New perspectives in the management of small cell lung cancer

Cristina Pangua, Jacobo Rogado, Gloria Serrano-Montero, José Belda-Sanchis, Beatriz Álvarez Rodríguez, Laura Torrado, Nuria Rodríguez De Dios, Xabier Mielgo-Rubio, Juan Carlos Trujillo, Felipe Couñago

Abstract
The treatment of small cell lung cancer (SCLC) is a challenge for all specialists involved. New treatments have been added to the therapeutic armamentarium in recent months, but efforts must continue to improve both survival and quality of life. Advances in surgery and radiotherapy have resulted in prolonged survival times and fewer complications, while more careful patient selection has led to increased staging accuracy. Developments in the field of systemic therapy have resulted in changes to clinical guidelines and the management of patients with advanced disease, mainly with the introduction of immunotherapy. In this article, we describe recent improvements in the management of patients with SCLC,
review current treatments, and discuss future lines of research.

**Key Words:** Small cell lung cancer; Whole-brain radiotherapy; Prophylactic cranial irradiation; Stereotactic body radiotherapy; Immunotherapy; Atezolizumab; Durvalumab

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**Core Tip:** The treatment of small cell lung cancer (SCLC) continues to be a challenge. Recent studies have described survival benefits achieved by new treatments or combinations of treatments that are both safe and effective. Immunotherapy has a new role in SCLC. Nevertheless, continued research efforts are needed. Here, we review the current management of SCLC and discuss recent improvements and future lines of research.

**INTRODUCTION**

Small cell lung cancer (SCLC) accounts for 14% of all lung cancers[1,2], and most cases are associated with tobacco use[3]. Although the global incidence of SCLC is falling, the ratio of male to female cases is currently 1:1[1,2]. SCLC is a fast-growing cancer, and most patients have extensive disease when diagnosed. In approximately one-third of cases, the cancer is limited to the thorax and can be treated with concurrent chemotherapy and radiotherapy. Just a small percentage of patients are amenable to surgery and adjuvant therapy. The goal of treatment in patients with extensive disease is to alleviate symptoms and prolong survival, although long-term survivorship in this setting is rare[4].

**LIMITED-STAGE DISEASE**

**Surgical treatment of SCLC**

Early-stage SCLC, stage I and IIA (T1-2N0M0) SCLC in the American Joint Committee on Cancer/International Union Against Cancer classification[5-7], accounts for 7% of all SCLCs and 0.29% of all lung cancers[8]. Numerous studies have shown excellent survival rates in patients with SCLC cT1-2N0M0 treated with surgery as part of a multimodal approach[6,9-28] (Table 1).

Surgical resection followed by adjuvant therapy is currently recommended by most clinical guidelines for operable stage I and IIA SCLC. Choice of adjuvant treatment varies according to pathologic tumor-node-metastasis stage: Chemotherapy for pN0, chemotherapy ± radiotherapy for pN1 and chemoradiotherapy for pN2[29-32] (Figure 1). The indications for the surgical treatment of SCLC can be summarized as follows: (1) Intraoperative diagnosis of a pulmonary SCLC nodule. Between 3% and 5% of SCLCs present as a pulmonary nodule. Multidisciplinary treatment involving surgical resection, systematic nodal dissection, and adjuvant chemotherapy or chemoradiotherapy can achieve survival rates comparable to those seen in non-SCLC[8]; (2) Diagnosis of stage I or IIA SCLC. Local or regional recurrence[33-39] (tumor and/or hilar Mediastinal lymph nodes) is the most common form of disease in patients who relapse after complete remission with chemoradiotherapy[40-45]. Surgery as part of a multimodal approach achieves better local disease control[46-50] than chemoradiotherapy[51-54]; (3) Mixed histology (SCLC with a non-SCLC component). Between 2% and 28% of patients have mixed SCLC/non-SCLC[55-59]. Recurrence or failure to respond to first-line chemotherapy is likely to be due to the non-SCLC component; and (4) Salvage surgery for local chemo-resistant SCLC or exclusively local recurrence after response to chemoradiotherapy. Selected patients in this setting might benefit from surgical resection[60-62].

Lobectomy is the preferred procedure for surgical resection, as it is associated with significantly better survival than sublobar resection[40,45,49,54,63]. The significant discrepancies observed between clinical and pathologic stages (mainly due to undetected lymph node metastasis before surgery) highlight the importance of accurate clinical nodal staging and systematic lymph node dissection[47,64]. The recommendations for ruling out hilar and mediastinal lymph node involvement are very similar across the different guidelines. Ideally, clinical staging should be performed using semi-invasive
| Ref.              | Study type & time period. LoE | Inclusion criteria | Number of patients | Neoadjuvant/adjuvant treatments | PCI | Survival data |
|------------------|------------------------------|--------------------|--------------------|---------------------------------|-----|---------------|
| Jin et al[9], 2018 | RS; SEER 2004-2013; 3A       | cII               | n = 2129; S: 387; RT 1032; S + RT: 154; No S or RT: 356 | S + AC: 501; CRT: 501                 | -   | 5-yr OS 66%   |
| Yang et al[10], 2018 | RS; NCDB 2003-2011; Propensity score match S + AC vs CRT; 3A | cT1-2N0/M0        | S + AC: 501; CRT: 501                 | S + AC: 501 | -   | 5-yr OS 53% (pIA); 44% (cIA-III SCLC) |
| Ahmed et al[11], 2017 | RS; SEER 2007-2013; 3A       | Stage I SCLC     | π = 1902; S: 427; S + RT: 115             | -               | -   | 5-yr OS 54% (platinum) |
| Wakeam et al[12], 2017 | RS; NCDB 2004-2013; 3A          | cT1-2N0/M0        | π = 5079                  | -               | -   | MST: 50 mo (S); MST: 60 + mo (S + RT) |
| Wakeam et al[13], 2017 | RS; NCDB 2004-2013; Stage-specific propensity score match S vs NST; 3A | cT1-3N0-2 SCLC  | π = 2619                   | No AD treatment 24% NC or NR 4%; AC 27%; AR 1%; ACR 32%; NC or NR and AC or AR 2%; Other 10% | - | MST cl 38.6 vs 22.9 mo S vs NST; MST cl IIA vs NST; MST clIIA 21.7 vs 16.0 mo S vs NST |
| Combs et al[14], 2015 | RS; NCDB 1998-2011; 3A         | cT1-3N0-2 SCLC   | π = 2476; S 841 cIA, 168 cIB    | All: S: 68%              | -   | 5-yr OS 54% (cIA); 36% (cIB) |
| Ogawa et al[15], 2012 | RS; Institutional 1995-2008; 4 | cII-III, pl-III SCLC | π = 28 (23 SCLC before S); S 21 cl, 5 cII, 7 cII2 | NC 8; AC 19, ACR 2 | - | 5-yr OS 47% |
| Ju et al[16], 2012 | RS; Institutional 1990-2009; 4 | pl-III           | n = 34                    | NC 3; AC 1, AR 19, 10 CRT     | - | 5-yr OS 66% |
| Vallières et al[6], 2009 | RS; IASLC 1990-2000; 3A         | Resected SCLC   | n = 349 (68 pIA, 91 pIB)         | -               | -   | 5-yr OS 53% (pIA); 44% (pIB) |
| Lim et al[17], 2008 | RS; Institutional 1980-2007; 4 | cIIIB             | π = 59                    | AC 13; AR 2; ACR 1         | - | 5-yr OS for all patients 52%; No difference in 5-yr survival across; cT and cN categories; No difference in 5-yr survival across; cII to cIIIB stages |
| Wang et al[18], 2007 | RS; Institutional; 4           | pl-III           | n = 122                   | QT & CRT (not specified)     | - | MST 50 mo; 5-yr OS 66% |
| Veronesi et al[19], 2007 | RS; Institutional; 4 | pl-III           | n = 23                    | AC all                  | - | MST 24 mo |
| Tsuchiya et al[20], 2005 | Prospective phase II trial; 1991-1996; 2B | cIIIA             | π = 62                    | AC 42 (69%)            | - | MST not reached in pl; MST 449 d for pl; MST 712 d for pIIA; 3-yr OS 61%; 3-yr survival rate cII, cIIIB 68%, 56% and 13% respectively |
| Brock et al[21], 2005 | RS; Institutional 1976-2002; 4 | Resected SCLC   | π = 82 (24 stage I, S + AC) | AC 55%               | 23% | 5-yr OS: 86% (platinum AC); 42% (non-platinum AC) |
| Nakamura et al[22], 2004 | RS; Institutional; 4 | cIIIA SCLC        | n = 69                    | S 37, NC 32, AC 41, ACR 7   | - | 5-yr survival 48.9 % cl, 33.3 % cII, 20.2 % cIIIA, 0 % cIIIB |
| Badzio et al[23], 2004 | Comparative RS; Institutional 1984-1996; 4 | cIIII balanced in both, S and NST groups | n = 134                   | S 67 (all AC); NST 67 (all QT) | 34% only S group | MST 22 mo (S); MST 11 mo (NST); 5-yr OS S 27%; NST 4% |
| Lewinski et al[24], 2001 | RS; Institutional 1976-2002; 4 | cIIIA SCLC     | n = 75                    | NC all                  | If CR to NC | MST N0 + 125 mo; MST N2 14 mo; MST resected 18 mo; 5-yr OS resected 29% |
| Cataldo et al[25], 2000 | RS; Institutional 1982-1992; 4 | cIIIA SCLC       | n = 60                    | AC 88%; plAR (11%); plII AR (21%) | 41% | 5-yr survival rate 40% pl, 36% plII and 15% plIII |
### Table: Inoue et al. [26], 2000

- **RS; Institutional 1975-1994; 4**
- **Resected SCLC**
- **n = 91 (32 cIA, 30 cIB)**
- **All 78% 5.5%**
- **MST 53 mo, 5-yr OS 49% (cIA); MST 25 mo, 5-yr OS 47% (cIB)**

### Table: Kobayashi et al. [27], 2000

- **RS; Institutional 1982-1992; 4**
- **cl-III SCLC**
- **n = 59**
- **NC 71%**
- **5-yr survival rate 55% pl, 33% pII, 23% pIII**

### Table: Eberhardt et al. [28], 1999

- **Prospective phase II trial; Institutional 1991-1995; 2B**
- **cIB-cIIIB**
- **n = 46**
- **IB/IIA had NC + S; IIB/IIIA had NCR + S**
- **MST all patients 36 mo; MST R0 patients 68 mo; 5-yr survival rate all patients 46%; 5-yr survival rate R0 patients 63%**

### Abbreviations

- **ACR**: Adjuvant chemoradiotherapy
- **AD**: Adjuvant
- **AC**: Adjuvant chemotherapy
- **cIA**: Clinical stage IA
- **cIB**: Clinical stage IB
- **CR**: Complete response
- **CRT**: Chemoradiotherapy
- **IASLC**: International Association for the Study of Lung Cancer
- **ISC-LCSG**: The Lung Cancer Study Group of the International Society of Chemotherapy
- **LoE**: Level of evidence
- **MST**: Median survival time
- **NC**: Neoadjuvant chemotherapy
- **NST**: Non-surgical treatment
- **NCDB**: National Cancer Data Base
- **OS**: Overall survival
- **PCI**: Prophylactic cranial irradiation
- **pIA**: Pathologic stage IA
- **pIB**: Pathologic stage IB
- **pII**: Pathologic stage II
- **pIIIA**: Pathologic stage IIIA
- **pIIIB**: Pathologic stage IIIB
- **Q**: Chemotherapy
- **R0**: Complete resection
- **RS**: Retrospective study
- **RT**: Radiotherapy
- **S**: Surgery
- **SCLC**: Small cell lung cancer
- **SEER**: Surveillance, Epidemiology, and End Results database

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**Figure 1** Proposed algorithm for the treatment of early-stage small cell lung cancer focused on surgical treatment.

1. **Medically operable?**
   - **Yes**
     - Surgery
   - **No**
     - RT (Including SBRT) + CT

2. **Lobectomy + systematic nodal dissection (avoid pneumonectomy)**
   - **pN0**
   - **pN1**
   - **pN2**

3. **CT**
   - **RT ± CT**
   - **RT + CT**

**Consider PCI**

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**Radiotherapy in limited-stage SCLC**

Thoracic radiotherapy and stereotactic body radiotherapy in early-stage SCLC: SCLC is usually classified as limited-stage (LS) or extensive-stage (ES) disease. With adequate treatment, overall survival (OS) is 16-22 mo in patients with LS-SCLC and 8-13 mo in those with ES-SCLC. The corresponding 5-year survival rates are < 20% and < 2% [66]. Radiotherapy is associated with better OS when given in the first few weeks after the start of chemotherapy (ideally during cycle 1 and never later than cycle 3), and the shorter the duration the better [67].

Hypofractionated radiotherapy is well tolerated and produces similar response rates to standard fractionation. Proposed schedules include 40 Gy in 16 fractions with chemotherapy and prophylactic cranial irradiation (PCI) [68] and 55 Gy in 25 once-daily fractions, also with chemotherapy and PCI [69]. Higher complete response rates and longer OS have been observed for hyperfractionated vs hypofractionated radiotherapy (45 Gy in 30 fractions twice daily vs 42 Gy in 15 fractions twice daily), but the differences were not statistically significant [70].

