

Review

Limited-Stage Small-Cell Lung Cancer: Current Progress and the Next Frontier

Tzen S. Toh ^{1,2,†} and Benjamin H. Lok ^{3,4,5,6,*} 

- ¹ The Medical School, University of Sheffield, Sheffield S10 2RX, UK; szen.toh@sanger.ac.uk
² Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield S10 2JF, UK
³ Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, ON M5G 2M9, Canada
⁴ Department of Radiation Oncology, University of Toronto, Toronto, ON M5T 1P5, Canada
⁵ Department of Medical Biophysics, University of Toronto, Toronto, ON M5G 1L7, Canada
⁶ Institute of Medical Science, University of Toronto, Toronto, ON M5S 1A8, Canada
* Correspondence: Benjamin.Lok@rmp.uhn.ca; Tel.: +1-(416)-946-2919; Fax: +1-(416)-946-6561
† Current address: Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton CB10 1SA, UK.

Simple Summary: Limited-stage (LS) small-cell lung cancer (SCLC) is a type of lung cancer that is confined to one side of the chest without cancer spread elsewhere. The outcomes of patients with this disease remain poor. Currently, patients with LS-SCLC are managed with chemotherapy and radiotherapy that is delivered together. In this review article, we highlight various advancements in treatments for LS-SCLC patients and challenges that are required to be overcome to achieve better patient outcomes.

Abstract: Limited-stage (LS) small-cell lung cancer (SCLC) is defined as disease confined to a tolerable radiation portal without extrathoracic metastases. Despite clinical research over two decades, the prognosis of LS-SCLC patients remains poor. The current standard of care for LS-SCLC patients is concurrent platinum-based chemotherapy with thoracic radiotherapy (RT). Widespread heterogeneity on the optimal radiation dose and fractionation regimen among physicians highlights the logistical challenges of administering BID regimens. Prophylactic cranial irradiation (PCI) is recommended to patients following a good initial response to chemoradiation due to improved overall survival from historical trials and the propensity for LS-SCLC to recur with brain metastases. However, PCI utilization is being debated due to the greater availability of magnetic resonance imaging (MRI) and data in extensive-stage SCLC regarding close MRI surveillance in lieu of PCI while spurring novel RT techniques, such as hippocampal-avoidance PCI. Additionally, novel treatment combinations incorporating targeted small molecule therapies and immunotherapies with or following radiation for LS-SCLC have seen recent interest and some concepts are being investigated in clinical trials. Here, we review the landscape of progress, limitations, and challenges for LS-SCLC including current standard of care, novel radiation techniques, and the integration of novel therapeutic strategies for LS-SCLC.

Keywords: limited-stage; small-cell lung cancer; radiotherapy; small molecules; immunotherapy; clinical trials



Citation: Toh, T.S.; Lok, B.H. Limited-Stage Small-Cell Lung Cancer: Current Progress and the Next Frontier. *Radiation* **2021**, *1*, 317–333. <https://doi.org/10.3390/radiation1040026>

Academic Editor: Jan Bussink

Received: 4 November 2021

Accepted: 10 December 2021

Published: 14 December 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Small-cell lung cancer (SCLC) is a subtype of lung cancer accounting for 13–15% of all lung cancer patients [1,2]. SCLC is much more prevalent in smokers [3]. Though formally staged by the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM classification, pragmatically SCLC patients are grouped using the Veterans Administration Lung Study Group two-stage system, dividing the cancer into limited-stage and extensive-stage disease. Limited-stage SCLC (LS-SCLC) is cancer on the ipsilateral hemithorax encompassable within a tolerable radiation portal and therefore is

eligible for curative intent treatment. Extensive-stage SCLC (ES-SCLC) is cancer that either spreads widely throughout the lungs, non-regional lymph nodes or to other organs [1]. Around 30% of patients with SCLC present with LS-SCLC [4].

Overall survival (OS) rates for SCLC patients remain particularly low. For LS-SCLC patients, 5-year OS is about 20–35% [5,6]. The current standard of care for the treatment of LS-SCLC is platinum-based chemotherapy with early concurrent thoracic radiation therapy followed by prophylactic cranial irradiation (PCI) for LS-SCLC patients with good response to initial treatment [4]. Here, we review the landscape of progress, limitations, and challenges for LS-SCLC including current standard of care, novel radiation techniques, and the integration of novel therapeutic strategies for LS-SCLC.

2. Current Role of Radiation in Managing LS-SCLC

2.1. Concurrent Chemotherapy with Thoracic Radiation

Concurrent thoracic chemoradiation is the mainstay of treatment for LS-SCLC receiving treatment for curative intent. The current backbone chemotherapy regimen for LS-SCLC patients is a platinum agent with etoposide [4,7].

Concurrent chemoradiotherapy was not firmly established until the early 1990s as clinical trials attempting to investigate this approach were not significantly powered. Two meta-analyses published in 1992 established concurrent chemoradiation improved OS and local disease control [8,9]. The larger of these meta-analyses, by Pignon et al. [9], included 13 clinical trials and 2140 LS-SCLC patients with a median follow up of 43 months showed chemoradiation improved OS at 3 years by 5.4% compared to chemotherapy solely [9].

Early radiotherapy versus late radiotherapy for LS-SCLC had been previously debated. A previous study showed late radiotherapy resulted in a higher risk of brain metastasis compared to early radiotherapy (28% vs. 18%) [10]. Early thoracic radiation for LS-SCLC patients also results in better 3-year progression-free survival (PFS), 3-year OS, and 5-year OS compared to late thoracic radiation (26% vs. 19%, 30% vs. 22%, and 20% vs. 11%, respectively) [10]. A meta-analysis by Fried et al. evaluated the use of early versus late delivery of thoracic radiotherapy to LS-SCLC patients. Seven randomized controlled trials were evaluated which collectively showed 5% OS benefit at 2-years for early radiotherapy [11].

2.2. Optimal LS-SCLC Radiation Fractionation

Radiotherapy dose fractionation for LS-SCLC has a long history of clinical trial development. Published in 1999, Turrisi et al. [5] randomized 417 patients to groups that either received hyperfractionated, twice-daily (BID) radiotherapy (1.5 Gy in 30 fractions) or a regular fractionated once-daily regimen (1.8 Gy in 25 fractions) to receive a total of 45 Gy. They showed that there was a significant difference with median survival; 19 months for the once-daily group and 23 months for the BID group with an increased rate of grade 3 esophagitis [5].

