gomes F, Faivre-Finn C, Mistry H, et al: Safety of G-CSF with concurrent chemo-radiotherapy in limited-stage small cell lung cancer—Secondary analysis of the randomised phase 3 CONVERT trial. Lung Cancer 153:165-170, 2021
45. Bunn PA, Crowley J, Kelly K, et al: Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: A prospective phase III randomized study of the Southwest oncology group. J Clin Oncol 13:1632-1641, 1995
46. Spigel DR, Vicente D, Ciuleanu TE, et al: Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331. Ann Oncol 32:631-641, 2021
47. Baize N, Monnet I, Greillier L, 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 21:1224-1233, 2020
48. Goto K, Ohe Y, Shibata T, et al: Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer (JCOG0605): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 17:1147-1157, 2016
49. Evans TL, Cho BC, Udud K, et al: Cabazitaxel versus topotecan in patients with small-cell lung cancer with progressive disease during or after first-line platinum-based chemotherapy. J Thorac Oncol 10:1221-1228, 2015
50. O'Brien ME, Ciuleanu TE, Tsekov H, 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 24: 5441-5447, 2006
51. Sekine I, Okamoto H, Horai T, et al: A randomized phase III study of single-agent amrubicin vs. carboplatin/etoposide in elderly patients with extensive-disease small-cell lung cancer. Clin Lung Cancer 15:96-102, 2014
52. Schild SE, Stella PJ, Brooks BJ, et al: Results of combined-modality therapy for limited-stage small cell lung carcinoma in the elderly. Cancer 103:2349-2354, 2005
53. Kubota K, Hida T, Ishikura S, et al: Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy (JCOG0202): A randomised phase 3 study. Lancet Oncol 15:106-113, 2014
54. Sculier JP, Lafitte JJ, Efremidis A, et al: A phase III randomised study of concomitant induction radiochemotherapy testing two modalities of radiosensitisation by cisplatin (standard versus daily) for limited small-cell lung cancer. Ann Oncol 19:1691-1697, 2008
55. McClay EF, Bogart J, Herndon JE II, et al: A phase III trial evaluating the combination of cisplatin, etoposide, and radiation therapy with or without tamoxifen in patients with limited-stage small cell lung cancer: Cancer and Leukemia Group B Study (9235). Am J Clin Oncol 28:81-90, 2005
56. Urban T, Chastang C, Lebas FX, et al: The addition of cisplatin to cyclophosphamide-doxorubicin-etoposide combination chemotherapy in the treatment of patients with small cell lung carcinoma: A randomized study of 457 patients. "Petites Cellules" Group. Cancer 86:2238-2245, 1999
57. Gregor A, Drings P, Burghouts J, et al: Randomized trial of alternating versus sequential radiotherapy/chemotherapy in limited-disease patients with small-cell lung cancer: A European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group study. J Clin Oncol 15:2840-2849, 1997
58. Goodman GE, Crowley JJ, Blasko JC, et al: Treatment of limited small-cell lung cancer with etoposide and cisplatin alternating with vincristine, doxorubicin, and cyclophosphamide versus concurrent etoposide, vincristine, doxorubicin, and cyclophosphamide and chest radiotherapy: A Southwest Oncology Group study. J Clin Oncol 8:39-47, 1990
59. Ai X, Pan Y, Shi J, et al: Efficacy and safety of niraparib as maintenance treatment in patients with extensive-stage SCLC after first-line chemotherapy: A randomized, double-blind, phase 3 study. J Thorac Oncol 16:1403-1414, 2021
60. Johnson ML, Zvirbule Z, Laktionov K, et al: Rovalpituzumab tesirine as a maintenance therapy after first-line platinum-based chemotherapy in patients with extensive-stage-SCLC: Results from the phase 3 MERU study. J Thorac Oncol 16:1570-1581, 2021
61. Hanna NH, Sandier AB, Loehrer PJ Sr, et al: Maintenance daily oral etoposide versus no further therapy following induction chemotherapy with etoposide plus ifosfamide plus cisplatin in extensive small-cell lung cancer: A Hoosier Oncology Group randomized study. Ann Oncol 13:95-102, 2002
62. Schiller JH, Adak S, Cella D, et al: Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593—A phase III trial of the Eastern Cooperative Oncology Group. J Clin Oncol 19:2114-2122, 2001
63. Jalal SI, Lavin P, Lo G, et al: Carboplatin and etoposide with or without palifosfamide in untreated extensive-stage small-cell lung cancer: A multicenter, adaptive, randomized phase III study (MATISSE). J Clin Oncol 35:2619-2623, 2017
64. Pujol JL, Lavole A, Quoix E, et al: Randomized phase II-III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: Results from the IFCT-0802 trial. Ann Oncol 26:908-914, 2015
65. Murray N, Livingston RB, Shepherd FA, et al: Randomized study of CODE versus alternating CAV/EP for extensive-stage small-cell lung cancer: An intergroup study of the National Cancer Institute of Canada Clinical Trials Group and the Southwest Oncology Group. J Clin Oncol 17:2300-2308, 1999
66. Furuse K, Fukuoka M, Nishiwaki Y, et al: Phase III study of intensive weekly chemotherapy with recombinant human granulocyte colony-stimulating factor versus standard chemotherapy in extensive-disease small-cell lung cancer. The Japan Clinical Oncology Group. J Clin Oncol 16:2126-2132, 1998
67. Wang J, Zhou C, Yao W, et al: Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 23:739-747, 2022
68. Sundstrøm S, Bremnes RM, Kaasa S, et al: Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: Results from a randomized phase III trial with 5 years' follow-up. J Clin Oncol 20:4665-4672, 2002
69. Roth BJ, Johnson DH, Einhorn LH, et al: Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: A phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 10:282-291, 1992
70. Cheng Y, Han L, Wu L, et al: Serplulimab, a novel anti-PD-1 antibody, plus chemotherapy versus chemotherapy alone as first-line treatment for extensive-stage small-cell lung cancer: An international randomized phase 3 study. J Clin Oncol 40, 2022 (suppl 16; abstr 8505)
71. Satouchi M, Kotani Y, Shibata T, et al: Phase III study comparing amrubicin plus cisplatin with irinotecan plus cisplatin in the treatment of extensive-disease small-cell lung cancer: JCOG 0509. J Clin Oncol 32:1262-1268, 2014
72. Sun Y, Cheng Y, Hao X, et al: Randomized phase III trial of amrubicin/cisplatin versus etoposide/cisplatin as first-line treatment for extensive small-cell lung cancer. BMC Cancer 16:265, 2016
73. Mavroudis D, Papadakis E, Veslemes M, et al: A multicenter randomized clinical trial comparing paclitaxel-cisplatin-etoposide versus cisplatin-etoposide as first-line treatment in patients with small-cell lung cancer. Ann Oncol 12:463-470, 2001