Treatment must be individualized. Some clinical guidelines recommend surgery and adjuvant chemotherapy for stage I and IIA disease [30,71]. This combination has achieved OS rates of 50%-70% [20, 21,72,73]. Nonetheless, stereotactic body radiotherapy (SBRT) should be considered in patients who are unfit for or refuse surgery, as it is not inferior to conventional treatment and has an acceptable safety.
In non-SCLC, proton therapy has been used to reduce doses to the brain. In a study of 30 patients at the University of Pennsylvania, PBRT at a median dose of 63.9 cobalt Gy equivalents must be delivered to the isocenter of the tumor. Because SCLC is highly radiosensitive, some groups have suggested using a lower dose, particularly in patients with ultracentral tumors.

**PCI**

Patients with SCLC are at high risk of brain metastases (BM)

Patients with SCLC are at high risk of brain metastases (BM)[84,85]. Research into the potential of PCI began in the late 1970s[86]. Brain magnetic resonance imaging (MRI) should be performed after chemoradiotherapy or systemic therapy[87], as 21.8%-32.5% of patients who achieve complete response subsequently develop BM[88,89]. A meta-analysis published by Aupérin et al[90] in 1999 showed that PCI was associated with a reduced incidence of BM at 3 years (59% vs 33%) and a 5.4% increase in OS. Subsequent meta-analyses have shown similarly favorable results for PCI in patients who had responded to treatment[91-94]. Most of these studies, however, were published before the introduction of restaging with brain MRI, and therefore the true benefit of PCI in LS-SCLC is not so clear[95,96]. Nonetheless, retrospective studies have described beneficial effects for PCI in patients with a previous negative brain MRI scan[97,98]. Patients who have undergone complete resection should benefit from PCI, except patients with stage I disease, who have a low risk of BM[99-101]. There is a growing interest in the use of brain MRI and stereotactic irradiation rather than PCI in patients with LS-SCLC[102], but prospective randomized trials are needed.

**Concomitant treatment in locally advanced disease**

Radical treatment with chemotherapy and concomitant radiotherapy is recommended for patients with stage IB-IIIC disease in good general health[4,103]. Eighty percent of patients with mediastinal involvement treated exclusively with chemotherapy experience local recurrence[104], but the addition of radiotherapy lowers this rate and increases survival[104,105]. The CONVERT trial, which compared fractionated and unfractionated radiotherapy in patients treated with cisplatin-etoposide, reported an overall response rate (ORR) of 70%-90%, an OS of 24-30 mo, and a 5-year OS rate of 25%-30%[106]. Another two trials investigated the combination of bevacinumab, an angiogenic, with conventional chemoradiotherapy, but had to be discontinued because of a relatively high incidence of severe adverse events (tracheoesophageal fistulae)[107].

**Perspectives for radiotherapy in LS-SCLC**

Radiotherapy with immunotherapy in LS-SCLC: Three trials are currently analyzing the combined use of radiotherapy and immunotherapy in LS-SCLC: The NRG Oncology and Alliance trial (ClinicalTrials.gov Identifier: NCT03811002) investigating chemoradiotherapy with and without atezolizumab; the phase II STIMULI trial (NCT02046733) analyzing nivolumab and ipilimumab after chemoradiotherapy and PCI; and the phase III ADRIATIC trial (NCT03703297) comparing durvalumab, durvalumab plus tremelimumab, and placebo in patients without progression after chemoradiotherapy.

**Hippocampal avoidance to reduce the neurotoxicity of PCI**

The role of PCI with hippocampal avoidance (HA) in patients with LS- or ES-SCLC without BM is being investigated in three phase III trials: The Dutch NKI/AVL trial (NCT01780675), the NRG Oncology CC003 trial (NCT02635009), and the Spanish PREMER-TRIAL (NCT02397733)[108]. The Dutch group found no significant differences in recall assessed using the revised version of the Hopkins Verbal Learning Test between patients who received PCI and those who received HA-PCI[109]. Using the Free and Cued Selecting Reminding Test, the Spanish group found a significant decline in 3-mo delayed recall [22.22% vs 5.08%; odds ratio (OR) = 5.33; 95% confidence interval (CI): 1.44-19.65; P = 0.006] and total recall (20.63% vs 6.78%; OR = 3.57; 95% CI: 1.09-11.68; P = 0.02] in the PCI vs HA-PCI group[110]. Another potentially interesting line of research is the use of Alzheimer disease drugs to preserve cognition in patients treated with PCI[111].

**Proton beam radiation therapy**

In non-SCLC, proton therapy has been used to reduce doses to the heart while maintaining high doses to the tumor[112]. Proton beam radiation therapy (PBRT) is potentially beneficial in SCLC, as patients tend to have bulky central disease at diagnosis. In a study of 30 patients at the University of Pennsylvania, PBRT at a median dose of 63.9 cobalt Gy equivalents achieved a promising median OS of 28.2 mo with low toxicity[113]. These results need to be validated in

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**References**

1. **American Society for Radiation Oncology (ASTRO)**. ASTRO’s Radiation Therapy Quality Standards Task Force: A review of the evidence for the development of mediastinal staging standards for small cell lung cancer (SCLC). J Thorac Oncol. 2019;14:1273-1282.
2. **European Organisation for Research and Treatment of Cancer (EORTC)**. EORTC Lung Breast Cancer Cooperative Group. A new staging system for small cell lung cancer. Eur J Cancer. 1997;33:1597-1602.
3. **National Comprehensive Cancer Network (NCCN)**. Small cell lung cancer. NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2020;18:226-244.
4. **International Collaboration on Lung Cancer (INCLC)**. The international collaboration on lung cancer staging: recent results and future developments. J Thorac Oncol. 2013;8:1028-1035.
5. **National Comprehensive Cancer Network (NCCN)**. Lung cancer. NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2020;18:1-61.
**Table 2 Thoracic radiotherapy and stereotactic body radiotherapy in early-stage small cell lung cancer**

| Ref. | Sample size | Fractionation | QT | Prophylactic cranial irradiation | Local control | Overall survival | Disease-free survival |
|------|-------------|---------------|----|---------------------------------|---------------|-----------------|----------------------|
| Videtic et al.[76], 2013 | n = 6 | 60 Gy (3 fx); 50 Gy (5 fx); 30 Gy (1 fx) | 4/6 | 4/6 | 100% (1 yr) | 63% (1 yr) | 75% (1 yr) |
| Shiyoama et al [77], 2015 | n = 64 | 48 Gy (4 fx) | 36/64 | 10/64 | 89% (2 yr) | 76% (2 yr) |
| Stahl et al.[79], 2017 | n = 285 | 48-60 Gy (3-5 fx) | 130/285 | 35% (3 yr) | 21.5% (5 yr) |
| Verma et al[75], 2017 | n = 74 | 50 Gy (5 fx) | 45/74 | 17/74 | 96% (3 yr) |
| Shiyoama et al [78], 2018 | n = 43 | 36-60 Gy (3-10 fx) | 8/43 | 8/43 | 80.2% (2 yr) | 72.3% (2 yr) | 44.6% (2 yr) |
| Verma et al[74], 2019 | n = 149 | 45-60 Gy (3-8 fx) | 149/149 | 83.8% (29.2 mo) |
| Newman et al [81], 2019 | n = 239 | BED > 100 Gy (max 8 fx) | 84/239 | 27% (5 yr); 36% (5 yr, with QT) |
| Singh et al[80], 2019 | n = 21 | BED 105.6 Gy (3-5 fx) | 4/21 | 100% (1, 2, 3 yr) | 73.1% (1 yr); 36.6% (2 yr) | 85.7% (1 yr); 42.9% (2 yr) |

BED: Biologically equivalent dose; fx: Fraction; QT: Chemotherapy.

further studies.

**ES SCLC**

**Initial management**

Chemotherapy with platinum compounds and etoposide has been the standard treatment for ES-SCLC for many decades. The COCIS meta-analysis showed that cisplatin- and carboplatin-based chemotherapy produced comparable results in terms of OS (9.6 vs 9.4 mo), progression free survival (PFS) (5.5 vs 5.3 mo), and ORR (67% vs 66% mo)[114]. Other strategies attempted, including maintenance treatments and combinations with antiangiogenics, have produced disappointing results[115-117]. The recently published results of the IMpower 133[118] and CASPIAN[119] trials comparing combinations of chemotherapy and immunotherapy followed by immunotherapy with standard platinum and etoposide chemotherapy in ES-SCLC have shown that the combined use of chemotherapy and immunotherapy prolongs OS.

IMPower133 is a phase III trial in which patients received four cycles of carboplatin and etoposide and either atezolizumab or placebo followed by maintenance atezolizumab[118]. The response rates in both arms were similar, but patients in the atezolizumab arm survived for a median of 2.3 mo longer [hazard ratio (HR) = 0.7; 95%CI: 0.54-0.91; P = 0.007]. The updated trial data presented at the 2019 European Society for Medical Oncology congress showed an increase in OS at both 12 mo (39% to 51.9%) and 18 mo (21% to 34%)[120,121].

The phase III CASPIAN trial has three treatment arms. Treatment with durvalumab plus chemotherapy (4-6 cycles of cisplatin or carboplatin plus etoposide) followed by durvalumab maintenance achieved an OS of 12.9 mo (vs 10.5 mo for standard chemotherapy) (HR = 0.75; 95%CI: 0.62-0.9; P = 0.0032), a 2-year PFS of 11% (vs 2.9%), and a 2-year response rate of 13.5% (vs 3.9%)[119,122]. In the third arm, tremelimumab plus durvalumab vs chemotherapy showed no benefit in antitumor activity and was associated with increased toxicity[123].

Results from other studies evaluating combinations of anti-programmed death 1 (PD-1) antibodies have been disappointing. While the combined use of pembrolizumab and chemotherapy increased PFS, it did not provide any significant improvements in OS[124]. In the phase II ECOG-ACRIN EAS161 trial, chemotherapy plus nivolumab followed by maintenance treatment achieved a non-significant improvement in PFS (3.5 vs 4.7 mo) and OS (11.3 vs 8.5 mo)[125] (Table 3). A systematic review and two meta-analyses published in 2020 concluded that a combination of chemotherapy with atezolizumab or durvalumab was the best first-line treatment for ES-SCLC[126,127]. Other options that have been explored include combinations of ipilimumab and chemotherapy (no benefit and greater toxicity)[128,129] and combinations of different chemotherapy agents, such as irinotecan plus etoposide and cisplatin plus irinotecan (also without benefits)[130-132].
### Table 3 Combined first-line immunotherapy options for extensive-stage small cell lung cancer

| Study   | n   | Design                  | Treatment                                      | RR            | PFS            | OS             |
|---------|-----|-------------------------|-----------------------------------------------|---------------|----------------|----------------|
| NCT01450761 | 1132 | Phase III; Randomized, double-blind; Drug: Imitumumab | Arm A: PE × 4C + ipilimumab × 4C; Control: PE × 4C + placebo × 4C | PR 62% vs 62%; SD 26% vs 27%; PD 6% vs 9% | 4.6 vs 4.4 mo; HR = 0.85, P = 0.0161 | 11.0 vs 10.9 mo; HR = 0.94, P = 0.3775 |
| Impower 133 | 403  | Phase III; Randomized, double-blind; Drug: Atezolizumab  | Arm A: PE + atezolizumab × 4C/atezolizumab; Control: PE + placebo × 4C/placebo | 60% vs 64% | 5.2 vs 4.3 mo; HR = 0.77, P = 0.02 | 12.3 vs 10.3 mo; HR = 0.70, P = 0.007 |
| CASPIAN | 805  | Phase III; Randomized, open-label; Drug: Durvalumab  | Arm B (n = 268): Durvalumab + PE × 4C/durvalumab; Control: PE × 4C | 68% vs 58% | 5.1 vs 5.4 mo; HR = 0.78, not tested | 13.0 vs 10.3 mo; HR = 0.73, P = 0.0047 |
| CASPIAN | 805  | Phase III; Randomized, open-label; Drug: Durvalumab + tremelimumab  | Arm A (n = 268): Durvalumab + tremelimumab + PE × 4C/durvalumab + tremelimumab; Control: PE × 4C | 58% both arms | 4.9 vs 5.4 mo; HR = 0.84 | 10.4 vs 10.5 mo; HR = 0.82, P = 0.045 |
| KEYNOTE 604 | 453  | Phase III; Randomized, double-blind; Drug: Pembrolizumab  | Arm A: Pembrolizumab + PE; Control: PE + placebo | 71% vs 62% | 4.5 vs 4.3 mo; HR = 0.75, P = 0.0023 | 10.8 vs 9.7 mo; HR = 0.80, P = 0.0164 |
| ECOG-ACRIN | 160  | Phase I; Randomized, open-label; Drug: Nivolumab  | Arm A: PE + nivolumab × 4C/nivolumab; Control: PE × 4C | 52.29% vs 47.71% | 5.5 vs 4.6 mo; HR = 0.65, P = 0.012 | 11.3 vs 8.5 mo; HR = 0.67, P = 0.038 |

4C: 4 cycles; OS: Overall survival; PD: Progressive disease; PE: Platinum and etoposide; PFS: Progression free survival; PR: Partial response; RR: Response rate; SD: Stable disease.