Published in 2017, the CONVERT trial did not show improved survival with the once-daily fractionation to 66 Gy when compared to the 45 Gy in 30 fractions BID regimen [6]. The CALGB 30610/RTOG 0538 trial is evaluating high-dose once-daily 70 Gy thoracic radiotherapy in comparison to the 45 Gy in 30 fractions BID regimen of thoracic radiotherapy in LS-SCLC patients. The abstract reported June 2021 concluded that the 70 Gy arm did not improve OS for LS-SCLC patients [12]. Though not designed as non-inferiority studies, these two trials suggest that patients treated with once-daily fractionation appear to have similar outcomes as patients treated with 45 Gy in 30 fractions BID.

Published in 2021, a randomized phase II clinical compared the efficacy of 45 Gy in 30 fractions BID to high-dose 60 Gy in 40 fractions BID in LS-SCLC patients. Two-year survival was higher in the 60 Gy group with 74.2% of patients alive compared to 48.1% in the 45 Gy group. The rates of toxicity between the two groups also did not differ significantly [13]. Further prospective studies will be required to establish the benefit of higher dose and fractionation in LS-SCLC patients.

Despite the 45 Gy in 30 fractions BID regimen being supported with randomized trial evidence, pragmatically, heterogeneity in clinical practice and utilization exists. A pan-Canadian survey of radiation oncologists was carried out in 2016 where responses from 52 radiation oncologists were further analyzed. For LS-SCLC patients, the most common dose and fractionation schedule most commonly used by Canadian radiation oncologists was 40–45 Gy in 15 once-daily fractions (40% of respondents), followed by 45 Gy in 30 BID fractions (just over 30% of respondents). 50 Gy in 25 once-daily fractions and 60–66 Gy in 30–33 once-daily fractions were also reported at similar rates among respondents (about 10% each, respectively) [14]. This heterogeneity of regimens and the prevalence of 40–45 Gy in 15 once-daily fractions is likely informed by historical precedent as evidenced by a Canadian randomized controlled trial reported in 1993 [10]. Interestingly, a retrospective study in 2021 comparing 40 Gy in 15 fractions once daily versus 45 Gy in 30 fractions BID showed no difference in OS, locoregional recurrence, or \geq grade 3 toxicities in LS-SCLC following propensity score adjustment [15].

A US-based survey of 309 radiation oncologists showed 60% of respondents stated they preferred a once-daily thoracic radiation regimen and 76% stated that a once-daily regimen was more common in clinical practice. 54.4% of respondents preferred a 60 Gy dose when administering once-daily thoracic radiotherapy followed by 20.4% having a preference of 66 Gy. 87.9% of US radiation oncologists preferred a total dose of 45 Gy when administering BID thoracic radiotherapy. Respondents from academic institutions had a higher likelihood of endorsing BID treatment in clinical practice (51% in academic institutions vs. 33% in private practice) [16]. These surveys highlight the logistical burden of BID schemas and preferences by physicians and patients for once-daily fractionation in clinical care. Studies evaluating the optimal dose and fractionation regimen for LS-SCLC patients are summarized in Table 1.

Table 1. Studies that evaluated the optimal dose and fractionation regimen for LS-SCLC patients with study information and key findings.

Study	Total Cohort of LS-SCLC Patients	Intervention vs. Control	Endpoints	Key Findings (Intervention vs. Control)	Statistics (Intervention vs. Control)
Prospective Studies for Radiotherapy Fractionation					
Turrisi et al., 1999 [5]	417	Twice-daily 45 Gy in 30 fractions vs. once-daily 45 Gy in 25 fractions thoracic radiotherapy	Median OS 2-year survival 5-year survival	23 vs. 19 months 47% vs. 41% 26% vs. 16%	
Faivre-Finn et al., 2017 [6]	547	Twice-daily 45 Gy in 30 fractions vs. once-daily 66 Gy in 33 fractions thoracic radiotherapy	Median OS 2-year survival	30 months vs. 25 months 56% vs. 51%	95% CI 24–34 months vs. 21–31 months 95% CI 50–62% vs. 45–57%
Grønberg et al., 2020 [17]	176	Twice-daily 60 Gy in 40 fractions vs. 45 Gy in 30 fractions thoracic radiotherapy	Median OS 2-year survival	42 months vs. 23 months 73% vs. 46%	95% CI, 32–51 months vs. 17–28 months 95% CI 32–51% vs. 36–60%
Bogart et al., 2021 [12]	638	45 Gy in 30 fractions BID thoracic radiotherapy [ref] vs. once-daily 70 Gy in 35 fractions	OS	HR 0.94	95% CI, 0.76–1.2

2.3. The Role of Prophylactic Cranial Irradiation

Given the tendency for subsequent development of brain metastases from SCLC, prophylactic cranial irradiation (PCI) has been recommended to LS-SCLC patients following a good response to initial treatment with chemoradiation. The role of PCI in managing LS-SCLC is significant; it has been shown to improve the rates of brain metastasis control and OS [18].

While PCI has shown clinical benefit in LS-SCLC patients to reduce the rate of brain metastasis and improve OS, randomized prospective studies for ES-SCLC and retrospective studies for LS-SCLC have also suggested that the improved sensitivity of magnetic resonance imaging (MRI) and increased use of close imaging surveillance may diminish the resulting OS benefit of PCI [19,20]. A 2017 phase III randomized trial for ES-SCLC showed PCI improved the 1-year brain metastasis rate to 33% from 59%, however, there was a lack of OS benefit with PCI as compared to the MRI surveillance only arm [20]. Further investigations remain to ascertain whether PCI provides an OS benefit with the availability of MRI and uptake of close imaging surveillance for LS-SCLC patients. According to retrospective studies, another subgroup of LS-SCLC patients where the absolute benefit of PCI may be lower are LS-SCLC patients with AJCC stage I-II disease, highlighting the importance of obtaining TNM classification and stage for all SCLC patients [21,22].

PCI utilization rates have not been consistent and are known to differ between institutions (Table 2). A retrospective study at the Princess Margaret Cancer Centre showed improvements in OS and brain failure free survival for those that received PCI, however they observed some patients declined PCI due to patient or physician concerns related to toxicity and also patients older than 65 years of age were significantly less likely to receive PCI [23]. An updated study from the same institution showed PCI maintained its association with OS, even in the MRI era [24]. Another study from Memorial Sloan Kettering Cancer Center showed that patient concerns regarding neurotoxicity was the most cited reason for the omission of PCI. Karnofsky performance status and clinical AJCC stage were significantly associated with OS but not PCI in this retrospective study [25].