74. Socinski MA, Smit EF, Lorigan P, et al: Phase III study of pemetrexed plus carboplatin compared with etoposide plus carboplatin in chemotherapy-naïve patients with extensive-stage small-cell lung cancer. J Clin Oncol 27:4787-4792, 2009
75. Fukuoka M, Furuse K, Saijo N, et al: Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst 83:855-861, 1991
76. Ignatiadis M, Mavroudis D, Veslemes M, et al: Sequential versus alternating administration of cisplatin/etoposide and topotecan as first-line treatment in extensive-stage small-cell lung cancer: Preliminary results of a phase III trial of the Hellenic Oncology Research Group. Clin Lung Cancer 7:183-189, 2005
77. Oh IJ, Kim KS, Park CK, et al: Belotecan/cisplatin versus etoposide/cisplatin in previously untreated patients with extensive-stage small cell lung carcinoma: A multi-center randomized phase III trial. BMC Cancer 16:690, 2016
78. Schneider BJ, Kalemkerian GP, Ramnath N, et al: Phase II trial of imatinib maintenance therapy after irinotecan and cisplatin in patients with c-Kit-positive, extensive-stage small-cell lung cancer. Clin Lung Cancer 11:223-227, 2010
79. Hart LL, Ferrarotto R, Andric ZG, et al: Myelopreservation with trilaciclib in patients receiving topotecan for small cell lung cancer: Results from a randomized, double-blind, placebo-controlled phase II study. Adv Ther 38:350-365, 2021
80. Weiss JM, Csoszi T, Maglakelidze M, et al: Myelopreservation with the CDK4/6 inhibitor trilaciclib in patients with small-cell lung cancer receiving first-line chemotherapy: A phase Ib/randomized phase II trial. Ann Oncol 30:1613-1621, 2019
81. Sheikh H, Colaco R, Lorigan P, et al: Use of G-CSF during concurrent chemotherapy and thoracic radiotherapy in patients with limited-stage small-cell lung cancer safety data from a phase II trial. Lung Cancer 74:75-79, 2011
82. Pujol JL, Greillier L, Audigier-Valette C, et al: A randomized non-comparative phase II study of anti-programmed cell death-ligand 1 atezolizumab or chemotherapy as second-line therapy in patients with small cell lung cancer: Results from the IFCT-1603 trial. J Thorac Oncol 14:903-913, 2019
83. Inoue A, Sugawara S, Yamazaki K, et al: Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. J Clin Oncol 26:5401-5406, 2008
84. von Pawel J, Schiller JH, Shepherd FA, et al: Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 17:658-667, 1999
85. Ardizzoni A, Favaretto A, Boni L, et al: Platinum-etoposide chemotherapy in elderly patients with small-cell lung cancer: Results of a randomized multicenter phase II study assessing attenuated-dose or full-dose with lenograstim prophylaxis—A Forza Operativa Nazionale Italiana Carcinoma Polmonare and Gruppo Studio Tumori Polmonari Veneto (FONICAP-GSTPV) study. J Clin Oncol 23:569-575, 2005
86. Arnold AM, Seymour L, Smylie M, et al: Phase II study of vandetanib or placebo in small-cell lung cancer patients after complete or partial response to induction chemotherapy with or without radiation therapy: National Cancer Institute of Canada Clinical Trials Group Study BR.20. J Clin Oncol 25:4278-4284, 2007
87. Nie K, Guo X, You Y, et al: S-1 maintenance therapy in extensive stage small-cell lung cancer-A randomized clinical study. Cancer Control 27:1073274820932004, 2020
88. Luo H, Zhang L, Yang B, et al: A randomized phase 2 trial of apatinib vs observation as maintenance treatment following first-line induction chemotherapy in extensive-stage small cell lung cancer. Invest New Drugs 38:148-159, 2020
89. Thomas M, Ponce-Aix S, Navarro A, et al: Immunotherapeutic maintenance treatment with toll-like receptor 9 agonist lefitolimod in patients with extensive-stage small-cell lung cancer: Results from the exploratory, controlled, randomized, international phase II IMPULSE study. Ann Oncol 29:2076-2084, 2018
90. Sun JM, Lee KH, Kim BS, et al: Pazopanib maintenance after first-line etoposide and platinum chemotherapy in patients with extensive disease small-cell lung cancer: A multicentre, randomised, placebo-controlled phase II study (KCSG-LU12-07). Br J Cancer 118:648-653, 2018
91. Ready NE, Pang HH, Gu L, et al: Chemotherapy with or without maintenance sunitinib for untreated extensive-stage small-cell lung cancer: A randomized, double-blind, placebo-controlled phase II study-CALGB 30504 (Alliance). J Clin Oncol 33:1660-1665, 2015
92. Byers LA, Bentsion D, Gans S, et al: Veliparib in combination with carboplatin and etoposide in patients with treatment-naïve extensive-stage small cell lung cancer: A phase 2 randomized study. Clin Cancer Res 27:3884-3895, 2021
93. Steffen McLouth LE, Zhao F, Owonikoko TK, et al: Patient-reported tolerability of veliparib combined with cisplatin and etoposide for treatment of extensive stage small cell lung cancer: Neurotoxicity and adherence data from the ECOG ACRIN cancer research group E2511 phase II randomized trial. Cancer Med 9:7511-7523, 2020