### PCI in ES-SCLC

The results of the first randomized trial to demonstrate a reduction in the risk of symptomatic BM (14.6% vs 40.4% at 1 year) and an improvement in OS (27.1% vs 13.3%) in chemotherapy responders who underwent PCI were published in 2007[133]. The results are supported by data from several meta-analyses[134-136], although as a shortcoming of the trial, pre-PCI brain imaging was not performed[133]. The results of a randomized trial conducted in Japan comparing PCI with close MRI follow-up in patients with ES-SCLC who had responded to chemotherapy and had a negative brain MRI were published in 2017. While they did not show an increase in OS (11.6 mo for PCI vs 13.7 mo for MRI follow-up; HR = 1.27, 95%CI: 0.96-1.68; P = 0.094), they did show a significant decrease in the incidence of BM[137].

A recent meta-analysis showed that PCI was only associated with prolonged OS in studies where brain imaging was not performed between chemotherapy and irradiation (HR = 0.70; 95%CI: 0.57-0.85). In other words, PCI did not offer any significant benefits when preceded by MRI or CT to test for BM (HR = 0.94; 95%CI: 0.74-1.18)[138]. Considering the above results and the neurotoxic effects of PCI[139], it would seem reasonable to consider periodic MRI examination as an alternative to PCI in patients with ES-SCLC. In such cases, a joint evaluation should be made by the medical and radiation oncologists[30]. The recommended dose for PCI is 25 Gy in 10 fractions, as higher doses do not appear to reduce the incidence of BM at 2 years and are associated with higher mortality and chronic neurotoxicity[140].

### Treatment of refractory and relapsed SCLC

Relapsed SCLC tends to be resistant to treatment and is associated with an OS of 4-5 mo. Response to second-line treatment varies according to PFS and is 10% in patients with a PFS < 3 mo (refractory SCLC) and 25% in those with a PFS of 3-6 mo (sensitive SCLC)[141-143].

**Relapse after PFS > 3 mo:** Rechallenge treatment with combinations of platinum-based chemotherapy has been investigated in patients with sensitive SCLC. Patients treated with carboplatin and etoposide had a longer PFS than those treated with topotecan, and the greatest benefits were observed for those who relapsed after 6 mo[144,145].

**Relapse after PFS of < 3 mo:** Until recently, topotecan was the only drug authorized by the US and Food and Drug Administration (FDA) to treat relapsed SCLC. In the 2006 phase III trial that led to its approval, it significantly improved survival compared with best supportive care only[146]. Another phase III trial comparing topotecan and CAV (cyclophosphamide, doxorubicin, and vincristine) reported similar survival and response rates for the two treatments, but found topotecan to be associated with better symptom control and lower toxicity[147]. An additional study evaluating topotecan plus afibercept, an antiangiogenic, reported an OS of 5 mo[148].

One recent advance in this setting is the recent approval by the FDA of lurbinectedin as a second-line treatment for SCLC. In a study of patients with SCLC without BM, lurbinectedin achieved an ORR of 35%, and a median response duration of 5.1 mo (> 6 mo in 25% of patients)[149]. The combination of
lurbinectedin and doxorubicin was investigated in two cohorts in a phase I trial and showed disease control rates of 81% and 70% and a median response duration of 4.5 and 5.2 mo.[150] These findings led to the design of the phase III ATLANTIS trial comparing lurbinectedin plus doxorubicin with topotecan and with CAV; a press release, however, announced no improvement in OS.[151] (Figure 2).

Amrubicin is available for the treatment of relapsed SCLC in Japan, but it has not been approved by the FDA. A phase III trial comparing amrubicin with topotecan showed superior symptom control for topotecan but no significant differences in OS.[152] Immune checkpoint inhibitors have also been tested. The CheckMate 032 trial comparing nivolumab alone with nivolumab plus ipilimumab in recurrent SCLC reported improved ORR and OS in both treatment arms regardless of prior treatment or PD-L1 expression.[153,154] With these data, the FDA approved nivolumab for use in previously treated patients.

The phase III CheckMate 331 trial showed similar OS for nivolumab vs standard chemotherapy in the second-line treatment of SCLC.[155] Pembrolizumab has also been tested in SCLC. A pooled analysis of the KEYNOTE-028 (phase Ib)[156] and KEYNOTE-158 (II)[157,158] trials found an ORR of 19.3%, leading to FDA approval. Atezolizumab was also tested in a phase II trial, but the primary endpoint was not met.[159] Paclitaxel every 3 wk for 6 cycles plus pembrolizumab after the second cycle until disease progression achieved a disease control rate of 80% and a median OS of 9.2 mo.[160] Other drugs tested in the setting of relapsed SCLC are temozolomide[161,162], irinotecan[163], paclitaxel[164,165], docetaxel[166], gemcitabine[167,168], and vinorelbine[169]. Finally, a recent phase Ib study showed that belatinectin was associated with better OS and disease control than topotecan in patients with sensitive SCLC.[170]

**Recent advances in systemic therapy**

New drugs linked to targets with a role in cell proliferation have been developed. These include poly (ADP-ribose) polymerase (PARP) inhibitors, delta-like ligand 3 inhibitors (DLL3), and drugs that selectively inhibit oncogenic transcription. The expression of DNA damage response proteins [especially PARP1/checkpoint kinase 1 (CHK1)] is elevated in SCLC, and *in vitro* studies have shown an antitumor effect for PARP inhibitors.[171] Monotherapy with PARP inhibitors has also been investigated in different clinical trials, but the results have been disappointing. In an early study, talazoparib showed an ORR of 8.7%.[172] No benefit was observed for maintenance treatment with olaparib after first-line chemotherapy with cisplatin and etoposide[173] or for the addition of veliparib vs placebo to first-line cisplatin and etoposide, with findings showing no significant differences in PFS (6.1 vs 5.5 mo) or OS (10.3 vs 8.9 mo).[174,175]

Discordant results have been reported for combinations of chemotherapy and PARP inhibitors in successive treatment lines. No significant differences were found for PFS or OS in a study comparing temozolomide plus veliparib vs temozolomide only.[176] Temozolomide combined with olaparib, however, was associated with a response rate of 41.7%, a PFS of 4.2 mo, and an OS of 8.5 mo in a phase I/II clinical trial.[177] No benefits have been observed for the combined use of PARP inhibitors and immunotherapy (durvalumab with olaparib, among others).[178] Future actions targeting this actionable molecular pathway in SCLC will probably involve combinations of PARP inhibitors and chemotherapy agents and immunotherapy, or new molecules. Promising results have been reported for CHK1 (SRA737) combined with low-dose gemcitabine and anti-PD-1/-programmed death ligand 1 (PD-L1) immune checkpoint inhibitors[179] and for PARP inhibitors combined with WEE1 inhibitors, which act at the cell-cycle level.[180]

Other treatments have also yielded positive results. Lurbinectedin, a selective oncogenic transcription inhibitor, was recently evaluated in combination with irinotecan in pretreated patients in a phase Ib/II basket trial. The results for the SCLC cohort showed an ORR of 62%, a clinical benefit rate of 81%, a disease control rate of 90%, and a PFS of 6.1 mo.[181] Other new molecules with different ligands under investigation include DLL3 inhibitors, such as rovalpituzumab-tesirine. This is a promising drug in pretreated patients expressing DLL3, although recent reports have described greater toxicity and little benefit compared with topotecan.[182-184] AMG 757, a half-life extended DLL3 bispecific T-cell engager, has also shown promising results in pretreated patients in an ongoing phase I trial, with an ORR of 14%, a disease control rate of 37%, and a very promising median duration of 6.2 mo.[185]

**Perspectives for radiotherapy in ES-SCLC**

Numerous questions remain to be answered regarding the role of radiotherapy in ES-SCLC.

**Consolidation radiotherapy in extensive SCLC**: What is the optimal radiation dose or indication for patients with complete thoracic response or partial distant response? The Chinese phase III trial (NCT02675088) is comparing 45 Gy at 3 Gy/d in 15 fractions vs 10 fractions (CREST trial schedule) with a primary endpoint of OS at 2 years[186]. How can radiotherapy be best combined with immunotherapy? The RAPTOR phase II/III trial (NCT04402788) is evaluating the use of radiotherapy to the chest and distant lesions after 4-6 cycles of carboplatin and etoposide plus atezolizumab.

**Stereotactic radiosurgery to treat BM**: Stereotactic radiosurgery has not traditionally been investigated in SCLC due to the high incidence of BM and poor prognosis. Nonetheless, there is growing evidence
Figure 2 Proposed algorithm for the treatment of relapsed small cell lung cancer.

that it may be appropriate\cite{187}. ENCEPHALON, a phase II trial (NCT03297788) is currently comparing stereotactic radiosurgery with whole-brain radiotherapy in patients with SCLC and 1-10 BM.

CONCLUSION

The treatment of SCLC will continue to be a challenge. Immunotherapy has a new role lung cancer and will be the future treatment standard alone or in combination, as well as the new radiotherapy techniques. As has been occurred in non-SCLC, the future of treatments in both early and advanced stages is through immunotherapy and targeted treatments. Furthermore, the use of different combinations of chemoimmunotherapy in recent months has improved the prognosis of patients with advanced SCLC. Nevertheless, continued research efforts are needed. Different lines of investigation are open and we hope that their findings will continue to improve prognosis and quality of life in this setting.

FOOTNOTES

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REFERENCES

1 National Cancer Institute. SEER Cancer Statistics Review, 1975-2017. [cited 20 January 2021]. Available from: https://seer.cancer.gov/archive/csr/1975_2017/

2 Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, Spitznagel EL, Piccirillo J. 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: 4539-4544 [PMID: 17086962 DOI: 10.1200/JCO.2005.04.4859]

3 Pesch B, Kendzia B, Gustavsson P, Jöckel KH, Johnen G, Pohblahan H, Olsson A, Ahrens W, Gross IM, Briske I, Wichmann HE, Merletti F, Richardi L, Simonato L, Fortes C, Siemiatyckyj J, Parent ME, Consonni D, Landi MT, Caporaso N, Zaridze D, Cassidy A, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Stücker I, Fabianova E, Dimitru RS, Bencko V, Foretova L, Janout V, Rudin CM, Brennan P, Boffetta P, Straif K, Brüning T. Cigarette smoking and lung cancer--relative risk estimates for the major histologic types from a pooled analysis of case-control studies. Int J Cancer 2012; 131: 1210-1219 [DOI: 10.1002/ijc.225329]

4 Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of small cell lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143: e400S-e419S [PMID: 23649448 DOI: 10.1378/chest.12-2363]

5 Dettorebeck FC. The eighth edition TNM stage classification for lung cancer: What does it mean on main street? J Thorac Cardiovasc Surg 2018; 155: 356-359 [PMID: 29061464 DOI: 10.1016/j.jtcs.2017.08.138]

6 Vallières E, Shepherd FA, Crowley J, Van Houtte P, Postmus PE, Carney D, Chansky K, Shaikh Z, Goldstraw P. International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 2009; 4: 1049-1059 [PMID: 19652623 DOI: 10.1097/JTO.0b013e3181b27799]

7 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Mary Kay Washington, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Bales CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR. TNM classification of malignant tumours / Description: Eighth edition. | Oxford, United Kingdom; Hoboken, NJ: John Wiley & Sons, Inc., 2017

8 Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer AM, DeCamp MM. Lobectomy leads to optimal survival in early-stage small cell lung cancer: a retrospective analysis. J Thorac Cardiovasc Surg 2011; 142: 538-546 [PMID: 21684554 DOI: 10.1016/j.jtcs.2010.11.062]

9 Jin K, Zhang K, Zhou F, Dai J, Zhang P, Jiang G. Selection of candidates for surgery as local therapy among early-stage small cell lung cancer patients: a population-based analysis. Cancer Commun (Lond) 2018; 38: 5 [PMID: 29764484 DOI: 10.1186/s40880-018-0272-5]

10 Yang CJ, Chan DY, Shah SA, Yerokun BA, Wang XF, D'Amico TA, Berry MF, Harpole DH Jr. Long-term Survival After Surgery Compared With Concurrent Chemoradiation for Node-negative Small Cell Lung Cancer. Ann Surg 2018; 268: 1105-1112 [PMID: 28475559 DOI: 10.1097/SLA.0000000000002287]

11 Ahmed Z, Kujtan L, Kennedy KF, Davis JR, Subramanian J. Disparities in the Management of Patients With Stage I Small Cell Lung Carcinoma (SCLC): A Surveillance, Epidemiology and End Results (SEER) Analysis. Clin Lung Cancer 2017; 18: e315-e325 [PMID: 28438510 DOI: 10.1016/j.cllc.2017.03.003]

12 Wakeam E, Byrne JP, Darling GE, Varghese TK Jr. Surgical Treatment for Early Small Cell Lung Cancer: Variability in Practice and Impact on Survival. Ann Thorac Surg 2017; 104: 1872-1880 [PMID: 29106866 DOI: 10.1016/j.athoracsur.2017.07.009]

13 Wakeam E, Acuna SA, Leigh NB, Giuliani ME, Finlayson SRG, Varghese TK, Darling GE. 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 [PMID: 28577955 DOI: 10.1016/j.lungcan.2017.04.021]

14 Combs SE, Hancock JG, Boffa DJ, Decker RH, Dettorrebeck FC, Kim AW. Bolstering the case for lobectomy in stages I, II, and IIIA small-cell lung cancer using the National Cancer Data Base. J Thorac Oncol 2015; 10: 316-323 [PMID: 25319182 DOI: 10.1016/j.jto.2015.04.020]

15 Ogawa S, Horio Y, Yatabe Y, Fukui T, Ito S, Hasegawa Y, Mitsudomi T, Hida T. Patterns of recurrence and outcome in patients with surgically resected small cell lung cancer. Int J Clin Oncol 2012; 17: 218-224 [PMID: 22173603 DOI: 10.1007/s10147-011-0777-4]