Given the associated side effects with PCI, its utility to manage LS-SCLC patients when MRI brain surveillance is available is being questioned. In addition to the retrospective studies highlighted above, some studies have shown no associated improvement in OS or PFS with PCI for LS-SCLC in the MRI era [19,26] while other studies do report an OS benefit with PCI [24,27]. Further prospective results from clinical trials that include LS-SCLC patients, such as the SWOG S1827 MAVERICK (SWOG S1827) trial comparing PCI to MR surveillance (NCT04155034), are awaited to provide modern prospective evidence.

Table 2. Various recent studies that detail the utility of PCI in LS-SCLC with study information and key findings.

Study and Publication Year	Total Cohort of SCLC Patients	SCLC Patients That Received PCI (<i>n</i> , % of Total Cohort)	Intervention vs. Control	Endpoints	Key Findings and Statistics (Intervention vs. Control)
Prospective Studies					
Aupérin et al., 1999 [18]	987	526 (53.2)	No PCI [ref] vs. PCI	OS Disease-free survival Time to symptomatic brain metastases	Pooled relative risk of 0.84 (95% CI, 0.73–0.97) Pooled relative risk of 0.46 (95% CI, 0.38–0.57) HR, 0.27 (95% CI, 0.16–0.44) 40.4% (95% CI, 32.1–48.6) vs.
** Slotman et al., 2007 [28]	286	143 (50.0)	No PCI [ref] vs. PCI	Cumulative risk of brain metastases within 1 year Disease-free survival 1-year survival HVLt-R delayed recall at 6 months after completion of PCI	14.6% (95% CI, 8.3–20.9) HR 0.76 (95% CI, 0.59–0.96) 13.3% (95% CI, 8.1–19.9) vs. 27.1% (95% CI, 19.4–35.5)
Redmond et al., 2017 [29]	20	20 (100.0)	Hippocampal-sparing PCI (no comparator)	Reliable Change Index at 6 months for HVLt-R delayed recall Reliable Change Index at 12 months for HVLt-R delayed recall 2-year survival Median progression-free survival	7.06 (SD 2.77, <i>n</i> = 14) 17.6% 7.10% 88% (95% CI, 68–100%) Not reached
Levy et al., 2019 [30]	547	449 (82.0)	Secondary analysis of PCI in CONVERT study thoracic BID [ref] vs. once daily [6]	* Brain relapse times * Median OS 3-year survival	HR 0.95 (95% CI, 0.60–1.50) 28 months (95% CI, 22–35) vs. 31 months (95% CI, 27–52) 48% (95% CI, 41–55) vs. 42% (95% CI, 36–49)

Table 2. Cont.

Study and Publication Year	Total Cohort of SCLC Patients	SCLC Patients That Received PCI (n, % of Total Cohort)	Intervention vs. Control	Endpoints	Key Findings and Statistics (Intervention vs. Control)
Retrospective Studies					
Giuliani et al., 2010 [23]	228	127 (55.7)	PCI vs. no PCI	Brain FFS Median OS	76.6% (95% CI, 68–87) vs. 46.7% (95% CI, 8–34) 21.7 months (95% CI, 17–36.8) vs. 11.2 (95% CI, 8.9–14.1)
Ozawa et al., 2015 [26]	124	29 (23.4)	PCI vs. no PCI (with MRI and SRS salvage)	* Median OS * Brain metastasis occurrence rates in 2 years	25 vs. 34 months 43.0% vs. 38.4%
Qiu et al., 2016 [31]	399	185 (46.4)	Early vs. late PCI	Symptomatic brain metastases at 6, 12 and 24 months 1-year OS rates 3-year OS rates	0, 3 and 13% vs. 7, 29 and 42% 96% vs. 82% 53% vs. 35%
Lok et al., 2017 [25]	208	115 (55.0)	PCI vs. no PCI (no significant difference in outcomes, all patients reported together)	Median OS 2-year OS rates 3-year OS rates	35.1 months 64% 49%
Farooqi et al., 2017 [32]	658	364 (55.3)	No PCI [ref] vs. PCI	Risk of death Risk of brain metastasis Median survival	HR 0.73 (95% CI 0.61–0.88) HR 0.56 (95% CI 0.40–0.78) 26 months (95% CI, 22–34 months)
Wu et al., 2017 [22]	283	114 (41.0)	PCI vs. no PCI (no significant difference in outcomes, all patients reported together)	2-year survival 5-year survival 2-year cumulative incidence of brain metastasis	53% 33% 17%
Pezzi et al., 2020 [19]	297	205 (69.0)	No PCI [ref] vs. PCI	* OS * 3-year incidence rate of brain metastasis	HR 0.844 (95% CI, 0.604–1.180) 11.20% (95% CI, 5.40–19.20) vs. 20.40% (95% CI, 12.45–29.67)
Yan and Toh et al., 2021 [24]	369	196 (71.0)	PCI [ref] vs. no PCI	OS Brain failure risk	HR 1.77 (95% CI, 1.31–2.40) HR 2.93 (95% CI, 1.85–4.63)

* no significant difference. ** study in ES-SCLC patients.

3. Novel Radiation Approaches to Manage LS-SCLC

3.1. Intensity Modulated Radiation Therapy (IMRT)

While treatment options for LS-SCLC patients have not dramatically altered in the last 20 years, conformal radiation techniques have improved outcomes for patients and decreased treatment-related toxicity.

3.1.1. IMRT for Thoracic RT

Lower conformality with 2D RT and 3D conformal radiation therapy (3DCRT) increases the amount of the surrounding normal tissue that receives high dose RT. As such, there is a risk of developing higher rates of toxicities with 2D or 3DCRT such as esophagitis or pneumonitis as compared to IMRT [33].

A retrospective study from MD Anderson Cancer Center analyzed clinical records for 223 LS-SCLC patients treated from 2000 to 2009. 119 of these patients received 3DCRT while the remaining 104 patients received IMRT. The authors show that LS-SCLC patients who received IMRT required significantly fewer percutaneous feeding tube insertions compared to those who received 3DCRT (5% vs. 17%) but there were no differences in outcomes between these two techniques [33].

3.1.2. IMRT for Hippocampal-Avoidance PCI (HA-PCI)

Given a lack of a wide variety of treatment options, further investigation is warranted for PCI utility to find a balance between improving patient outcomes and quality of life through the reduction in treatment-related toxicity and disease control. With the advent of conformal RT techniques, such as IMRT or volumetric modulated arc therapy (VMAT), selective avoidance of brain sub-structures with potential for decreased neurotoxicity rates while maintaining disease control has become possible.