94. Morikawa N, Inoue A, Sugawara S, et al: Randomized phase II study of carboplatin plus irinotecan versus carboplatin plus amrubicin in patients with chemo-naïve extensive-stage small-cell lung cancer: North Japan Lung Cancer Study Group (NJLCG) 0901. Lung Cancer 111:38-42, 2017
95. Glisson B, Besse B, Dols MC, et al: A randomized, placebo-controlled, phase 1b/2 study of rilotumumab or ganitumab in combination with platinum-based chemotherapy as first-line treatment for extensive-stage small-cell lung cancer. Clin Lung Cancer 18:615-625.e8, 2017
96. Socinski MA, Kaye FJ, Spigel DR, et al: Phase 1/2 study of the CD56-targeting antibody-drug conjugate lorvotuzumab mertansine (IMGN901) in combination with carboplatin/etoposide in small-cell lung cancer patients with extensive-stage disease. Clin Lung Cancer 18:68-76.e2, 2017
97. Sanborn RE, Patel JD, Masters GA, et al: A randomized, double-blind, phase 2 trial of platinum therapy plus etoposide with or without concurrent vandetanib (ZD6474) in patients with previously untreated extensive-stage small cell lung cancer: Hoosier Cancer Research Network LUN06-113. Cancer 123;303-311, 2017
98. Langer CJ, Albert I, Ross HJ, et al: Randomized phase II study of carboplatin and etoposide with or without obatoclax mesylate in extensive-stage small cell lung cancer. Lung Cancer 85:420-428, 2014
99. Rudin CM, Salgia R, Wang X, et al: Randomized phase II study of carboplatin and etoposide with or without the bcl-2 antisense oligonucleotide oblimersen for extensive-stage small-cell lung cancer: CALGB 30103. J Clin Oncol 26:870-876, 2008
100. Owonikoko TK, Aisner J, Wang XV, et al: E5501: Phase II study of topotecan sequenced with etoposide/cisplatin, and irinotecan/cisplatin sequenced with etoposide for extensive-stage small-cell lung cancer. Cancer Chemother Pharmacol 73:171-180, 2014
101. Ramalingam S, Belani CP, Day R, et al: Phase II study of topotecan and paclitaxel for patients with previously untreated extensive stage small-cell lung cancer. Ann Oncol 15:247-251, 2004
102. Owonikoko TK, Dahlberg SE, Sica GL, et al: Randomized phase II trial of cisplatin and etoposide in combination with veliparib or placebo for extensive-stage small-cell lung cancer: ECOG-ACRIN 2511 study. J Clin Oncol 37:222-229, 2019
103. Spigel DR, Townley PM, Waterhouse DM, et al: Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: Results from the SALUTE trial. J Clin Oncol 29:2215-2222, 2011
104. Park S, Shim J, Mortimer PGS, et al: Biomarker-driven phase 2 umbrella trial study for patients with recurrent small cell lung cancer failing platinum-based chemotherapy. Cancer 126:4002-4012, 2020
105. Naito T, Tanaka F, Ono A, et al: Prognostic impact of circulating tumor cells in patients with small cell lung cancer. J Thorac Oncol 7:512-519, 2012
106. Hellmann MD, Callahan MK, Awad MM, et al: Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. Cancer Cell 33:329, 2018
107. Osterlind K, Hansen M, Hirsch FR, et al: Combination chemotherapy of limited-stage small-cell lung cancer. A controlled trial on 221 patients comparing two alternating regimens. Ann Oncol 2: 41-46, 1991
108. Li L, Tang S, Yin JC, et al: Comprehensive next-generation sequencing reveals novel predictive biomarkers of recurrence and thoracic toxicity risks after chemoradiation therapy in limited stage small cell lung cancer. Int J Radiat Oncol Biol Phys 112:1165-1176, 2022
109. Zhang Z, Zhang C, Luo Y, et al: mA regulator expression profile predicts the prognosis, benefit of adjuvant chemotherapy, and response to anti-PD-1 immunotherapy in patients with small-cell lung cancer. BMC Med 19:284, 2021
110. Zhang Z, Zhang C, Yang Z, et al: mA regulators as predictive biomarkers for chemotherapy benefit and potential therapeutic targets for overcoming chemotherapy resistance in small-cell lung cancer. J Hematol Oncol 14:190, 2021
111. Gao C, Gu X, Chen Y, et al: Identification of potential prognostic and predictive biomarkers for immune-checkpoint inhibitor response in small cell lung cancer. Med Sci Monit 27:e932275, 2021
112. Yuen AR, Zou G, Turrisi AT, et al: Similar outcome of elderly patients in intergroup trial 0096: Cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. Cancer 89:1953-1960, 2000
113. Kim E, Biswas T, Bakaki P, et al: Comparison of cisplatin/etoposide versus carboplatin/etoposide concurrent chemoradiation therapy for limited-stage small cell lung cancer (LS-SCLC) in the elderly population (age >65 years) using national SEER-Medicare data. Pract Radiat Oncol 6:e163-e169, 2016
114. Yang CF, Chan DY, Speicher PJ, et al: Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol 34:1057-1064, 2016
115. Karam I, Jiang SY, Khaira M, et al: Outcomes of small cell lung cancer patients treated with cisplatin-etoposide versus carboplatin-etoposide. Am J Clin Oncol 38:51-54, 2015
116. Jones GS, Khakwani A, Pascoe A, et al: Factors associated with survival in small cell lung cancer: An analysis of real-world national audit, chemotherapy and radiotherapy data. Ann Palliat Med 10:4055-4068, 2021
117. Moher D, Liberati A, Tetzlaff J, et al: Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PLoS Med 6:e1000097, 2009