16 Ju MH, Kim HR, Kim JB, Kim YH, Kim DK, Park SI. Surgical outcomes in small cell lung cancer. Korean J Thorac Cardiovasc Surg 2012; 45: 40-44 [PMID: 22363907 DOI: 10.5090/kjtcs.2012.45.1.40]

17 Lim E, Belcher E, Yap YK, Nicholson AG, Goldstraw P. The role of surgery in the treatment of limited disease small cell
lungs cancer: time to reevaluate. J Thorac Oncol 2008; 3: 1267-1271 [PMID: 18978561 DOI: 10.1097/JTO.0b013e318198a86f]

Wang HJ, Sun KL, Zhang XR, Sun Y, Shi YK. [Combined modality therapy for small cell lung cancer patient with limited stage disease]. Zhonghua Zhong Liu Za Zhi 2007; 29: 701-703 [PMID: 18246803]

Veronesi G, Scapani A, Lطلاق P, Lòscio F, Galano G, Gandini S, De Braud F, Spaggiari L. Adjuvant surgery after carboplatin and VP16 in resectable small cell lung cancer. J Thorac Oncol 2007; 2: 131-134 [PMID: 17410028]

Wolter M, Suzuki K, Ichinose Y, Watanabe Y, Yasumitsu T, Ichikawa N, Kato H. Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: the Japan Clinical Oncology Lung Cancer Study Group Trial (JOCOG9101). J Thorac Cardiovasc Surg 2005; 129: 977-983 [PMID: 15867769 DOI: 10.1016/j.jtcvs.2004.05.030]

Brock MV, Hooker CM, Syphard JE, Westra W, Xu L, Alberge AJ, Mason D, Baylin SB, Herman JG, Yung RC, Brahmer J, Rudin CM, Ettinger DS, Yang SC. Surgical resection of limited disease small cell lung cancer in the new era of platinum chemotherapy: Its time has come. J Thorac Oncol 2005; 129: 64-72 [PMID: 15632826 DOI: 10.1016/j.jto.2004.08.022]

Nakamura H, Kato Y, Kato H. Outcome of surgery for small cell lung cancer − response to induction chemotherapy predicts survival. Thorac Cardiovasc Surg 2004; 52: 206-210 [PMID: 15293157 DOI: 10.1055/s-2004-821075]

Badzio A, Kurowski K, Karnicka-Mlodkowska H, Jaszem J. A retrospective comparative study of surgery followed by chemotherapy vs. non-surgical management in limited-disease small cell lung cancer. Eur J Cardiothorac Surg 2004; 26: 183-188 [PMID: 15200999 DOI: 10.1016/j.ejcts.2004.04.012]

Leśniński T, Zaluski M, Turski C, Pietraszek A. Small cell lung cancer I–III A: cytotherapy chemotherapy followed by resection with continuation of chemotherapy. Eur J Cardiothorac Surg 2001; 20: 391-398 [PMID: 11463565 DOI: 10.1016/s1010-7940(01)00767-4]

Cataldo I, Bidoli P, Brega Massone PP, Conti B, Lepaguge C. Long term survival for resectable small cell lung cancer. Lung Cancer (Amsterdam, Netherlands) 2000; 29: 130 [DOI: 10.1016/s0169-5002(00)00842-9]

Ione M, Miyoshi S, Yasumitsu T, Mori T, Iuchi K, Maeda H, Matsuda H. Surgical results for small cell lung cancer based on the new TNM staging system. Thoracic Surgery Study Group of Osaka University, Osaka, Japan. Ann Thorac Surg 2000; 70: 1615-1619 [PMID: 11093496 DOI: 10.1016/s0003-4975(00)01401-6]

Kobayashi S, Okada S, Hasumi T, Sato N, Fujimura S. The significance of surgery for bulky N2 small-cell lung cancer: a clinical and in vitro analysis of long-term survivors. Surg Today 2000; 30: 978-986 [PMID: 11113091 DOI: 10.1007/s005950070117]

Eberhardt W, Stamatis G, Stuschke M, Wilke H, Müller MR, Kolks S, Flaschow M, Schütte J, Stahl M, Schlenker L, Budach V, Greschuchna D, Stüben G, Teschler H, Sack H, Seeger S. Prognostically orientated multimodality treatment including surgery for selected patients of small-cell lung cancer patients stages IB to IIIB: long-term results of a phase II trial. Br J Cancer 1999; 81: 1206-1212 [PMID: 10584883 DOI: 10.1007/sj.69608830]

Ganti AKP, Loo BW, Bassetti M, Blakely C, Chiang A, D’Amico TA, D’Avella C, Dowlati A, Downey RJ, Edelman M, Florsheim C, Gold KA, Goldman JW, Greulich JC, Hanc C, Iams W, Iyengar P, Kelly K, Khalil M, Koczysaw M, Merritt RE, Mohindra N, Molina J, Moran C, Pokharel S, Puris S, Qin A, Rushthoven C, Sands J, Santana-Davila R, Shahfique M, Waqar SN, Gregory KM, Hughes M. Small Cell Lung Cancer. Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021; 19: 1441-1464 [PMID: 34902832 DOI: 10.6004/jnccn.2021.0055]

Simone CB 2nd, Bógart JA, Cabrera AR, Daly ME, DeNunzio NJ, Detterbeck F, Faire-Flint C, Gatzchet N, Gore E, Jabbour SK, Kruser TJ, Schneider BJ, Slotman B, Turrisi A, Wu AJ, Zeng J, Rosenzweig KE. Radiation Therapy for Small Cell Lung Cancer: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2020; 10: 158-173 [PMID: 32222430 DOI: 10.1016/j.prro.2020.02.009]

Rudin CM, Giaccone G, Ismaila N. Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline. J Oncol Pract 2012; 8: 83-86 [PMID: 29424581 DOI: 10.1200/JOP.2015.008201]

Früh M, De Ruysscher D, Popat S, Crino L, Peters S, Felip E; ESMO Guidelines Working Group. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 Suppl 6: v99-v105 [PMID: 23813929 DOI: 10.1093/annonc/mdt178]

Shepherd FA, Ginsberg RJ, Feld R, Evans WK, Johansen E. Surgical treatment for limited small-cell lung cancer. The University of Toronto Lung Oncology Group experience. J Thorac Cardiovasc Surg 1991; 101: 385-393 [PMID: 1847981]

Rea F, Callegaro D, Favaretto A, Loy M, Paccagnella A, Fantoni U, Festi G, Sartori F. Long term results of surgery and chemotherapy in small cell lung cancer. Eur J Cardiothorac Surg 1998; 14: 398-402 [PMID: 9845145 DOI: 10.1016/s1010-7940(98)80203-6]

Stich BJ, Hallemeier CL, Olivier KR, Harmsen WS, Allen MS, Ganes YI. Long-Term Outcomes and Patterns of Failure After Surgical Resection of Small-Cell Lung Cancer. Clin Lung Cancer 2015; 16: e67-e73 [PMID: 25823413 DOI: 10.1016/j.clc.2015.02.004]

Xu L, Zhang G, Song S, Zheng Z. Surgery for small cell lung cancer: A Surveillance, Epidemiology, and End Results (SEER) Survey from 2010 to 2015. Medicine (Baltimore) 2019; 98: e17214 [PMID: 31577711 DOI: 10.1097/md.0000000000017214]

Lüchtenborg M, Riaz SP, Lim E, Page R, Baldwin DR, Jakobsen E, Vedsted P, Lind M, Peake MD, Mellemgaard A, Spicer J, Lang-Lazdunski L, Möller H. Survival of patients with small cell lung cancer undergoing lung resection in England, 1998-2009. Thorax 2014; 69: 269-273 [PMID: 24172710 DOI: 10.1136/thoraxjnsj-2013-203844]

Takei H, Kondo H, Miyakoa E, Asamura H, Yoshino I, Date H, Okumura M, Tada H, Fujii Y, Nakanishi Y, Eguchi K, Dosaka-Akita H, Kobayashi H, Sawabata N, Yokoi K; Japanese Joint Committee of Lung Cancer Registry, Surgery for small cell lung cancer: a retrospective analysis of 243 patients from Japanese Lung Cancer Registry in 2004. J Thorac Oncol 2014; 9: 1140-1145 [PMID: 25157766 DOI: 10.1097/JTO.0000000000000226]

Weksler B, Nason KS, Shende M, Landreneau RJ, Pennathur A. Surgical resection should be considered for stage I and II
small cell carcinoma of the lung. *Ann Thorac Surg* 2012; 94: 889-893 [PMID: 22429675 DOI: 10.1016/j.athoracsur.2012.01.015]

40 Yu JB, Decker RH, Detterbeck FC, Wilson LD. Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. *J Thorac Oncol* 2010; 5: 215-219 [PMID: 20101146 DOI: 10.1097/JTO.0b013e3181cd2025]

41 Liu T, Chen Z, Dang J, Li G. The role of surgery in stage I to III small cell lung cancer: A systematic review and meta-analysis. *PLoS One* 2018; 13: e0210001 [PMID: 30596754 DOI: 10.1371/journal.pone.0210001]

42 Hou SZ, Cheng ZM, Wu YB, Sun Y, Liu B, Yuan MX, Wang XD. Evaluation of short-term and long-term efficacy of surgical and non-surgical treatment in patients with early-stage small cell lung cancer: A comparative study. *Cancer Biomark* 2017; 19: 249-256 [PMID: 28453459 DOI: 10.3233/CBM-160332]

43 Lucchi M, Mussi A, Chella A, Janni A, Ribechini A, Menconi GF, Angeletti CA. Surgery in the management of small cell lung cancer. *Eur J Cardiothorac Surg* 1997; 12: 689-693 [PMID: 9458136 DOI: 10.1016/s0169-5002(01)00187-1]

44 Engelhardt KE, Coughlin JM, DeCamp MM, Denlinger CE, Meyerson SL, Bharat A, Odell DD. Survival after adjuvant radiation therapy in localized small cell lung cancer treated with complete resection. *J Thorac Cardiovasc Surg* 2019; 158: 1665-1677.e2 [PMID: 31627955 DOI: 10.1016/j.jtcvs.2019.08.031]

45 Iwata T, Nishiyama N, Nagano K, Isumi N, Mizuguchi S, Tsuikitoh M, Torita M, Omori R, Chung K, Hanada S, Inoue K. Role of pulmonary resection in the diagnosis and treatment of limited-stage small cell lung cancer: revision of clinical diagnosis based on findings of resected specimen and its influence on survival. *Gen Thorac Cardiovasc Surg* 2012; 60: 43-52 [PMID: 22237738 DOI: 10.1007/s11748-011-0847-4]

46 Schneider BJ, Saxena A, Downey RJ. Surgery for early-stage small cell lung cancer. *J Natl Compr Canc Netw* 2011; 9: 1132-1139 [PMID: 21975913 DOI: 10.1080/jnccn.2011.0994]

47 Thomas CR Jr, Giroux DJ, Janaki LM, Turrisi AT 3rd, Crowley JJ, Taylor SA, McCracken JD, Shankir Giri PG, Gordon Jr, Livingston RB, Gandara DR. Ten-year follow-up of Southwest Oncology Group S829: a phase II trial of concomitant cisplatin-etoposide and daily thoracic radiotherapy in localized small-cell lung cancer. *Lung Cancer* 2001; 33: 213-219 [PMID: 1169-5002 DOI: 10.1016/s0169-5002(01)00181-7]

48 Takenaka T, Takenoya M, Inamasu E, Yoshida T, Toyokawa G, Nosaki K, Hiroi F, Yamaguchi M, Shimokawa M, Seto T, Ichinose Y. Role of surgical resection for patients with limited disease-small cell lung cancer. *Lung Cancer* 2015; 88: 52-56 [PMID: 25662387 DOI: 10.1016/j.lungcan.2015.01.010]

49 Schreiber D, Rinner J, Weedon J, Vogtampa D, Wortham A, Kim A, Han P, Choi K, Rotman M. Survival outcomes with the use of surgery in limited-stage small cell lung cancer: should its role be re-evaluated? *Cancer* 2011; 116: 1350-1357 [PMID: 20082453 DOI: 10.1002/cncr.284583]

50 Zhong L, Suo J, Wang Y, Han J, Zhou H, Wei H, Zhu J. Prognosis of limited-stage small cell lung cancer with comprehensive treatment including radical resection. *World J Surg Oncol* 2020; 18: 27 [PMID: 32013993 DOI: 10.1186/s12957-020-1807-1]

51 Shepherd FA, Ginsberg RJ, Evans WK, Feld R, Cooper JD, Ilves R, Todd TR, Pearson FG, Waters PF, Baker MA. Reduction in local recurrence and improved survival in surgically treated patients with small cell lung cancer. *J Thorac Cardiovasc Surg* 1983; 86: 498-506 [PMID: 6312199]

52 Granetzny A, Bosseila A, Wagner W, Krukenemeyer G, Vogt U, Hecker E, Koch OM, Klinke F. Surgery in the tri-modality treatment of small cell lung cancer. Stage-dependent survival. *Eur J Cardiothorac Surg* 2006; 30: 212-216 [PMID: 16829087 DOI: 10.1016/j.ejcts.2005.05.002]

53 Yin K, Song D, Zhang H, Cai F, Chen J, Dang J. Efficacy of surgery and prophylactic cranial irradiation in stage II and III small cell lung cancer. *J Cancer* 2018; 9: 3500-3506 [PMID: 30310506 DOI: 10.7150/jca.26157]