Accordingly, published in 2021, the PREMER clinical trial randomized 150 SCLC patients (107 limited-stage and 43 extensive-stage) and showed that HA-PCI, delivered by IMRT or VMAT, reduced the risk of worse delayed free recall (DFR) on the Free and Cued Selective Reminding Test (FCSRT) at 3 months without any significant difference in OS and brain metastases [34]. We also eagerly await the NRG CC003 study, which is planning to randomize up to 400 SCLC patients (LS and ES stage) to assess the 6-month deterioration in Hopkins Verbal Learning Test-Revised (HVLT-R) Delayed Recall associated with HA-PCI as compared to conventional PCI.

3.2. Stereotactic Body Radiation Therapy (SBRT)

Stereotactic body radiation therapy (SBRT) has been utilized for patients with stage I NSCLC [35–37]. There is limited evidence for the use of SBRT for LS-SCLC patients. Given that SCLC is generally considered to be more radiosensitive compared to NSCLC, the combination of SBRT and chemotherapy may be an option for the 5% of patients that present with clinical stage I SCLC, however evidence is currently sparse [35].

A single-institution retrospective study in 2013 reported eight inoperable LS-SCLC patients treated with SBRT and chemotherapy demonstrated this strategy as a safe and effective alternative. 3-year survival and disease-free survival rates were reported at 72% and 86%, respectively, with minimal toxicity [38]. Another small retrospective study in 2015 of six patients with stage I SCLC showed the use of SBRT to manage the primary tumour had 100% local control at year with no associated regional nodal failure and distant failure in the liver was reported in one patient. 1-year OS was at 63% and disease-free survival (DFS) was 75% [39]. A multi-institutional study across 24 institutions primarily evaluated the use of SBRT in T1-T2N0M0 SCLC patients and interrogated the benefit of chemotherapy. Adding chemotherapy to SBRT showed an OS benefit of 31.4 months in comparison to 14.3 months in the group without. DFS was 61.3 months in the group that received both chemotherapy and SBRT compared to 9 months without [40].

The National Comprehensive Cancer Network (NCCN) recommends the use of SBRT for stage I-IIA SCLC patients that do not undergo surgery. The strategy for SBRT mirrors

those for NSCLC based on NCCN recommendations [41]. In comparison to the UK's National Institute for Health and Care Excellence (NICE) guidance and the Cancer Care Ontario (CCO) guidelines, this recommendation is noticeably not present [42,43]. Due to lack of data, currently there are no known guidelines or recommendations regarding SBRT for the more advanced stages (i.e., IIB-IIIIC) LS-SCLC. Further prospective studies are required to adequately determine efficacy of SBRT, optimal dose and fractionation, along with chemotherapy sequencing for the treatment of LS-SCLC patients.

3.3. Proton Beam Therapy

After correction of other prognostic factors, it has been shown for NSCLC patients that there is a correlation between radiation therapy doses to the heart and OS [44]. This has led to further evaluation of proton beam therapy to reduce doses of radiation to the heart while ensuring there is adequate delivery of radiation to the lung cancer. There has been emerging evidence for outcomes for LS-SCLC patients treated with proton beam therapy. A single-institution prospective study investigating outcomes for 30 LS-SCLC patients that received proton beam therapy showed a median OS of 28.2 months with limited incidence of high-grade toxicities [45]. While these results are encouraging, further evaluation is required in clinical trials.

3.4. Stereotactic Radiosurgery (SRS) and Whole-Brain Radiation Therapy (WBRT)

Though SCLC patients with brain metastases are considered ES-SCLC, stereotactic radiosurgery (SRS) is worth briefly reviewing. Whole brain RT (WBRT) remains the standard of care for SCLC patients with brain metastases and evidence for the routine use of SRS remains limited for SCLC. In 2004, the RTOG 9508 trial reported the outcomes of 331 cancer patients with a variety of disease sites and histologies (i.e., only 6–9% patients had small cell histology) randomized to receive WBRT alone with and without SRS boost and identified a OS advantage for patients with a single brain metastasis treated with WBRT and SRS boost [46]. Of note, a 2020 paper reported the First-line Radiosurgery for Small-Cell Lung Cancer (FIRE-SCLC) multi-institutional cohort study that retrospectively evaluated the outcomes of SRS in 710 SCLC patients [47]. Results from FIRE-SCLC comparing SRS showed a median OS of 8.5 month and the time to central nervous system progression (TCCP) was 8.1 months. For those with single brain metastasis, the median OS was 11 months and TCCP was 11.7 months [47]. These results suggest SRS could be an option for selected SCLC patients and further evaluation in prospective clinical trials are warranted for SCLC.

4. Novel Therapeutic Strategies for LS-SCLC

4.1. Targeted Therapies and Molecular Subtypes

The availability of high throughput next-generation genome sequencing technologies has allowed lung cancers to be molecularly profiled leading to the establishment of driver mutations contributing to tumour proliferation. For example, studies have shown that the epidermal growth factor receptor (*EGFR*) oncogene drives tumour growth and proliferation in NSCLC [48–55]. Immunotherapies targeting the programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis such as nivolumab, pembrolizumab, and atezolizumab have shown efficacy in NSCLC [56–59].

While targeted small molecule therapies are routinely considered in the management of NSCLC, these are not currently the mainstay of treatment for SCLC patients due to the lack of currently targetable oncogenes with sufficient prevalence in SCLC. Rather, SCLC's high mutational burden is suggested to be strongly associated with tobacco exposure with 98% of cases appearing in smokers [60]. New molecular pathways require further investigation to establish their roles in SCLC and also whether targeted treatments improve LS-SCLC patient outcomes. Candidate therapeutic targets in SCLC are challenging to identify given that prevalent mutations in SCLC are mainly loss of function with the involvement of tumour suppressor genes *RB1* and *TP53* [60].

4.1.1. DNA Damage Response Inhibitors (DDR)

As the inactivation of *RB1* and *TP53*, SCLC tumours exhibit increased susceptibility to DNA damage. Mediators in the DNA damage response (DDR) pathway, such as poly (ADP-ribose) polymerase (PARP), have been investigated as potential therapeutic targets [60,61].

Several studies have shown that a combination of DDR inhibitors with chemotherapy or other targeted treatments could be a potential option for SCLC patients [62,63]. SLFN11 has been suggested as a potential biomarker of sensitivity of DNA damage chemotherapy and PARP inhibition in SCLC [62,64–66]. After *RB1* and *TP53*, gene amplification of *MYC* is among the most common genetic abnormalities found in 20% of SCLCs [60]. A phase II clinical trial combining paclitaxel with or without alisertib, an aurora kinase A (AURKA) and AURKB inhibitor, showed slight improvement in PFS in a general SCLC patient population. However, subtype analysis showed doubling of PFS in patients with *MYC*-high SCLC tumours [67,68].