118. Arriagada R, Pignon JP, Le Chevalier T: Initial chemotherapeutic doses and long-term survival in limited small-cell lung cancer. N Engl J Med 345:1281-1282, 2001
119. Veslemes M, Polyzos A, Latsi P, et al: Optimal duration of chemotherapy in small cell lung cancer: A randomized study of 4 versus 6 cycles of cisplatin-etoposide. J Chemother 10:136-140, 1998
120. Noda K, Nishiwaki Y, Kawahara M, et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85-91, 2002
121. Skarlos DV, Samantas E, Kosmidis P, et al: Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. Ann Oncol 5:601-607, 1994
122. Azar I, Yazdanpanah O, Jang H, et al: Comparison of carboplatin with cisplatin in small cell lung cancer in US Veterans. JAMA Netw Open 5:e2237699, 2022
123. Simone CB II, Bogart JA, Cabrera AR, et al: Radiation therapy for small cell lung cancer: An ASTRO clinical practice guideline. Pract Radiat Oncol 10:158-173, 2020
124. Horn L, Mansfield AS, Szczęsna A, et al: First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 379:2220-2229, 2018
125. Mansfield AS, Każarnowicz A, Karaseva N, et al: Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): A randomized phase I/III trial. Ann Oncol 31:310-317, 2020
126. Paz-Ares L, Dvorkin M, Chen Y, et al: Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): A randomised, controlled, open-label, phase 3 trial. Lancet 394:1929-1939, 2019
127. Goldman JW, Dvorkin M, Chen Y, et al: Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): Updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 22:51-65, 2021
128. Cheng Y, Han L, Wu L, et al: Effect of first-line serplulimab vs placebo added to chemotherapy on survival in patients with extensive-stage small cell lung cancer: The ASTRUM-005 randomized clinical trial. JAMA 328:1223-1232, 2022
129. Rudin CM, Awad MM, Navarro A, et al: Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: Randomized, double-blind, phase III KEYNOTE-604 study. J Clin Oncol 38:2369-2379, 2020
130. Leal T, Wang Y, Dowlati A, et al: Randomized phase II clinical trial of cisplatin/carboplatin and etoposide (CE) alone or in combination with nivolumab as frontline therapy for extensive-stage small cell lung cancer (ES-SCLC): ECOG-ACRIN EA5161. J Clin Oncol 38, 2020 (suppl 15; abstr 9000)
131. Ma X, Wang S, Zhang Y, et al: Efficacy and safety of immune checkpoint inhibitors (ICIs) in extensive-stage small cell lung cancer (SCLC). J Cancer Res Clin Oncol 147:593-606, 2021
132. Zatloukal P, Cardenal F, Szczesna A, et al: A multicenter international randomized phase III study comparing cisplatin in combination with irinotecan or etoposide in previously untreated small-cell lung cancer patients with extensive disease. Ann Oncol 21:1810-1816, 2010
133. Lara PN Jr, Natale R, Crowley J, et al: Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: Clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 27:2530-2535, 2009
134. Hermes A, Bergman B, Bremnes R, et al: Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: A randomized phase III trial. J Clin Oncol 26: 4261-4267, 2008
135. Hanna N, Bunn PA Jr, Langer C, et al: Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 24:2038-2043, 2006
136. Niell HB, Herndon JE II, Miller AA, et al: Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. J Clin Oncol 23:3752-3759, 2005
137. Loehrer PJ Sr, Ansari R, Gonin R, et al: Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: A Hoosier Oncology Group study. J Clin Oncol 13:2594-2599, 1995
138. Eckardt JR, von Pawel J, Pujol JL, et al: Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol 25:2086-2092, 2007
139. Aix SP, Ciuleanu TE, Navarro A, et al: Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): A multicentre, randomised, open-label, phase 3 trial. Lancet Respir Med 11:74-86, 2023
140. Kondo R, Watanabe S, Shoji S, et al: A phase II study of irinotecan for patients with previously treated small-cell lung cancer. Oncology 94:223-232, 2018
141. Smit EF, Fokkema E, Biesma B, et al: A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer 77:347-351, 1998
142. Pietanza MC, Kadota K, Huberman K, et al: Phase II trial of temozolomide in patients with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. Clin Cancer Res 18:1138-1145, 2012
143. Masters GA, Declerck L, Blanke C, et al: Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol 21:1550-1555, 2003