54 Che K, Shen H, Qu X, Pang Z, Jiang Y, Liu S, Yang X, Du J. Survival Outcomes for Patients with Surgical and Non-Surgical Treatments in Stages I-III Small-Cell Lung Cancer. *J Cancer* 2018; 9: 1421-1429 [PMID: 29721052 DOI: 10.7150/jca.23583]

55 Babakooi S, Fu P, Yang M, Linden PA, Dowlati A. Combined SCLC clinical and pathologic characteristics. *Clin Lung Cancer* 2013; 14: 113-119 [PMID: 23010092 DOI: 10.1016/j.clcc.2012.07.002]

56 Zhang C, Yang H, Zhao H, Lang B, Yu X, Xiao P, Zhang X. Clinical outcomes of surgically resected combined small cell lung cancer: a two-institutional experience. *J Thorac Dis* 2017; 9: 151-158 [PMID: 28203418 DOI: 10.21037/jtd.2017.01.07]

57 Lei Y, Feng H, Qiang H, Wang Z, Chen Q, Qian J, Zhang Y, Zhong R, Fan X, Chu T. Clinical characteristics and prognostic factors of surgically resected combined small cell lung cancer: a retrospective study. *Lung Cancer* 2020; 146: 244-251 [PMID: 32529885 DOI: 10.1016/j.lungcan.2020.06.021]

58 Mangum MD, Greco FA, Hainsworth JD, Hendle KR, Johnson DH. Combined small-cell and non-small-cell lung cancer. *J Clin Oncol* 1989; 7: 607-612 [PMID: 25402894 DOI: 10.1200/JCO.1989.7.5.607]

59 Men Y, Hui Z, Liang J, Feng Q, Chen D, Zhang H, Xiao Z, Zhou Z, Yin W, Wang L. Further understanding of an uncommon disease of combined small cell lung cancer: clinical features and prognostic factors of 114 cases. *Chin J Cancer Res* 2016; 28: 486-494 [PMID: 27877007 DOI: 10.21147/j.o1000-9604.2016.05.03]

60 Shepherd FA, Ginsberg RJ, Evans WK, Feld R, Cooper JD, Ilves R, Todd TR, Pearson FG, Waters PF, Baker MA. Surgery in the tri-modality treatment of small cell lung cancer: a retrospective study. *Lung Cancer* 1991; 101: 196-200 [PMID: 1846927]

61 Yamada K, Sajo N, Kojima A, Ohe Y, Tamura T, Sasaki S, Eguchi K, Shinaki T, Goya T, Kondo H. A retrospective analysis of patients receiving surgery after chemotherapy for small cell lung cancer. *Jpn J Clin Oncol* 1991; 21: 39-45 [PMID: 1648633]

62 Nakanishi K, Mizuno T, Sakakura N, Kuroda H, Shimizu J, Hida T, Tatabye Y, Sakao Y. Salvage surgery for small cell lung cancer after chemoradiotherapy. *Jpn J Clin Oncol* 2019; 49: 389-392 [PMID: 30753585 DOI: 10.1093/jjco/hzy010]

63 Du X, Tian D, Liu L, Tang Z, Xiao J, Liu W, Yuan S, Cao X, Zhou H, Zhang J. Surgery in patients with small cell lung cancer: A period propensity score matching analysis of the Seer database, 2010-2015. *OncoLett* 2019; 18: 4865-4881 [PMID: 31611997 DOI: 10.3892/ol.2019.10792]
Japanese multiinstitutional study. Kimura T, Hirokawa Y, Takeda A, Ouchi A, Hareyama M, Kokubo M, Hara R, Itami J, Yamada K. Stereotactic Onishi H Carcinoma According to Addition of Chemotherapy and Prophylactic Cranial Irradiation: A Multicenter Analysis. Verma V 10.1007/s13566-019-00395-x for early-stage small cell lung cancer. From the RSSearch Patient Registry. Singh R DOI:

Stahl JM Shioyama Y 10.1016/j.ijrobp.2015.07.243 Radiation Oncology Study Group (JROSG). Multi-institutional Retrospective study of Stereotactic Body Radiation Therapy for stage I Small Cell Lung Cancer: Japan Shioyama Y 306 [PMID: 27463850] Small cell lung cancer clinical practice guidelines in oncology. J Nail Compr Canc Netw 2006; 4: 602-622 [DOI: 10.16137/jncn.2006.0505]

 Davis S, Crino L, Tonato M, Darwish S, Pelicci PG, Grignani F. A prospective analysis of chemotherapy following surgical resection of clinical stage I-II small-cell lung cancer. Am J Clin Oncol 1993; 16: 93-95 [PMID: 8383917] DOI: 10.1097/00000425-199304000-00001

 Yang CF, Chan DY, Spector PJ, Gulack BC, Wang X, Hartwig MG, Onishi H, Takayama K, Matsuo Y, Takeda A, Yamashita H, Miyakawa A, Murakami N, Aoki M, Crawford J, Downey RJ, Ettinger DS, Fossella F, Grecca JC, Jahan T, Kalemkerian GP, Kessinger A, Koczyswos M, Langer CJ, Martins R, Marymont MH, Niell HB, Rennath N, Robert F, Williams CC Jr, National Comprehensive Cancer Network (NCCN). Small cell lung cancer clinical practice guidelines in oncology. J Natl Compr Canc Netw 2006; 4: 602-622 [DOI: 10.16137/jncn.2006.0505]

 Verma V, Hasan S, Wegner RE, Abel S, Colonias A. Stereotactic ablative radiation therapy versus conventionally fractionated radiation therapy for stage I small cell lung cancer. Radiother Oncol 2019; 131: 145-149 [PMID: 30773182 DOI: 10.1016/j.radonc.2018.12.006]

 Verma V, Simone CB 2nd, Allen PK, Gajjar SR, Shah C, Zhen W, Harkenrider MM, Hallemeier CL, Jabbour SK, Minh HS, Nath SK, Husain ZA, Simone CB 2nd, Kim AW, Decker RH. Trends in stereotactic body radiation therapy-based treatment model for stage I medically inoperable small cell lung cancer. Lung Cancer 2017; 103: 11-16 [PMID: 28024690 DOI: 10.1016/j.lungcan.2016.11.019]

 Shioyama Y, Nagata Y, Konimaya T, Takayama K, Shibamoto Y. Ueki N, Yamada K, Kozuka T, Kimura T, Matsuo Y. Multi-institutional Retrospective study of Stereotactic Body Radiation Therapy for stage I Small Cell Lung Cancer: Japan Radiation Oncology Study Group (JROSG). Int J Radiat Oncol Biol Phys 2015; 93: S101 [DOI: 10.1016/j.ijrobp.2015.07.243]

 Shioyama Y, Onishi H, Takayama K, Matsuo Y, Takeda A, Yamashita H, Miyakawa A, Murakami N, Aoki M, Matsushita H, Matsumoto Y, Shibamoto Y; Japanese Radiological Society Multi-Institutional SBRT Study Group (JRS-SBRTSG). Clinical Outcomes of Stereotactic Body Radiotherapy for Patients With Stage I Small-Cell Lung Cancer: Analysis of a Subset of the Japanese Radiological Society Multi-Institutional SBRT Study Group Database. Technol Cancer Res Treat 2018; 17: 1533033818783904 [PMID: 29983096 DOI: 10.1177/1533033818783904]

 Stahl JM, Corso CD, Verma V, Park HS, Nath SK, Huisan ZA, Simone CB 2nd, Kim AW, Decker RH. Trends in stereotactic body radiation therapy for stage I small cell lung cancer. Lung Cancer 2017; 103: 11-16 [PMID: 28024690 DOI: 10.1016/j.lungcan.2016.11.019]

 Singh R. Ansinnelli H, Sharma D, Jenkins J, Davis J, Vargo JA, Sharma S. Clinical Outcomes Following Stereotactic Body Radiation Therapy (SBRT) for Stage I Medically Inoperable Small Cell Lung Carcinoma: A Multi-Institutional Analysis From the RSSearch Patient Registry. Am J Clin Oncol 2019; 42: 602-606 [PMID: 31227223 DOI: 10.1097/COC.0000000000000565]

 Newman NB, Sherry AD, Byrne DW, Osmundson EC. Stereotactic body radiotherapy versus conventional radiotherapy for early-stage small cell lung cancer. J Radiat Oncol Biol Phys 2019; 8: 239-248 [PMID: 31402969 DOI: 10.1016/s1356-619-00395-x]

 Verma V, Simone CB 2nd, Allen PK, Lin SH. Outcomes of Stereotactic Body Radiotherapy for T1-T2N0 Small Cell Carcinoma According to Addition of Chemotherapy and Prophylactic Cranial Irradiation: A Multicenter Analysis. Clin Lung Cancer 2017; 18: 675-681 [PMID: 28408183 DOI: 10.1016/j.clc.2017.03.009]

 Onishi H, Araki T, Shirato H, Nagata Y, Hiroaka M, Gomi K, Yamashita T, Niibe Y, Karasawa K, Hayakawa K, Takay K, Kinura T, Hirokawa Y, Takeda A, Ouchi A, Hareyama M, Kokubo M, Hara R, Itami J, Yamada K. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese mult institutional study. Cancer 2004; 101: 1623-1631 [PMID: 15378503 DOI: 10.1002/cncr.20539]
ICINONSE Y, Haru N, Ohta M, Motohiro A, Hata K, Yagawa K. Brain metastases in patients with limited small cell lung cancer achieving complete remission. Correlation with TNM staging. *Chest* 1989; 96: 1332-1335 [PMID: 2555114 DOI: 10.1378/chest.96.6.1332]

ARRIAGADA R, Le Chevalier T, Rivière A, Chomy P, Monnet I, Bardet E, Santos-Miranda JA, Le Péhoux C, Tarayre M, Benhamou S, Laplanche A. Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 95 randomized patients. *Ann Oncol* 2002; 13: 748-754 [PMID: 12075544 DOI: 10.1093/annonc/md2123]

ARRIAGADA R, Le Chevalier T, Borie F, Rivière A, Chomy P, Monnet I, Tardivon A, Viader F, Tarayre M, Benhamou S. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst* 1995; 87: 183-190 [PMID: 7707405 DOI: 10.1093/jnci/87.3.183]

SEUTE T, Leffers P, ten Velde GP, Twijnsstra A. Detection of brain metastases from small cell lung cancer: consequences of changing imaging techniques (CT versus MRI). *Cancer* 2008; 112: 1827-1834 [PMID: 18311784 DOI: 10.1002/cncr.23361]

MANAPOV F, Klatuke G, Fietkau R. Prevalence of brain metastases immediately before prophylactic cranial irradiation in limited disease small cell lung cancer patients with complete remission to chemoradiotherapy: a single institution experience. *J Thorac Oncol* 2008; 3: 652-655 [PMID: 18520807 DOI: 10.1097/JTO.0b013e318175fa76]

CHU X, Li S, Xia B, Chu L, Yang X, Ni J, Zou L, Li Y, Xie C, Lin J, Zha Z. Patterns of brain metastasis immediately before prophylactic cranial irradiation (PCI): implications for PCI optimization in limited-stage small cell lung cancer. *Radiother Oncol* 2019; 14: 171 [PMID: 31533763 DOI: 10.1016/j.ijrobp.2019.04.011]

AUPÉRIN A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, Kristjansen PE, Johnson BE, Ueoka H, Wagner H, Aisner J. 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: 476-484 [PMID: 10441603 DOI: 10.1056/NEJM199908233410108]

MEERT AP, Paesmans M, Berghmans T, Martin B, Mascaux C, Vallerot JM, Lafitte JJ, Sculier JP. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer* 2003; 1: 5 [PMID: 11432756 DOI: 10.1186/1471-2407-1-5]

VIANI GA, Boin AC, Ikeda YY, Vianna BS, Silva RS, Santanella F. Thirty years of prophylactic cranial irradiation in patients with small cell lung cancer: a meta-analysis of randomized clinical trials. *J Bras Pneumol* 2012; 38: 372-381 [PMID: 22782608 DOI: 10.1590/s1806-371320120003000013]

ZHANG W, Jiang W, Luan L, Wang L, Zheng X, Wang G. Prophylactic cranial irradiation in resected small cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer* 2014; 14: 793 [PMID: 25361811 DOI: 10.1186/1471-2407-14-793]

YANG Y, Zhang D, Zhou X, Bao W, Ji Y, Sheng L, Cheng L, Chen Y, Du X, Qiu G. Prophylactic cranial irradiation in resected small cell lung cancer: A systematic review and meta-analysis. *J Cancer* 2018; 9: 433-439 [PMID: 29344290 DOI: 10.7150/jca.21465]

MAMESAYA N, Wakuda K, Omae K, Miyawaki E, Kotake M, Fujiwara T, Kawamura T, Kobayashi H, Nakashima K, Omori S, Ono A, Komenotsu H, Naio T, Murakami H, Mori K, Harada H, Endo M, Nakajima T, Takahashi T. Efficacy of prophylactic cranial irradiation in patients with limited-disease small-cell lung cancer who were confirmed to have no brain metastasis via magnetic resonance imaging after initial chemoradiotherapy. *Oncotarget* 2018; 9: 17664-17674 [PMID: 29707139 DOI: 10.18632/oncotarget.24830]