Lurbinectedin, an inhibitor of gene transcription and RNA polymerase II, received FDA approval in 2020 as a second-line treatment option for SCLC [69]. Topotecan was previously the only other option in the second-line setting but its use is limited due to toxicity concerns and modest efficacy [70–72]. A single-arm, phase II basket trial evaluated the efficacy of lurbinectedin in 105 SCLC patients that experienced recurrence or resistance to initial treatment. Overall response rate by investigator assessment was 35.2% and the rate of disease control was 68.6% [73]. The most common grade 3–4 adverse events reported in this phase II trial were anaemia (9%), leucopenia (29%), neutropenia (46%), and thrombocytopenia (7%) [73]. The most reported side effect associated with lurbinectedin was myelosuppression in the initial phase I trial in advanced solid tumours [74]. The toxicity profile of lurbinectedin may make its incorporation for LS-SCLC management challenging, especially with concurrent chemoradiotherapy.

4.1.2. Delta-like Protein 3 (DLL3)

Whole-genome sequencing analysis revealed inactivating mutations in the primary *NOTCH* family of genes in 25% of SCLC tumours [75]. Overexpression of a negative regulator of *NOTCH* signaling, delta-like protein 3 (DLL3), was found in a majority of SCLC patients [76]. An anti-DLL3 antibody-drug conjugate called rovalpituzumab tesarine (Rova-T) showed antitumor activity when evaluated in a phase I clinical trial with patients who had recurrent SCLC [77] OS benefit [78–82].

However, DLL3 has remained of interest and has shown to act as a biomarker of sensitivity [76–78]. Results are awaited for an ongoing phase I clinical trial (NCT03319940) evaluating AMG 757, a half-life extended bispecific T-cell engager (BiTE) immunotherapy against DLL3 [83].

4.2. Immunotherapies

Successes in establishing the routine use of immunotherapies for SCLC patients had been limited [84,85]. In ES-SCLC, trials investigating the efficacy of immunotherapies including rilotumumab, ganitumab, and ipilimumab in combination with chemotherapy trials did not show significant OS benefit [86–89]. The landmark 2018 published study showed the addition of atezolizumab to chemotherapy in first-line treatment of ES-SCLC improved OS and progression-free survival (PFS) compared to chemotherapy alone [88]. In 2019, atezolizumab combined with carboplatin and etoposide received FDA approval based on the IMpower133 clinical trial for ES-SCLC.

Durvalumab combined with first-line chemotherapy is another treatment that showed significant OS benefit when treating ES-SCLC patients [90]. Pembrolizumab in addition to chemotherapy in the first line treatment of patients with ES-SCLC was shown to have prolonged OS in the Keynote-604 study (HR, 0.80; 95% CI, 0.64 to 0.98). However, a higher significance threshold was set in this study and was not achieved (p -value = 0.164) [91]. Despite ongoing study, there has yet to be well defined biomarkers that predict benefit from immune-checkpoint inhibitors [85], however one promising biomarker approach for

ES-SCLC reported by Gay et al. [92] leveraged the IMpower133 patient samples and defined an inflamed gene signature (SCLC-I) that correlated with atezolizumab benefit. This SCLC subtype had uniquely expressed genes that included numerous immune checkpoints and human leukocyte antigens in the absence of a transcriptional signature [92]. Whether this SCLC-I subtype in ES-SCLC would extend into LS-SCLC patients and associated treatment approaches remains unanswered.

Specific to LS-SCLC, a phase I/II trial published in 2020 investigated concurrent chemoradiation with pembrolizumab for LS-SCLC patients reported pembrolizumab was well tolerated. Patients were followed-up for a median time of 23.1 months with median PFS of 19.7 months. Median OS was reported to be 39.5 months [93]. However, other immunotherapies are being evaluated in randomized studies for LS-SCLC, such as the NRG LU0005 trial (NCT03811002), a phase II/III trial that is comparing concurrent atezolizumab with chemoradiation compared to chemoradiation alone and its effects on PFS and OS.

Unfortunately, the recent phase II STIMULI trial of 153 randomized LS-SCLC patients showed no improvement in PFS with the addition of consolidation nivolumab-ipilimumab following chemoradiation for LS-SCLC [94]. Another ongoing study is the ADRIATIC trial (NCT03703297) that is evaluating the effects of consolidation durvalumab and tremelimumab on the PFS and OS of LS-SCLC patients without progression following concurrent chemoradiation [95].

We eagerly await the results of these ongoing studies that will define the role for immunotherapy for LS-SCLC patients. Studies about ongoing and completed prospective studies for immunotherapies in LS-SCLC are summarized in Table 3.

Table 3. Ongoing and completed prospective studies for immunotherapies in LS-SCLC.

Study and Publication Year	Total Cohort of LS-SCLC Patients	Intervention	Endpoints	Key Findings and Statistics (Intervention vs. Control)
Completed Trials				
Welsh et al., 2020 [93]	40	Concurrent pembroluzimab	Maximum tolerated dose Median progression-free survival Median OS	No grade 5 toxicities, 3 grade 4 events (2 neutropenia, 1 respiratory failure). [<i>n</i> = 40] 19.7 months (95% CI, 8.8–30.5) [<i>n</i> = 40] 39.5 months (95% CI, 8.0–71.0) [<i>n</i> = 40]
Peters et al., 2021 [94]	153	Consolidation immunotherapy (nivolumab and ipilimumab) vs. observation after standard chemo-radiotherapy and PCI [ref]	* Progression-free survival * OS	HR 1.02 (95% CI, 0.66–1.58) HR 0.95 (95% CI, 0.59–1.52)
Ongoing Trials				
Senan et al., 2019 [95]	600 (estimated enrollment)	Consolidation durvalumab ± tremelimumab vs. placebo	Progression-free survival OS	Currently ongoing
Ross et al., 2020 [96]	506 (estimated enrollment)	Concurrent chemoradiation plus atezolizumab vs. chemoradiation	Progression-free survival OS	Currently ongoing

* no significant difference.

4.3. Pre-Clinical and Translational Studies

Efforts to define molecular subtypes of SCLC are ongoing. Gene expression profiling of SCLC from cell lines, patient tissue, and murine models have identified differential expression of transcriptional regulators (ASCL1, NEUROD1, POU2F3, YAP1, and ATOH1) or immune-related genes (SCLC-I) as candidate molecular subtypes [92,97,98].