144. von Pawel J, Jotte R, Spigel DR, et al: Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. J Clin Oncol 32:4012-4019, 2014
145. Genestreti G, Tiseo M, Kenmotsu H, et al: Outcomes of platinum-sensitive small-cell lung cancer patients treated with platinum/etoposide rechallenge: A multi-institutional retrospective analysis. Clin Lung Cancer 16:e223-e228, 2015
146. Pallis AG, Shepherd FA, Lacombe D, et al: Treatment of small-cell lung cancer in elderly patients. Cancer 116:1192-1200, 2010
147. Li D, Sun CL, Kim H, et al: Geriatric assessment-driven intervention (GAIN) on chemotherapy-related toxic effects in older adults with cancer: A randomized clinical trial. JAMA Oncol 7:e214158, 2021
148. Soo WK, King MT, Pope A, et al: Integrated Geriatric Assessment and Treatment Effectiveness (INTEGERATE) in older people with cancer starting systemic anticancer treatment in Australia: A multicentre, open-label, randomised controlled trial. Lancet Healthy Longev 3:e617-e627, 2022
149. Mohile SG, Dale W, Somerfield MR, et al: Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol 36: 2326-2347, 2018
150. Quon H, Shepherd FA, Payne DG, et al: The influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined modality treatment of limited stage small cell lung cancer. Int J Radiat Oncol Biol Phys 43:39-45, 1999
151. Okamoto H, Watanabe K, Kunikane H, et al: Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. Br J Cancer 97:162-169, 2007
152. Asao T, Watanabe S, Tanaka T, et al: A phase II study of carboplatin and etoposide plus durvalumab for previously untreated extensive-stage small-cell lung cancer (ES-SCLC) patients with a poor performance status (PS): NEJ045A study protocol. BMC Cancer 22:1135, 2022
153. Treat J, Huang CH, Lane SR, et al: Topotecan in the treatment of relapsed small cell lung cancer patients with poor performance status. Oncologist 9:173-181, 2004
154. Ferrer L, Giaj Levra M, Brevet M, et al: A brief report of transformation from NSCLC to SCLC: Molecular and therapeutic characteristics. J Thorac Oncol 14:130-134, 2019
155. Marcoux N, Gettinger SN, O'Kane G, et al: EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: Clinical outcomes. J Clin Oncol 37: 278-285, 2019
156. Roca E, Gurizzan C, Amoroso V, et al: Outcome of patients with lung adenocarcinoma with transformation to small-cell lung cancer following tyrosine kinase inhibitors treatment: A systematic review and pooled analysis. Cancer Treat Rev 59:117-122, 2017
157. Lin JJ, Langenbucher A, Gupta P, et al: Small cell transformation of ROS1 fusion-positive lung cancer resistant to ROS1 inhibition. NPJ Precis Oncol 4:21, 2020
158. Paz-Ares L, Goldman J, Garassino M, et al: LBA89PD-L1 expression, patterns of progression and patient-reported outcomes (PROs) with durvalumab plus platinum-etoposide in ES-SCLC: Results from CASPIAN. Ann Oncol 30, 2019
159. George J, Lim JS, Jang SJ, et al: Comprehensive genomic profiles of small cell lung cancer. Nature 524:47-53, 2015
160. Trivedi P, Cheeseman P, Portmann B, et al: Serum type III procollagen peptide as a non-invasive marker of liver damage during infancy and childhood in extrahepatic biliary atresia, idiopathic hepatitis of infancy and alpha 1 antitrypsin deficiency. Clin Chim Acta 161:137-146, 1986
161. Gay CM, Stewart CA, Park EM, et al: Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell 39:346-360.e7, 2021
162. Rudin CM, Poirier JT, Byers LA, et al: Molecular subtypes of small cell lung cancer: A synthesis of human and mouse model data. Nat Rev Cancer 19:289-297, 2019
163. Poirier JT, George J, Owonikoko TK, et al: New approaches to SCLC therapy: From the laboratory to the clinic. J Thorac Oncol 15:520-540, 2020
164. Daniel D, Kuchava V, Bondarenko I, et al: Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: A multicentre, randomised, double-blind, placebo-controlled phase II trial. Int J Cancer 148:2557-2570, 2020
165. Smith TJ, Bohlke K, Lyman GH, et al: Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 33:3199-3212, 2015
166. Smith TJ, Khatcheressian J, Lyman GH, et al: 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 24: 3187-3205, 2006
167. Febres-Aldana CA, Chang JC, Ptashkin R, et al: Rb tumor suppressor in small cell lung cancer: Combined genomic and IHC analysis with a description of a distinct Rb-proficient subset. Clin Cancer Res 28:4702-4713, 2022