FARRIS MK, Whless WH, Hughes RT, Soike MH, Masters AH, Helis CA, Chan MD, Cramer CK, Ruiz J, Lycan T, Petty WI, Ahrendt T, Leyerer CM, Blackstock AW. Limited-Stage Small Cell Lung Cancer: Is Prophylactic Cranial Irradiation Necessary? *Pract Radiat Oncol* 2019; 9: e599-e607 [PMID: 31271904 DOI: 10.1016/j.pradon.2019.06.014]

QIU G, DU X, Zhou X, Bao W, Chen L, Chen J, Ji Y, Wang S. Prophylactic cranial irradiation in 399 patients with limited-stage small cell lung cancer. *Oncol Lett* 2016; 11: 2654-2660 [PMID: 27073534 DOI: 10.3892/ol.2016.4231]

ECE Z, Roengvoraphoj O, Niyazi M, Hildebrandt G, Fietkau R, Belka C, Manapov F. Treatment Response and Prophylactic Cranial Irradiation Are Prognostic Factors in a Real-life Limited-disease Small Lung Cancer Patient Cohort Comprehensive Staged With Cranial Magnetic Resonance Imaging. *Clin Lung Cancer* 2017; 18: e23-e249 [PMID: 28065620 DOI: 10.1016/j.cllc.2016.11.005]

LE PÉCHOUX C, Al Mohles K, Dharmien F. Place actuelle de l'irradiation prophylactique cérébrale [Present role of prophylactic cranial irradiation]. *Bull Cancer* 2013; 100: 35-43 [PMID: 23306411 DOI: 10.1684/bdc.2012.1678]

WU AJ, Gillis A, Foster A, Woo K, Zhang Z, Gelblum DY, Downey RJ, Rosenzweig KE, Ong L, Perez CA, Pietanza MC, Krug L, Rudin CM, Rimm A. Patterns of failure in limited-stage small cell lung cancer: Implications of TNM stage for prophylactic cranial irradiation. *Radiother Oncol* 2017; 125: 130-135 [PMID: 28778345 DOI: 10.1016/j.radonc.2017.07.019]

LOU Y, Zhong R, Xu J, Qiao R, Teng J, Zhang Y, Zhan X, Chu T, Zhong H, Han B. Does surgically resected small-cell lung cancer without lymph node involvement benefit from prophylactic cranial irradiation? *Thorac Cancer* 2020; 11: 1239-1244 [PMID: 32142599 DOI: 10.1111/1759-7714.13387]

OZAWA Y, Omae M, Fuji M, Matsui T, Kato M, Sagisaka S, Asada K, Karayama Y, Shirai T, Yasuda K, Nakamura Y, Inui N, Yamada K, Yokomura K, Suda T. Management of brain metastasis with magnetic resonance imaging and stereotactic irradiation attenuated benefits of prophylactic cranial irradiation in patients with limited-stage small cell lung cancer. *BMC Cancer* 2015; 15: 589 [PMID: 26275617 DOI: 10.1186/s12885-015-1593-2]

WARDE P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? *J Clin Oncol* 1992; 10: 890-895 [PMID: 1316951 DOI: 10.1200/JCO.1992.10.6.890]

COHEN MH, Ihde DC, Bunn PA Jr, Fossiek BE Jr, Matthews MJ, Shackney SE, Johnston-early A, Makuch R, Minna JD. Cyclic alternating combination chemotherapy for small cell bronchogenic carcinoma. *Cancer Treat Rep* 1979; 63: 163-170 [PMID: 2211144]

PIGONON JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, Brodin O, Joss R, Kies MS, Lebeau B. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992; 327: 1618-1624 [PMID: 1331787 DOI: 10.1056/NEJM1992123032272302]


Ortega-Franco A, extensive-stage SCLC (ES-SCLC). IMpower133: updated overall survival (OS) analysis of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide in controlled, open-label, phase 3 trial.

Reck M, 10.1016/S0140-6736(19)32222-6

Armstrong J, Byrne N, Shire N, Jiang H, Goldman JW; CASPIAN investigators. Durvalumab plus platinum-etoposide combination with chemotherapy in previously untreated extensive small-cell lung cancer: results from the IFCT-0802 trial.

Nishio M, Reck M, Mok T, Lam S, Shames DS, Liu J, Ding B, Lopez-Chavez A, Kabbinavar F, Lin W, Sandler A, Liu CB 2nd. Prospective study of proton-beam radiation therapy for limited-stage small cell lung cancer.

Brown PD, JPM, Van Meerbeeck JP, Ubbels F, Kwint MH, Kuenen MA, Deprez S, De Ruiter MB, Boogerd W, Sikorska K, Van Tinteren H, Schagen SB. Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance in SCLC (NCT01780675). J Thorac Oncol 2021; 16: 840-849 [PMID: 33545387 DOI: 10.1016/j.jtho.2020.12.024]

Rodriguez de Dios N, Murcia M, Coufago F, Lopez JL, Rico M, Samper PM, Vallejo C, Luna J, Trueba I, Cigarral C, Faere N, Manero RM, Duran X, Samper P. Treatment Design and Rationale for a Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for SCLC: PREMIR Trial on Behalf of the Oncologic Group for the Study of Lung Cancer/Spanish Radiation Oncology Group-Radiation Oncology Clinical Research Group. Clin Lung Cancer 2018; 19: e693-e697 [PMID: 29891263 DOI: 10.1016/j.clc.2018.05.003]

Belderbos JSA, De Ruyscher DKM, De Jaeger K, Koppe F, Lambrecht MLF, Lievens YN, Dielman EMT, Jaspers JPM, Van Meerbeeck JP, Ubbels F, Kwint MH, Kuenen MA, Deprez S, De Ruiter MB, Boogerd W, Sikorska K, Van Tinteren H, Schagen SB. Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance in SCLC (NCT01780675). J Thorac Oncol 2021; 16: 840-849 [PMID: 33545387 DOI: 10.1016/j.jtho.2020.12.024]

Thromboesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. J Clin Oncol 2010; 28: 43-48 [PMID: 19901100 DOI: 10.1200/JCO.2009.24.7351]

Rodriguez de Dios N, Murcia M, Coufago F, Lopez JL, Rico M, Samper PM, Vallejo C, Luna J, Trueba I, Cigarral C, Faere N, Manero RM, Duran X, Samper P. Treatment Design and Rationale for a Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for SCLC: PREMIR Trial on Behalf of the Oncologic Group for the Study of Lung Cancer/Spanish Radiation Oncology Group-Radiation Oncology Clinical Research Group. Clin Lung Cancer 2018; 19: e693-e697 [PMID: 29891263 DOI: 10.1016/j.clc.2018.05.003]

Belderbos JSA, De Ruyscher DKM, De Jaeger K, Koppe F, Lambrecht MLF, Lievens YN, Dielman EMT, Jaspers JPM, Van Meerbeeck JP, Ubbels F, Kwint MH, Kuenen MA, Deprez S, De Ruiter MB, Boogerd W, Sikorska K, Van Tinteren H, Schagen SB. Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance in SCLC (NCT01780675). J Thorac Oncol 2021; 16: 840-849 [PMID: 33545387 DOI: 10.1016/j.jtho.2020.12.024]

Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, Blumenschein GR Jr, Heymach JV, Vapoorian AA, Swisger SG, Allen PK, Choi NC, DeLaney TF, Hahn SM, Cox JD, Lu CS, Mohan R. Bayesian Adaptive Randomization Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Patients With Advanced Non–Small-Cell Lung Cancer. J Clin Oncol 2018; 36: 1813-1822 [PMID: 29293386 DOI: 10.1200/JCO.2017.74.0720]

Rwigema JM, Vermu V, Lin L, Berman AT, Levin WP, Evans TL, Aggarwal C, Rengan R, Langer C, Cohen RB, Simonne CB 2nd. Prospective study of proton-beam radiation therapy for limited-stage small cell lung cancer. Cancer 2017; 123: 4244-4251 [PMID: 28678434 DOI: 10.1002/cncr.30387]

Rossi A, Di Maio M, Chiodini P, Rudd RM, Okamoto H, Skarlos DV, Früh M, Qian W, Lam S, Samantais E, Shibata T, Perrone F, Giallo C, Griddelli C, Martelli O, Lee SM. 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: 1692-1698 [PMID: 22473169 DOI: 10.1200/JCO.2011.40.4905]

Rossi A, Garassino MC, Cinquini M, Shubrali P, Di Maio M, Farina G, Griddelli C, Torri V. Maintenance or consolidation therapy in small-cell lung cancer: a systematic review and meta-analysis. Lung Cancer 2010; 70: 119-128 [PMID: 20188431 DOI: 10.1016/j.lungcan.2010.02.001]

Tiseo M, Boni L, Ambrosio F, Camerini A, Baldini E, Cinieri S, Brighenti M, Zanelli F, Defaia E, Chiarri R, Dazzi C, Tibuldi C, Turolla GM, D'Alessandro V, Zilembo N, Trolese AR, Grossi F, Riccardi F, Ardizzone A. Italian, Multicenter, Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Extensive-Disease Small-Cell Lung Cancer: The GOIRC-AIFA FARM6PMFJM Trial. J Clin Oncol 2017; 35: 1281-1287 [PMID: 28135143 DOI: 10.1200/JCO.2016.69.4844]

Pujol JJ, Lavole A, Quexs E, Moliner O, Soquet PJ, Barlesi F, Le Caer H, Moro-Sibilot D, Fournel P, Oster JP, Chatellain P, Barre P, Jeannin G, Mourlanette P, Derollez M, Herman D, Renaudt A, Dayen C, Lamy PJ, Langlais A, Morin F, Zalcman G; French Cooperative Thoracic Intergroup (IFCT). Randomized phase II–III study of bevacizumab in combination with chemotherapy in previously untreated small-cell lung cancer: results from the IFCT-0802 trial. Ann Oncol 2015; 26: 908-914 [PMID: 25688059 DOI: 10.1093/annonc/mdv065]

Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, Huenner F, Losonczy G, Johnson ML, Nishio M, Reck M, Mok T, Lam S, Shames DS, Liu J, Dang B, Lopez-Chavez A, Kabbinavar F, Lin W, Sandler A, Liu SV; IMpower133 Study Group. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018; 379: 2220-2229 [PMID: 30208641 DOI: 10.1056/NEJMoa1809064]

Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Stassenko D, Hochmair MJ, Ozgüroğlu M, Ji H, Voitko O, Poltoratsky A, Ponce S, Verderame F, Havel L, Bondarenko I, Kazarnowicz A, Losonczy G, Conev NV, Armstrong J, Byrne N, Shire N, Jiang H, Goldman JW; CAPSIAN investigators. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CAPSIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019; 394: 1929-1939 [PMID: 31590988 DOI: 10.1016/S0140-6736(19)32222-6]

Reck M, Liu SV, Mansfield AS, Mok TSK, Scherpereel A, Reinmuth N, Garassino MC, CastroDe Carpeno J, Califano R, Nishio M, Orlandi F, Alatorre Alexander AJ, Leal TA, Cheng Y, Lee JS, Lam S, McClendan M, Deng Y, Phan S, Horn L. IMpower133: updated overall survival (OS) analysis of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide in extensive-stage SCLC (ES-SCLC). Ann Oncol 2019; 30 Suppl 9: v710-v717 [DOI: 10.1016/j.annonc.2019.mzd264]

Ortega-Franco A, Ackermann C, Paz-Ares L, Califano R. First-line immune checkpoint inhibitors for extensive stage small-cell lung cancer: clinical developments and future directions. ESMO Open 2021; 6: 100003 [PMID: 33450659 DOI: 10.1016/j.euto.2020.07.008]
Pangua C et al. New perspectives in SCLC

10.1016/j.esmoop.2020.100063

122 Paz-Ares LG, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statensko G, Hochmair M, Özgüroğlu M, Ji JH, Voitko O, Polorotatskiy A, Verderame F, Havel L, Bondarenko I, Armstrong J, Byrne N, Jiang H, Wade Goldman J. Durvalumab + tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): Updated Results from the phase III CASPIAN study. J Clin Oncol 2020; 38: 9082

123 Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statensko G, Hochmair MJ, Özgüroğlu M, Ji JH, Garassino MC, Voitko O, Polorotatskiy A, Sone S, Verderame F, Havel L, Bondarenko I, Kazmierowicz A, Losonczy G, Conev NV, Armstrong J, Byrne N, Thiagajaran P, Jiang H, Paz-Ares L. CASPIAN investigators. 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: 51-65 [PMID: 33285907 DOI: 10.1016/S1470-2045(20)30539-8]

124 Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csoszi T, Cheema PK, Rodriguez-Abreu D, Wollner M, Yang JC, Mazieres J, Orlandi FJ, Luft A, Gümüş M, Kato T, Kalenkerian GP, Luo Y, Ebianah V, Pietanza MC, Kim HR; KEYNOTE-644 investigators. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-644 Study. J Clin Oncol 2020; 38: 2369-2379 [PMID: 32468956 DOI: 10.1200/JCO.20.00793]

125 Leaf T, Wang Y, Dowlati A, Andrew Lewis D, Chen Y, Ramesh Mohindra A, Razaq M, Ahuja HG, Liu J, King DM, Sweeney JC, Ramalingam SS. 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 EAS161. J Clin Oncol 2020; 38: 9000 [DOI: 10.1200/JCO.2020.38.15_suppl.9000]