5. Discussion

5.1. Current Limitations

The primary modality of LS-SCLC treatment remains concurrent chemoradiation with platinum-based chemotherapy [4,7]. Concurrent chemoradiation has long been established as the standard of care for LS-SCLC patients, particularly by two meta-analyses in 1992 showing this treatment modality improved OS and local disease control [8]. Turissi et al. [5] showed a significant difference in median survival for patients that received BID radiotherapy compared to those that received a once-daily regimen [5]. However, it is noted that the findings from the CONVERT trial suggested an increased dose of once-daily radiotherapy to 66 Gy did not show OS benefit compared to the 45 Gy/30 BID regimen [6]. Through collaborative decision-making with their physician, eligible patients without brain metastasis can undergo PCI which has been established by prospective studies to improve OS and reduce subsequent intracranial metastases [18].

There remain further controversies in the management of LS-SCLC. Optimal LS-SCLC radiation fractionation is still being debated between the benefits of the current recommended fractionation scheme and increasing it [5,6]. The role of PCI in the MRI era is being evaluated with the rationale for surveillance with MRI brain to lower PCI-related neurotoxicity in LS-SCLC patients while maintaining OS [20].

5.2. Risks and Benefits with Multi-Modal Combinatorial Therapies

Further consideration by clinicians is required to balance the risk and benefit of further treatment with studies increasingly investigating new targeted therapies and immunotherapies to treat SCLC patients. While the first-line of treatment for LS-SCLC patients remains concurrent chemoradiation, there is potential for further addition of novel combination or adjuvant therapies. For novel combination therapies with concurrent chemoradiation, caution needs to be exercised with respect to treatment tolerability, whereas additional adjuvant therapies may be more tolerable however may forgo potential concurrent treatment synergy. For example, prospective studies investigating the use of immunotherapy in both concurrent or consolidation following chemoradiation are underway to leverage the orthogonal mechanisms of action among each individual treatment and an acceptable toxicity profile [94,95].

5.3. Molecular Subtyping of SCLC Leading towards an Understanding of Inter- and Intra-Tumour Heterogeneity

SCLC is moving from being studied as a homogenous disease and towards being classified as a heterogenous disease (e.g., transcription factor subtypes: SCLC-A, SCLC-N, SCLC-P, SCLC-Y, SCLC-I, etc.) [97,98]. This distinction is crucial as a more comprehensive molecular definition of SCLC subtypes can help enable the discovery of biomarkers that suggest drug sensitivity or resistance and stratify patients according to their response to targeted therapies, the bedrock of precision medicine [99,100].

Single-cell RNA-sequencing (scRNA-seq) has enabled further exploration of inter- and intra-tumour heterogeneity, cell types, and cell states [101,102]. scRNA-seq technology is increasingly gaining higher throughput capabilities and sustainable cost, allowing a greater number of single-cells to be profiled at this resolution [102]. Bulk-sequencing technologies used to measure gene expression may not be able to capture the complete heterogeneity in a diverse biological system such as tumours; these technologies only measure the average expression levels of each gene in a large population of cells [103].

Further study using mouse and human models in combination with time-series analysis of scRNA-seq data has revealed MYC as a driver of dynamic evolution of SCLC subtypes [104]. It is suggested that MYC can convert SCLC subtypes in a context-specific manner; with the loss of *RB1* and *TP53*, MYC can promote a pulmonary neuroendocrine cell from SCLC-A to SCLC-N to SCLC-Y in vivo. This study suggests that intratumoural subtype heterogeneity is critical to be considered when designing future clinical trials [104].

Characterisation of generated circulating tumor cell (CTC)-derived xenografts from SCLC patients using scRNA-seq of chemosensitive and chemoresistant CTC-derived xenografts suggests increased intratumoural heterogeneity following therapy resistance. Multiple subsets of unique SCLC cells may develop within a tumour and there needs further consideration of diverse therapeutic strategies to maximize treatment response before the development of resistance mechanisms [105]. With the era of precision medicine well underway, SCLC patients have yet to have benefited from the promise of various targeted therapies. Subtype identification for SCLC has yielded promising targets that require further interrogation [97,98]. As SCLC moves towards being considered a heterogeneous disease, subtype identification may help select patients that may benefit maximally from a particular treatment and reduce the failure rate of clinical trials. With more SCLC subtypes being defined to enable precision medicine [97,98], it is also key for clinicians to consider how to effectively recruit for and design statistically sound clinical trials. However, it remains a challenge to find effective therapeutic strategies for LS-SCLC given a significant majority of studies are focused on ES-SCLC.

As the throughput of scRNA-seq technologies improve in parallel with falling costs, tumour heterogeneity can be further explored to reveal new subtypes of SCLC and their plasticity to deliver on the promise of precision medicine. More crucially, the integration and innovation with radiation in combination with chemotherapy and novel therapeutics represent the next frontier in managing LS-SCLC patients. While this remains an exciting prospect, prospective studies to carefully consider the benefit to LS-SCLC patients while managing tolerability will be necessary.

6. Conclusions

Novel treatment options for LS-SCLC patients remain promising but compartmentalized as a majority of novel treatments are tested first in ES-SCLC. The landscape of LS-SCLC can be transformed with the integration of new targeted therapeutics and immunotherapies to standard-of-care concurrent chemoradiation. Prospective studies are eagerly awaited to determine the routine use of PCI in the MRI era, novel radiation techniques such as HA-PCI, proton therapy, SRS, and SBRT, along with the ideal dose fractionation schedule for LS-SCLC patients. In order to capture tumour heterogeneity, scRNA-seq in addition to bulk sequencing technologies may improve SCLC subtype identification which may lead to biomarker-selected clinical trials. Despite the longstanding challenges with the management of LS-SCLC, novel approaches to treatment and biology are poised to bring much needed improvement to patient outcomes.

Author Contributions: T.S.T. and B.H.L. designed the review outline, wrote the review, did the literature search, designed the tables, and carried out data extraction and interpretation. All authors have read and agreed to the published version of the manuscript.

Funding: B.H.L. acknowledges research support from the Conquer Cancer Foundation of ASCO, International Association for the Study of Lung Cancer (IASLC), Ontario Molecular Pathology Research Network of the Ontario Institute for Cancer Research, Lung Cancer Research Foundation, Canada Foundation for Innovation (CFI#38347), Cancer Research Society, Canadian Institutes of Health Research (PJT169200), National Institute of Health/National Cancer Institute (U01CA253383), and the Clinical and Translational Science Center at Weill Cornell Medical Center and MSKCC (UL1TR00457).