168. Gadgeel SM, Pennell NA, Fidler MJ, et al: Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). J Thorac Oncol 13:1393-1399, 2018
169. Owonikoko TK, Kim HR, Govindan R, et al: Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): Results from the double-blind, randomized phase III CheckMate 451 study. Ann Oncol 30:ii77, 2019
170. Chung HC, Piha-Paul SA, Lopez-Martin J, et al: Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: Results from the KEYNOTE-028 and KEYNOTE-158 studies. J Thorac Oncol 15:618-627, 2020
171. Seute T, Leffers P, ten Velde GP, et al: Detection of brain metastases from small cell lung cancer: Consequences of changing imaging techniques (CT versus MRI). Cancer 112:1827-1834, 2008
172. Sen T, Rodriguez BL, Chen L, et al: Targeting DNA damage response promotes antitumor immunity through STING-mediated T-cell activation in small cell lung cancer. Cancer Discov 9:646-661, 2019
173. Krebs M, Ross K, Kim S, et al: P1.15-004 An open-label, multitumor phase II basket study of olaparib and durvalumab (MEDIOLA): Results in patients with relapsed SCLC. J Thorac Oncol 12: S2044-S2045, 2017
174. Thomas A, Vilimas R, Trindade C, et al: Durvalumab in combination with olaparib in patients with relapsed SCLC: Results from a phase II study. J Thorac Oncol 14:1447-1457, 2019
175. Patel MI, Lopez AM, Blackstock W, et al: Cancer disparities and health equity: A policy statement from the American Society of Clinical Oncology. J Clin Oncol 38:3439-3448, 2020
176. US Cancer Statistics Working Group: United States Cancer Statistics: 1999–2012 Incidence and Mortality Web-Based Report. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, 2015
177. Jones K, Siegel B, Mead H, et al: Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. New York, NY, Commonwealth Fund, 2008
178. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2013. Bethesda, MD, National Cancer Institute, 2016
179. Tapan U, Furtado VF, Qureshi MM, et al: Racial and other Healthcare disparities in patients with extensive-stage SCLC. JTO Clin Res Rep 2:100109, 2021
180. Blom EF, Ten Haaf K, Arenberg DA, et al: Disparities in receiving guideline-concordant treatment for lung cancer in the United States. Ann Am Thorac Soc 17:186-194, 2020
181. Schnipper LE, Davidson NE, Wollins DS, et al: Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. J Clin Oncol 34: 2925-2934, 2016
182. Schnipper LE, Davidson NE, Wollins DS, et al: American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. J Clin Oncol 33: 2563-2577, 2015
183. Streeter SB, Schwartzberg L, Husain N, et al: Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. J Oncol Pract 7:46s-51s, 2011
184. Dusetzina SB, Winn AN, Abel GA, et al: Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol 32:306-311, 2014
185. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: The cost of cancer care. J Clin Oncol 27:3868-3874, 2009
186. Liu Q, Tan C, Yi L, et al: Cost-effectiveness analysis of pembrolizumab plus chemotherapy as first-line therapy for extensive-stage small-cell lung cancer. PLoS One 16:e0258605, 2021
187. Roth JA, Yuan Y, Othus M, et al: A comparison of mixture cure fraction models to traditional parametric survival models in estimation of the cost-effectiveness of nivolumab for relapsed small cell lung cancer. J Med Econ 24:79-86, 2021
188. Zhou K, Zhou J, Huang J, et al: Cost-effectiveness analysis of atezolizumab plus chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer. Lung Cancer 130:1-4, 2019
189. Chouaid C, Bassinet L, Fuhrman C, et al: Routine use of granulocyte colony-stimulating factor is not cost-effective and does not increase patient comfort in the treatment of small-cell lung cancer: An analysis using a Markov model. J Clin Oncol 16:2700-2707, 1998
190. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:96-112, 2017
191. Gilligan T, Coyle N, Frankel RM, et al: Patient-clinician communication: American Society of Clinical Oncology consensus guideline. J Clin Oncol 35:3618-3632, 2017
192. Griggs J, Maingi S, Blinder V, et al: American Society of Clinical Oncology position statement: Strategies for reducing cancer health disparities among sexual and gender minority populations. J Clin Oncol 35:2203-2208, 2017
193. Alpert AB, Gampa V, Lytle MC, et al. I'm not putting on that floral gown: Enforcement and resistance of gender expectations for transgender people with cancer. Patient Educ Couns 104: 2552-2558, 2021.
194. Alpert AB, Manzano C, Ruddick R. Degendering oncologic care and other recommendations to eliminate barriers to care for transgender people with cancer. ASCO Daily News, 2021
195. National Center for Transgender Equality: Understanding Transgender People: The Basics. https://transequality.org/issues/resources/understanding-transgender-people-the-basics
196. UCSF Transgender Care & Treatment Guidelines. Terminology & Definitions. https://transcare.ucsf.edu/guidelines/terminology