126 Zhou T, Zhang L, Luo F, Zhao Y, Hou X, Liu T, Wang K, Zhao H, Huang Y, Zhang L. Comparison of First-Line Treatments for Patients With Extensive-Stage Small Lung Cancer: A Systematic Review and Network Meta-analysis. JAMA Netw Open 2020; 3: e2015748 [PMID: 33074323 DOI: 10.1001/jamanetworkopen.2020.15748]

127 Facchinetti F, Di Maio M, Tiseo M, Adding PD-1/PD-L1 Inhibitors to Chemotherapy for the First-Line Treatment of Extensive Stage Small Cell Lung Cancer (SCLC): A Meta-Analysis of Randomized Trials. Cancers (Basel) 2020; 12 [PMID: 32947924 DOI: 10.3390/cancers12092645]

128 Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Lu H, Cuillerot JM, Lynch TJ. Iplilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol 2013; 24: 75-83 [PMID: 22858559 DOI: 10.1093/annonc/mds013]

129 Reck M, Luft A, Szczesna A, Havel L, Kim SW, Akerley W, Pietanza MC, Wu YL, Zielinski C, Thomas M, Felip E, Gold K, Horn L, Aerts J, Nakagawa K, Lorigan P, Pieters A, Kong Sanchez T, Fairchild J, Spigel D. Phase III Randomized Trial of Iplilimumab Plus Etoposide Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol 2016; 34: 3740-3748 [PMID: 27458307 DOI: 10.1200/JCO.2016.67.6601]

130 Zatloukal P, Cardenal F, Szczesna A, Gorbunova V, Moiseyenko V, Zhang X, Cisar L, Soria JC, Domine M, Thomas M. 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 2013; 24: 1810-1816 [PMID: 23021298 DOI: 10.1093/annonc/mdq036]

131 Lara PN Jr, Natalie R, Crowley J, Lenz HJ, Redman MW, Carleton JE, Jett J, Langer CJ, Kuebler JP, Dakhil SR, Chansky K, Gandara DR. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacoeconomic results from SWOG S0124. J Clin Oncol 2009; 27: 2530-2535 [PMID: 19345243 DOI: 10.1200/JCO.2008.20.1061]

132 Hanna N, Bunn PA Jr, Langer G, Einhorn L, Guthrie T Jr, Beck T, Ansari R, Ellis P, Byrne M, Morrison M, Hariharan S, Wang B, Sandler A. 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: 2038-2043 [PMID: 16648503 DOI: 10.1200/JCO.2005.04.8595]

133 Slotman B, Faireve-Finn C, Kramer G, Rankin F, Snee M, Hatton M, Postmus P, Collette L, Musat E, Senan S; EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007; 357: 664-672 [PMID: 17699816 DOI: 10.1056/NEJMoa071780]

134 Rule WG, Foster NR, Meyers JP, Ashman JB, Vora SA, Kozelsky TF, Garces YI, Urbanic JJ, Schild SE. Prophylactic cranial irradiation in elderly patients with small cell lung cancer: findings from a North Central Cancer Treatment Group pooled analysis. J Geriatr Oncol 2015; 6: 119-126 [PMID: 25482023 DOI: 10.1016/j.jgo.2014.11.002]

135 Ge W, Xu H, Yan Y, Cao D. The effects of prophylactic cranial irradiation versus control on survival of patients with extensive-stage small-cell lung cancer: a meta-analysis of 14 trials. Radiat Oncol 2018; 13: 155 [PMID: 30139360 DOI: 10.1186/s13014-018-1101-3]

136 Wen P, Wang TF, Li M, Yu Y, Zhou YL, Wu CL. Meta-analysis of prophylactic cranial irradiation or not in treatment of extensive-stage small-cell lung cancer: The dilemma remains. Cancer Radiother 2020; 24: 44-52 [PMID: 32044160 DOI: 10.1016/j.crad.2019.10.001]

137 Takahashi T, Yamanaka T, Seto T, Harada H, Nokihara H, Saka H, Nishio M, Kaneda H, Takayama K, Ishimoto O, Takeda K, Yoshioha K, Tachihara M, Sakai H, Goto K, Yamamoto N. Prophylactic cranial irradiation versus observation in patients with extensive-stage small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017; 18: 663-671 [PMID: 28343976 DOI: 10.1016/S1470-2045(17)30230-9]

138 Yin X, Yan D, Qiu M, Huang L, Yan SX. Prophylactic cranial irradiation in small cell lung cancer: a systematic review and meta-analysis. BMC Cancer 2019; 19: 95 [PMID: 30665432 DOI: 10.1186/s12885-018-5251-3]

139 Gondi V, Paulus R, Brunner DW, Meyers CA, Gore EM, Wolfson A, Werner-Vasik M, Sun AY, Choy H, Vovsas B. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. Int J Radiat Oncol Biol Phys 2013; 86: 656-664 [PMID: 23597420 DOI: 10.1016/j.ijrobp.2013.02.033]

140 Le Péchoux C, Dunant A, Senan S, Wolfson A, Quoix E, Faivre-Finn C, Ciucaleu T, Arriagada R, Jones R, Wanders R,
Lerouge D, Laplanche A; Prophylactic Cranial Irradiation (PCI) Collaborative Group. 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, ROGTO 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol* 2009; 10: 467-474 [PMID: 19386548 DOI: 10.1016/S1470-2045(09)70101-9]

Hurwitz JI, McCoy F, Seullin P, Fennell DA. New advances in the second-line treatment of small cell lung cancer. *Oncologist* 2009; 14: 986-994 [PMID: 19819197 DOI: 10.1634/theoncologist.2009-0026]

Schneider BJ. Management of recurrent small cell lung cancer. *J Natl Comp Curr* 2008; 6: 323-331 [PMID: 18377589 DOI: 10.1002/jncr.200802]

Owonikoko TK, Behera M, Chen Z, Bhimani C, Curran WJ, Khuri FR, Ramalingam SS. A systematic evaluation of efficacy of second-line chemotherapy in sensitizing and refractory small-cell lung cancer. *J Thorac Oncol* 2012; 7: 866-872 [PMID: 22727888 DOI: 10.1097/JTO.0b013e318247cf7b]

Baize N, Monnet I, Greillier L, Geier M, Lena H, Janicot H, Vergnerengue A, Crequit J, Lamy R, Auliac JB, Letreut J, Le Caer H, Gervais R, Dansin E, Madroszyk A, Renault PA, Le Garff G, Falchero L, Berard H, Schott R, Saulnier P, Chouaid C; Groupe Français de Pneumologie-Cancérologie 01-13 investigators. Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol* 2020; 21: 1224-1233 [PMID: 32888454 DOI: 10.1016/S1470-2045(20)30461-7]

Naito Y, Yamada K, Imamura Y, Ishii H, Matsuo N, Tokito T, Kinoshita T, Azuma K, Hoshino T. Rechallenge treatment with a platinum-based regimen in patients with sensitive relapsed small-cell lung cancer. *Med Oncol* 2018; 35: 61 [PMID: 29610997 DOI: 10.1007/s12032-018-1123-6]

O'Brien M, Culeaune TE, Tsekov H, Shparyk Y, Cuceviá B, Hujsaz G, Thatcher N, Ross GA, Dane GC, Crofts T. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol* 2006; 24: 5441-5447 [PMID: 17135646 DOI: 10.1200/JCO.2006.06.5821]

von Pawel J, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysogon NG, Stewart DJ, Clark PI, Palmer MC, Depeyre A, Carmichael J, Krebs JB, Ross G, Lane GW, Gralla R. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999; 17: 658-667 [PMID: 10908612 DOI: 10.1200/JCO.1999.17.2.658]

Allen JW, Moon J, Redman M, Gadgeel SM, Kelly K, Mack S, Saha HM, Mohamed MK, Jahnzehb M, Gandara DR. Southwest Oncology Group S0802: a randomized, Phase II trial of weekly topotecan with and without ziv-afibercept in patients with platinum-treated small-cell lung cancer. *J Clin Oncol* 2014; 32: 2463-2470 [PMID: 25002722 DOI: 10.1200/JCO.2013.51.4109]

Trigo J, Subbiah V, Besse B, Moreno V, López R, Sala MA, Peters S, Ponce S, Fernando C, Alfaro V, Gómez J, Kahatt C, Zeaiter A, Zaman K, Boni V, Arrondeau J, Martínez M, Delord JP, Amin A, Camidge DR, Horn L, Calvo E, Li A, Lin WH, Callahan MK, Spigel DR. Nivolumab versus amrubicin versus topotecan or cyclophosphamide, doxorubicin, and vincristine with small-cell lung cancer who have failed one prior platinum-containing line. *Future Oncol* 2020; 15: 231-239 [PMID: 30632750 DOI: 10.2217/fon-2018-0597]

von Pawel J, Jotte R, Spigel DR, O'Brien ME, Socinski MA, Steins M, Bosquée L, Bubis J, Nackaerts K, Trigo JM, Clingan P, Schütte W, Lorigan P, Reck M, Domine M, Shepherd FA, Li S, Renschler MF. Randomized phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol* 2020; 21: 645-654 [PMID: 32224306 DOI: 10.1016/S1470-2045(20)30068-1]

Calvo E, Moreno V, Flynn M, Holgado E, Olmedo ME, Lopez Criado MP, Kahatt C, Lopez-Vilarino JA, Siguero M, Fernandez-Teruel C, Cullell-Young M, Soto Matos-Pita A, Forster M. Antitumor activity of lurbinectin (PM01183) and doxorubicin in relapsed small-cell lung cancer: results from a phase I single-arm trial [abstract]. *Ann Oncol* 2017; 28: 2559-2566 [PMID: 28961837 DOI: 10.1093/annonc/mdx357]

Farago AF, Drapkin BI, Lopez-Vilarino de Ramos IA, Galmarini CM, Núñez R, Kahatt C, Paz-Ares L. ATLANTIS: a Phase III study of lurbinectin/doxorubicin versus topotecan or cyclophosphamide/doxorubicin/vincristine in patients with small-cell lung cancer who have failed one prior platinum-containing line. *Future Oncol* 2019; 15: 231-239 [PMID: 30632750 DOI: 10.2217/fon-2018-0597]

von Pawel J, Jotte R, Spigel DR, O'Brien ME, Socinski MA, Mezger J, Leventhal MD, Gillis GL, Hidalgo MA, Redman M, Grillo LC, Shepherd FA, Fields SZ, Kleisbauer JP, Yeo J, Winters SE, Martinez G, Forster M, Renshaw MF. Randomized phase III trial of annrubucin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol* 2014; 32: 4012-4019 [PMID: 25385727 DOI: 10.1200.JCO.2013.51.5392]

Antonia SJ, López-Martín JA, Bendell J, Ott PA, Taylor M, Eder JP, Pietanza MC, Le DT, de Braud F, Morse MA, Ascierto PA, Khuri FR, Ramalingam SS. A systematic analysis of second-line chemotherapy in sensitive and refractory small-cell lung cancer. *J Thorac Oncol* 2012; 7: 866-872 [PMID: 22727888 DOI: 10.1097/JTO.0b013e318247cf7b]

Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hahn CL, de Braud F, Antonia SJ, Ascierto PA, Moreno V, Atmaca A, Salvagno S, Taylor M, Amin A, Camidge DR, Horn L, Calvo E, Li A, Lin WH, Callahan MK, Spigel DR. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. *J Thorac Oncol* 2020; 15: 426-435 [PMID: 31629915 DOI: 10.1016/j.jtho.2019.10.004]

Spigel DR, Vicente D, Culeaune TE, Gething S, Peters S, Horn L, Audigier-Valette C, Pardo Aranda N, Juan-Vidal O, Chung HC, Zeaiter A, Zaman K, Boni V, Arrondeau J, Martínez M, Delord JP, Amin A, Camidge DR, Horn L, Calvo E, Li A, Lin WH, Callahan MK, Spigel DR. Lurbinectin as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol* 2018; 36: 8506-8506 [DOI: 10.1200/JCO.2018.36.15_suppl.8506]

Chung HC, Piha-Paul SA, Lopez-Martín J. Pembrolizumab after two or more lines od prior therapy in patients with advance small-cell lung cancer (SCLC). Proceedings of the AACR Annual Meeting; 2019; Leeds, GA. Atlanta 2019;
Abstract CT073

159 Pujol JI, Greillier L, Audigier-Valette C, Moro-Sibilot D, Uwer L, Hureau J, Guisier F, Carmier D, Madejaine J, Otto J, Gounant V, Merle P, Mounierante P, Monlior O, Renault A, Rabeau A, Antoine M, Denis MG, Bornmart S, Langlaiss A, Morin F, Souquet PJ. 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: 903-913 [PMID: 30664809 DOI: 10.1016/j.jtho.2019.01.008]

160 Kim YJ, Keam B, Ock CY, Song S, Kim M, Kim SH, Kim KH, Kim JS, Kim TM, Kim DW, Lee JS, Heo DS. A phase II study of pembrolizumab and paclitaxel in patients with relapsed or refractory small-cell lung cancer. Lung Cancer 2019; 136: 122-128 [PMID: 31494530 DOI: 10.1016/j.lungcan.2019.08.031]

161 Pietanza MC, Kadota K, Huberman K, Sima CS, Fiore JJ, Sumner DK, Travis WD, Heguy A, Ginsberg MS, Holody AJ, Chan TA, Rizvi NA, Azzoli CG, Riely GJ, Kris MG, Krug LM. 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: 1138-1145 [PMID: 22228633 DOI: 10.1158/1078-0432.CCR-11-2059]