Conflicts of Interest: B.H.L. discloses funding and honoraria from AstraZeneca and funding from Pfizer. T.S.T. declares no conflict of interest.

References

- Ahmad, I.; Chufal, K.S.; Gupta, S.; Bhatt, C.P. Defining Limited Stage Small Cell Lung Cancer: A Radiation Oncologist's Perspective. *BMJ Case Rep.* **2018**, *2018*. [[CrossRef](#)] [[PubMed](#)]
- Rudin, C.M.; Brambilla, E.; Faivre-Finn, C.; Sage, J. Small-Cell Lung Cancer. *Nat. Rev. Dis. Primers* **2021**, *7*, 3. [[CrossRef](#)] [[PubMed](#)]
- Furrukh, M. Tobacco Smoking and Lung Cancer: Perception-Changing Facts. *Sultan Qaboos Univ. Med. J.* **2013**, *13*, 345–358. [[CrossRef](#)] [[PubMed](#)]
- Anna, F.; Farago, F.K.K. Current Standards for Clinical Management of Small Cell Lung Cancer. *Transl. Lung Cancer Res.* **2018**, *7*, 69.
- Turrisi, A.T., 3rd; Kim, K.; Blum, R.; Sause, W.T.; Livingston, R.B.; Komaki, R.; Wagner, H.; Aisner, S.; Johnson, D.H. Twice-Daily Compared with Once-Daily Thoracic Radiotherapy in Limited Small-Cell Lung Cancer Treated Concurrently with Cisplatin and Etoposide. *N. Engl. J. Med.* **1999**, *340*, 265–271. [[CrossRef](#)] [[PubMed](#)]
- Faivre-Finn, C.; Snee, M.; Ashcroft, L.; Appel, W.; Barlesi, F.; Bhatnagar, A.; Bezjak, A.; Cardenal, F.; Fournel, P.; Harden, S.; et al. Concurrent Once-Daily versus Twice-Daily Chemoradiotherapy in Patients with Limited-Stage Small-Cell Lung Cancer (CONVERT): An Open-Label, Phase 3, Randomised, Superiority Trial. *Lancet Oncol.* **2017**, *18*, 1116–1125. [[CrossRef](#)]
- Noronha, V.; Sekhar, A.; Patil, V.M.; Menon, N.; Joshi, A.; Kapoor, A.; Prabhaskar, K. Systemic Therapy for Limited Stage Small Cell Lung Carcinoma. *J. Thorac. Dis.* **2020**, *12*, 6275. [[CrossRef](#)] [[PubMed](#)]
- Warde, P.; Payne, D. Does Thoracic Irradiation Improve Survival and Local Control in Limited-Stage Small-Cell Carcinoma of the Lung? A Meta-Analysis. *J. Clin. Oncol.* **1992**, *10*, 890–895. [[CrossRef](#)]
- Pignon, J.P.; Arriagada, R.; Ihde, D.C.; Johnson, D.H.; Perry, M.C.; Souhami, R.L.; Brodin, O.; Joss, R.A.; Kies, M.S.; Lebeau, B. A Meta-Analysis of Thoracic Radiotherapy for Small-Cell Lung Cancer. *N. Engl. J. Med.* **1992**, *327*, 1618–1624. [[CrossRef](#)]
- Murray, N.; Coy, P.; Pater, J.L.; Hodson, I.; Arnold, A.; Zee, B.C.; Payne, D.; Kostashuk, E.C.; Evans, W.K.; Dixon, P. Importance of Timing for Thoracic Irradiation in the Combined Modality Treatment of Limited-Stage Small-Cell Lung Cancer. The National Cancer Institute of Canada Clinical Trials Group. *J. Clin. Oncol.* **1993**, *11*, 336–344. [[CrossRef](#)]
- Fried, D.B.; Morris, D.E.; Poole, C.; Rosenman, J.G.; Halle, J.S.; Detterbeck, F.C.; Hensing, T.A.; Socinski, M.A. Systematic Review Evaluating the Timing of Thoracic Radiation Therapy in Combined Modality Therapy for Limited-Stage Small-Cell Lung Cancer. *J. Clin. Oncol.* **2004**, *22*, 4837–4845. [[CrossRef](#)] [[PubMed](#)]
- Bogart, J.A.; Wang, X.F.; Masters, G.A.; Gao, J.; Komaki, R.; Kuzma, C.S.; Heymach, J.; Petty, W.J.; Gaspar, L.E.; Waqar, S.N.; et al. Phase 3 Comparison of High-Dose Once-Daily (QD) Thoracic Radiotherapy (TRT) with Standard Twice-Daily (BID) TRT in Limited Stage Small Cell Lung Cancer (LSCLC): CALGB 30610 (Alliance)/RTOG 0538. *J. Clin. Oncol.* **2021**, *39*, 8505. [[CrossRef](#)]
- High-Dose versus Standard-Dose Twice-Daily Thoracic Radiotherapy for Patients with Limited Stage Small-Cell Lung Cancer: An Open-Label, Randomised, Phase 2 Trial. *Lancet Oncol.* **2021**, *22*, 321–331. [[CrossRef](#)]
- Shahi, J.; Wright, J.R.; Gabos, Z.; Swaminath, A. Management of Small-Cell Lung Cancer with Radiotherapy—a Pan-Canadian Survey of Radiation Oncologists. *Curr. Oncol.* **2016**, *23*, 184. [[CrossRef](#)] [[PubMed](#)]
- Yan, M.; Sigurdson, S.; Greifer, N.; Kennedy, T.A.C.; Toh, T.S.; Lindsay, P.E.; Weiss, J.; Hueniken, K.; Yeung, C.; Sugumar, V.; et al. A Comparison of Hypofractionated and Twice-Daily Thoracic Irradiation in Limited-Stage Small-Cell Lung Cancer: An Overlap-Weighted Analysis. *Cancers* **2021**, *13*, 2895. [[CrossRef](#)] [[PubMed](#)]
- Farrell, M.J.; Yahya, J.B.; Degnin, C.; Chen, Y.; Holland, J.M.; Henderson, M.A.; Jaboin, J.J.; Harkenrider, M.M.; Thomas, C.R., Jr.; Mitin, T. Radiation Dose and Fractionation for Limited-Stage Small-Cell Lung Cancer: Survey of US Radiation Oncologists on Practice Patterns. *Clin. Lung Cancer* **2019**, *20*, 13–19. [[CrossRef](#)] [[PubMed](#)]
- Gronberg, B.H.; Killingberg, K.T.; Fløtten, Ø.; Bjaanaes, M.M.; Madebo, T.; Langer, S.; Schytte, T.; Brustugun, O.T.; Nyman, J.; Stokke, K.; et al. Randomized Phase II Trial Comparing the Efficacy of Standard-Dose with High-Dose Twice-Daily Thoracic Radiotherapy (TRT) in Limited Disease Small-Cell Lung Cancer (LD SCLC). *J. Clin. Oncol.* **2020**, *38*, 9007. [[CrossRef](#)]
- Aupérin, A.; Arriagada, R.; Pignon, J.P.; Le Péchoux, C.; Gregor, A.; Stephens, R.J.; Kristjansen, P.E.; Johnson, B.E.; Ueoka, H.; Wagner, H.; et al. Prophylactic Cranial Irradiation for Patients with Small-Cell Lung Cancer in Complete Remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N. Engl. J. Med.* **1999**, *341*, 476–484. [[CrossRef](#)] [[PubMed](#)]
- Pezzi, T.A.; Fang, P.; Gjyshi, O.; Feng, L.; Liu, S.; Komaki, R.; Lin, S.H. Rates of Overall Survival and Intracranial Control in the Magnetic Resonance Imaging Era for Patients with Limited-Stage Small Cell Lung Cancer with and without Prophylactic Cranial Irradiation. *JAMA Netw. Open* **2020**, *3*, e201929. [[CrossRef](#)]
- Takahashi, T.; Yamanaka, T.; Seto, T.; Harada, H.; Nokihara, H.; Saka, H.; Nishio, M.; Kaneda, H.; Takayama, K.; Ishimoto, O.; et al. Prophylactic Cranial Irradiation versus Observation in Patients with Extensive-Disease Small-Cell Lung Cancer: A Multicentre, Randomised, Open-Label, Phase 3 Trial. *Lancet Oncol.* **2017**, *18*, 663–671. [[CrossRef](#)]
- Koh, M.; Song, S.Y.; Jo, J.H.; Park, G.; Park, J.W.; Kim, S.S.; Choi, E.K. The Value of Prophylactic Cranial Irradiation in Limited-Stage Small Cell Lung Cancer: Should It Always Be Recommended? *Radiat. Oncol. J.* **2019**, *37*, 156. [[CrossRef](#)] [[PubMed](#)]
- Wu, A.J.; Gillis, A.; Foster, A.; Woo, K.; Zhang, Z.; Gelblum, D.Y.; Downey, R.J.; Rosenzweig, K.E.; Ong, L.; Perez, C.A.; et al. Patterns of Failure in Limited-Stage Small Cell Lung Cancer: Implications of TNM Stage for Prophylactic Cranial Irradiation. *Radiation Oncol.* **2017**, *125*, 130–135. [[CrossRef](#)] [[PubMed](#)]
- Giuliani, M.; Sun, A.; Bezjak, A.; Ma, C.; Le, L.W.; Brade, A.; Cho, J.; Leigh, N.B.; Shepherd, F.A.; Hope, A.J. Utilization of Prophylactic Cranial Irradiation in Patients with Limited Stage Small Cell Lung Carcinoma. *Cancer* **2010**, *116*, 5694–5699. [[CrossRef](#)]