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Systemic Therapy for Small-Cell Lung Cancer: ASCO-Ontario Health (Cancer Care Ontario) Guideline

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Nofisat Ismaila
Employment: GlaxoSmithKline(I)
Stock and Other Ownership Interests: GlaxoSmithKline(I)

Raetasha Dabney
Employment: Magellan Health
Speakers' Bureau: Myriad Genetics

Millie Das
Honoraria: Plexus, IDEO, Springer, Medical Educator Consortium, Dedham Group, DAVA Oncology, MJH Healthcare Holdings LLC, Association of Northern California Oncologists, Aptitude Health, Med Learning Group
Consulting or Advisory Role: AstraZeneca, BeiGene, Sanofi, Regeneron, Eurofins, Advarra, Janssen
Research Funding: Novartis, Verily, Varian Medical Systems, AbbVie, United Therapeutics, Cellsight Technologies, Genentech/Roche, Merck
Expert Testimony: Kazan, McClain, Satterly & Greenwood
Uncompensated Relationships: Genentech

Peter Ellis
Honoraria: AstraZeneca, Pfizer, Lilly, Bristol Myers Squibb, Merck, Jazz Pharmaceuticals, Novartis Canada Pharmaceuticals Inc, Janssen Oncology, Sanofi/Aventis, Roche Canada

Jill Feldman
Honoraria: Blueprint Medicines, Janssen Oncology
Consulting or Advisory Role: EQRx