162 Zauderer MG, Drilon A, Kadota K, Huberman K, Sima CS, Bergagnini I, Sumner DK, Travis WD, Heguy A, Ginsberg MS, Holody AJ, Riely GJ, Kris MG, Krug LM, Pietanza MC. 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: 237-240 [PMID: 25194605 DOI: 10.1016/j.lungcan.2014.08.007]

163 Masuda N, Fukuoka M, Kusuzuki Y, Matsu K, Takafuji N, Kudoh S, Negoro S, Nishihata M, Nakagawa K, Takada M. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 1992; 10: 1225-1229 [PMID: 13221891 DOI: 10.1200/JCO.1992.10.8.1225]

164 Yamamoto N, Tsutururi J, Yoshinura N, Asai G, Moriyama A, Nakagawa K, Kudoh S, Takada M, Minato Y, Fukuoka M. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. Anticancer Res 2006; 26: 777-781 [PMID: 16739535]

165 Smith EF, Fokkema E, Biesma B, Groen HJ, Snoek W, Postmus PE. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer 1998; 77: 347-351 [PMID: 9461009 DOI: 10.1038/bjc.1998.54]

166 Smyth JD, Smith IE, Sessa C, Schoffski P, Wanders J, Franklin H, Kaye SB. Activity of docetaxel (Taxotere) in small cell lung cancer. The Early Clinical Trials Group of the EORTC. Eur J Cancer 1994; 30A: 1058-1060 [PMID: 7654428 DOI: 10.1016/0959-8049(94)90455-3]

167 Masters GA, Declercq L, Blanke C, Sandler A, DeVore R, Miller K, Johnson D; Eastern Cooperative Oncology Group. Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol 2002; 21: 1550-1555 [PMID: 12697880 DOI: 10.1200/JCO.2003.09.130]

168 Hoang T, Kim K, Jaslofski A, Koch P, Beatty P, McGovern J, Quisumbing M, Shapiro G, Witte R, Schiller JH. Phase II study of second-line gemcitabine in sensitive or refractory small cell lung cancer. Lung Cancer 2003; 42: 97-102 [PMID: 14512193 DOI: 10.1016/S0169-5002(03)00273-3]

169 Furuse K, Kubota K, Kawahara M, Nakada M, Kimura I, Fujii M, Ohta M, Hasegawa K, Yoshida K, Nakajima S, Osgura T, Niihata H. Phase II study of vinorelbine in heavily previously treated small cell lung cancer. Japan Lung Cancer Vinorelbine Study Group. Oncology 1996; 53: 169-172 [PMID: 8604245 DOI: 10.1159/000022755]

170 Kang JH, Lee KH, Kim DW, Kim SW, Kim HR, Kim JH, Choi JH, An HJ, Kim JS, Jang JS, Kim BS, Kim HT. A randomised phase 2b study comparing the efficacy and safety of belotecan vs. topotecan as monotherapy for sensitive-relapsed small-cell lung cancer. Br J Cancer 2021; 124: 713-720 [PMID: 33914080 DOI: 10.1038/s41416-020-01055-z]

171 Byers LA, Wang J, Nilsson MB, Fujimoto J, Saintigny P, Yordy J, Giri U, Peyton M, Fan YH, Diao L, Masropour F, Shen L, Liu W, Dachemam T, Bumala P, Bhardwaj V, Welsh J, Weber S, Glisson BS, Kalhor N, Wistuba II, Girard L, Lippman SM, Mills GB, Coombs KR, Weinstein JN, Minna JD, Meyham J. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov 2012; 2: 798-811 [PMID: 22961660 DOI: 10.1158/2155-9289.CD-12-0112]

172 de Bono J, Ramanathan RK, Mina L, Chugh R, Glaspy J, Rafii S, Kaye S, Sachdev J, Meyham J, Smith DC, Henshaw JW, Herrriott A, Patterson M, Curtin NJ, Byers LA, Wainberg ZA. Phase I Dose-Escalation, Two-Part Trial of the PARP Inhibitor Talazoparib in Patients with Advanced Germline BRCA1/2 Mutations and Selected Sporadic Cancers. Cancer Discov 2017; 7: 620-629 [PMID: 28242752 DOI: 10.1158/2159-8290.CD-16-1250]

173 Penella W, Gaunt P, Steele N, Ahmed S, Muletaro AI, Shah R, Danson S, Hodgkinson E, James K, Watkins B, Fletcher P, Billingham L. P1.07-015 STOMP: A UK National Cancer Research Network Randomised, Double Blind, Multicentre Phase II Trial of Olaparib as Maintenance Therapy in SCLC. J Thorac Oncol 2017; 12: S704-S705 [DOI: 10.1016/j.jtho.2016.11.926]

174 Owoenikou TK, Dahberg SE, Sica GL, Wagner LL, Wade JL 3rd, Skrakolovic G, Lash BW, Leach JW, Leal TB, Aggarwal C, Ramalingam SS. 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 2019; 37: 222-229 [PMID: 30523756 DOI: 10.1200/JCO.2018.00264]

175 Poirier JT, George J, Owoenikou TK, Berns A, Brambilla E, Byers LA, Carbone D, Chen HJ, Christensen CL, Dive C, Farago AF, Govindan R, Ham C, Hellmann MD, Horn L, Johnson JE, Ju YS, Kang S, Krasnow M, Lee J, Lee SH, Lehman J, Lok B, Lovly C, MacPherson D, McFadden D, Minna J, Oser M, Park K, Park KS, Pommier Y, Quanartha V, Ready N, Sage J, Scagliotti G, Sok ML, Sutherland KD, Travis WD, Veddy NCS, Ward SJ, Wistuba II, Wong KK, Zhang H, Daigneault J, Wiens J, Rudin CM, Olivier TG. New Approaches to SCLC Therapy: From the Laboratory to the Clinic. J Thorac Oncol 2020; 15: 520-540 [PMID: 32018053 DOI: 10.1016/j.jtho.2020.01.016]

176 Pietanza MC, Waqar SN, Krug LM, Dowlati A, Hann CL, Chiappori A, Owoenikou TK, Wool KM, Cardnell RJ, Fujimoto J, Long L, Diao L, Wang J, Bensman Y, Hurtado B, de Groot P, Sulman EP, Wistuba II, Chen A, Fleisher M, Meyham J, Kris MG, Rudin CM, Byers LA. Randomized, Double-Blind, Phase II Study of Temozolomide in Combination With Either Veliparib or Placebo in Patients With Relapsed-Sensitive or Refractory Small-Cell Lung Cancer. J Clin Oncol 2018; 36: 2386-2394 [PMID: 29906251 DOI: 10.1200/JCO.2018.77.7672]

177 Farago AF, Yeap BY, Stanizione M, Hung YP, Heist RS, Marcoux JP, Zhong J, Rangachari D, Barbie DA, Phat S, Myers
Cohort Study. First-line Radiosurgery vs Whole-Brain Radiotherapy for Small Cell Lung Cancer Brain Metastases: The FIRE-SCLC

Combs SE, Kessel KA, Rieken S, Patel S, Guckenberger M, Andratschke N, Kavanagh BD, Robin TP. Evaluation of

Bernstein K, Silverman JS, Grills IS, Siddiqui ZA, Yuan JC, Sheehan JP, Cordeiro D, Nosaki K, Seto T, Deibert CP, C, Yu JB, Braunstein S, Mathieu D, Touchette CJ, Lee CC, Yang HC, Aizer AA, Cagney DN, Chan MD, Kondziolka D, Akabane A, Sato Y, Niranjan A, Faramand AM, Lunsford LD, McInerney J, Tuanquin LC, Zacharia BE, Chiang V, Singh

Sensitivity in Preclinical Models of Small-Cell Lung Cancer.

Hughes PE. AMG 757, a Half-Life Extended, DLL3-Targeted Bispecific T-Cell Engager, Shows High Potency and

Therapy in DLL3-High SCLC: Results From the Phase 3 TAHOE Study.

Komarnitsky P, Reinmuth N. Efficacy and Safety of Rovalpituzumab Tesirine Compared With Topotecan as Second-Line

W, Cetnar J, Cappuzzo F, Okamoto I, Erman M, Langer SW, Kato T, Groen H, Sun Z, Luo Y, Tanwani P, Caffrey L, RJ, Strouse B, Hedrick MP, Hassan CA, Heymach JW, Wang J, Byers LA. Combination Treatment of the Oral CHK1

Inhibitor, SRA737, and Low-Dose Gemcitabine Enhances the Effect of Programmed Death Ligand 1 Blockade by Modulating the Immune Microenvironment in SCLC. J Thorac Oncol 2019; 14: 2152-2163 [PMID: 31470128 DOI: 10.1016/j.jtho.2019.08.009]

Lallo A, Frese KK, Morrow CJ, Sloane R, Guliati S, Schenk MW, Trapani F, Simms N, Galvin M, Brown S, Hodgkinson CL, Priest L, Hughes A, Lai Z, Cadogan E, Khandelwal G, Simpson KL, Miller C, Blackhall F, O'Connor MJ, Dive C. The Combination of the PARP Inhibitor Olaparib and the WEE1 Inhibitor AZD1775 as a New Therapeutic Option for Small Cell Lung Cancer. Clin Cancer Res 2018; 24: 5153-5164 [PMID: 29941481 DOI: 10.1158/1078-0432.CCR-17-2805]

Ponce S, Coté GM, Falcon A, Jimenez-Aguilar E. Efficacy and safety profile of lurbinectedin-irinotecan in patients with relapsed SCLC. Results from a phase Ib/II trial. Proceedings of the 2020 World Conference on Lung Cancer, 2021 Jan 28-31; Leeds, Singapore

Rudin CM, Pietanza MC, Bauer TM, Ready N, Morgensztern D, Glisson BS, Byers LA, Johnson ML, Burris HA 3rd, Robert F, Han TH, Bheddah S, Theiss N, Watson L, Mathur D, Vennapusa B, Zayed H, Lally S, Strickland DK, Govindan R, Dyulla SJ, Peng SL, Spigel DR; SCRX16-001 investigators. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. Lancet Oncol 2017; 18: 42-51 [PMID: 27932068 DOI: 10.1016/S1470-2045(16)30565-4]

Morgensztern D, Besse B, Greillier L, Santana-Davila R, Ready N, Hann CL, Glisson BS, Farago AF, Dowlati A, Rudin CM, Le Moulec S, Lally S, Yalamanchili S, Wolf J, Govindan R, Carbone DP. 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: 6958-6966 [PMID: 31506387 DOI: 10.1158/1078-0432.CCR-19-1133]

Blackhall F, Jao K, Greillier L, Cho BC, Penkov K, Reguart N, Majem M, Nakaerts K, Syrigos K, Hansen K, Schuette W, Cetnar J, Cappuzzo F, Okamoto I, Erman M, Langer SW, Kato T, Groen H, Sun Z, Luo Y, Tanwani P, Caffrey L, Komarnitsky P, Reinmuth N. Efficacy and Safety of Rovalpituzumab Tesirine Compared With Topotecan as Second-Line Therapy in DLL3-High SCLC: Results From the Phase 3 TAHOE Study. J Thorac Oncol 2021; 16: 1547-1558 [PMID: 33607312 DOI: 10.1016/j.jtho.2021.02.009]

Giffin MJ, Cooke K, Lobenhofer EK, Estrada J, Zhan J, Deegen P, Thomas M, Murawsky CM, Werner J, Liu S, Lee F, Homann O, Friedrich M, Pearson JT, Raam T, Yang Y, Caenepeel S, Stevens J, Beltran PJ, Canon J, Coxon A, Bailis JM, Hughes PE. AMG 757, a Half-Life Extended, DLL3-Targeted Bispecific T-Cell Engager, Shows High Potency and Sensitivity in Preclinical Models of Small-Cell Lung Cancer. Clin Cancer Res 2021; 27: 1526-1537 [PMID: 33203642 DOI: 10.1158/1078-0432.CCR-20-2845]

Slotman BJ, van Tinteren H, Praag JO, Kneegiens JL, El Sharouyi S, Hatton M, Keijser A, Faireve-Finn C, Senan S. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015; 386: 38-42 [PMID: 25230595 DOI: 10.1016/S0140-6736(14)61085-0]

Rusthoven CG, Yamamoto M, Bernhardt D, Smith DE, Gao D, Serizawa T, Yomo S, Aiyama H, Higuchi Y, Shuto T, Akabane A, Sato Y, Niranjan A, Faramand AM, Lunsford LD, Mcinerney J, Tuanquin LC, Zacharia BE, Chiang V, Singh C, Yu JB, Braunstein S, Mathieu D, Touchette CJ, Lee CC, Yang HC, Aizer AA, Cagney DN, Chan MD, Konidzioka D, Bernstein K, Silverman JS, Grills IS, Siddiqui ZA, Yuan J, Sheehan JP, Cordeiro D, Nosaki K, Seto T, Deibert CP, Verma V, Day S, Halasz LM, Warnick RE, Trifiletti DM, Palmer JD, Atia A, Li B, Cifarelli CP, Brown PD, Vargo JA, Combs SE, Kessel KA, Rieken S, Patel S, Guenkenberger M, Andratschke N, Kavanagh BD, Robin TP. Evaluation of First-line Radiosurgery vs Whole-Brain Radiotherapy for Small Cell Lung Cancer Brain Metastases: The FIRE-SCLC Cohort Study. JAMA Oncol 2020; 6: 1028-1037 [PMID: 32496530 DOI: 10.1001/jamaoncol.2020.1271]