Christine Hann
Consulting or Advisory Role: AstraZeneca, Amgen, Janssen Oncology, Puma Biotechnology, Daiichi Sankyo Europe GmbH
Research Funding: AbbVie (Inst), Bristol Myers Squibb (Inst), Amgen (Inst), AstraZeneca (Inst), Genentech (Inst)

Swati Kulkarni
Honoraria: AstraZeneca
Consulting or Advisory Role: BMS

Janessa Laskin
Honoraria: Roche Canada, AstraZeneca, Pfizer, Jazz Pharmaceuticals
Consulting or Advisory Role: Pfizer, Takeda Science Foundation, Lilly
Research Funding: Roche Canada (Inst)

Rami Manochakian
Stock and Other Ownership Interests: Alpha 2
Consulting or Advisory Role: Takeda, Guardant Health, AstraZeneca, Novocure, Turning Point Therapeutics, Janssen, Alpha 2, Cardinal Health, Oncohost

Isabel Preeshagul
Consulting or Advisory Role: Onc Live, Dava Oncology, G1 Therapeutics, LabCorp, Pfizer, Novartis, Genentech, Jazz Pharmaceuticals, Intellisphere, AstraZeneca, Boehringer Ingelheim, G1 Therapeutics, Takeda

Ashish Saxena
Honoraria: Genentech/Roche, MJH Life Sciences, PER, Medscape, Association of Physician Assistants in Oncology, OncLive/MJH Life Sciences, MJH Healthcare Holdings, LLC, Advarra
Consulting or Advisory Role: AstraZeneca, Blueprint Medicines, AstraZeneca, AstraZeneca/MedImmune, Jazz Pharmaceuticals, AstraZeneca/MedImmune, G1 Therapeutics, Boehringer Ingelheim
Research Funding: Genentech (Inst), AstraZeneca (Inst), Bayer (Inst), Merck (Inst), Boston Biomedical (Inst), Celgene (Inst), Immunomedics (Inst), Array BioPharma (Inst), Jounce Therapeutics (Inst), Guardant Health (Inst), Seagen (Inst), Blueprint Medicines (Inst), Bristol Myers Squibb (Inst), Novocure (Inst), Endocyte (Inst), Daiichi Sankyo (Inst), Calithera Biosciences, Alphamab (Inst), Spectrum Pharmaceuticals (Inst), VM Pharma (Inst), Top Alliance BioScience (Inst)

Frank Weinberg
Consulting or Advisory Role: Regeneron, Jazz Pharmaceuticals
Speakers' Bureau: Amgen

Gregory P. Kalemkerian
Consulting or Advisory Role: BioMed Valley Discoveries, Takeda, Synlogic
Research Funding: Takeda (Inst), Merck (Inst), AbbVie (Inst), Blueprint Medicines (Inst), Cullinan Oncology (Inst), Daiichi Sankyo/Astra Zeneca (Inst), Bristol Myers Squibb Foundation (Inst)

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Systemic Therapy for Small-Cell Lung Cancer Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Humera Khurshid, MD (Co-Chair)	Brown University, Providence, RI	Medical Oncology
Gregory P. Kalemkerian, MD (Co-Chair)	University of Michigan, Ann Arbor, MI	Medical Oncology
Jessica Bian, MD	Maine Health, South Portland, ME	Medical Oncology
Raetasha Dabney, MD	Texas Oncology, Grapevine, TX	PGIN representative
Millie Das, MD	Stanford University, Stanford, CA	Medical Oncology
Peter Ellis, MD (Ontario Health representative)	Juravinski Cancer Center, Hamilton Health Sciences, Hamilton, Ontario, Canada	Medical Oncology
Jill Feldman	EGFR Resisters Patient Advocacy Group, Deerfield, IL	Patient representative
Christine Hann, MD, PhD	Johns Hopkins University, Baltimore, MD	Medical Oncology
Swati Kulkarni, MD (Ontario Health representative)	Western University, Windsor Regional Cancer Program, Windsor, Ontario, Canada	Medical Oncology
Janessa Laskin, MD, PhD	University of British Columbia, Vancouver, British Columbia, Canada	Medical Oncology
Rami Manochakian, MD	Mayo Clinic, Jacksonville, FL	Medical Oncology
Deebya Raj Mishra, MD	Janata Clinic, Aloknagar, Kathmandu, Nepal	LMIC representative
Isabel Preeshagul, DO	Memorial Sloan Kettering Cancer Center, Montvale, NJ	Medical Oncology
Pavan Reddy, MD	Cancer Center of Kansas, Wichita, KS	PGIN representative
Ashish Saxena, MD, PhD	Weill Cornell Medicine, New York, NY	Medical Oncology
Frank Weinberg, MD, PhD	University of Illinois, Chicago, IL	Medical Oncology
Nofisat Ismaila, MD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects
	In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects
	All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists
	In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists
	Most informed people would choose the recommended course of action, but a substantial number would not