24. Yan, M.; Toh, T.S.; Lindsay, P.E.; Weiss, J.; Hueniken, K.; Yeung, C.; Sugumar, V.; Pinto, D.; Tadic, T.; Sun, A.; et al. Limited-Stage Small Cell Lung Cancer: Outcomes Associated with Prophylactic Cranial Irradiation over a 20-Year Period at the Princess Margaret Cancer Centre. *Clin. Transl. Radiat. Oncol.* **2021**, *30*, 43–49. [[CrossRef](#)]
25. Lok, B.H.; Ma, J.; Foster, A.; Perez, C.A.; Shi, W.; Zhang, Z.; Li, B.T.; Rudin, C.M.; Rimner, A.; Wu, A.J. Factors Influencing the Utilization of Prophylactic Cranial Irradiation in Patients with Limited-Stage Small Cell Lung Cancer. *Adv. Radiat. Oncol.* **2017**, *2*, 548–554. [[CrossRef](#)] [[PubMed](#)]
26. Ozawa, Y.; Omae, M.; Fujii, M.; Matsui, T.; Kato, M.; Sagisaka, S.; Asada, K.; Karayama, M.; Shirai, T.; Yasuda, K.; et al. 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. [[CrossRef](#)]
27. Farris, M.K.; Wheless, W.H.; Hughes, R.T.; Soike, M.H.; Masters, A.H.; Helis, C.A.; Chan, M.D.; Cramer, C.K.; Ruiz, J.; Lycan, T.; et al. Limited-Stage Small Cell Lung Cancer: Is Prophylactic Cranial Irradiation Necessary? *Pract. Radiat. Oncol.* **2019**, *9*, e599–e607. [[CrossRef](#)]
28. Slotman, B.; Faivre-Finn, C.; Kramer, G.; Rankin, E.; Snee, M.; Hatton, M.; Postmus, P.; Collette, L.; Musat, E.; Senan, S. Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer. *N. Engl. J. Med.* **2007**, *357*, 664–672. [[CrossRef](#)]
29. Redmond, K.J.; Hales, R.K.; Anderson-Keightly, H.; Zhou, X.C.; Kummerlowe, M.; Sair, H.I.; Duhon, M.; Kleinberg, L.; Rosner, G.L.; Vannorsdall, T. Prospective Study of Hippocampal-Sparing Prophylactic Cranial Irradiation in Limited-Stage Small Cell Lung Cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2017**, *98*, 603–611. [[CrossRef](#)]
30. Levy, A.; Le Pêchoux, C.; Mistry, H.; Martel-Lafay, I.; Bezjak, A.; Lerouge, D.; Padovani, L.; Taylor, P.; Faivre-Finn, C. Prophylactic Cranial Irradiation for Limited-Stage Small-Cell Lung Cancer Patients: Secondary Findings from the Prospective Randomized Phase 3 CONVERT Trial. *J. Thorac. Oncol.* **2019**, *14*, 294–297. [[CrossRef](#)] [[PubMed](#)]
31. 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. [[CrossRef](#)] [[PubMed](#)]
32. Farooqi, A.S.; Holliday, E.B.; Allen, P.K.; Wei, X.; Cox, J.D.; Komaki, R. Prophylactic Cranial Irradiation after Definitive Chemoradiotherapy for Limited-Stage Small Cell Lung Cancer: Do All Patients Benefit? *Radiother. Oncol.* **2017**, *122*, 307–312. [[CrossRef](#)] [[PubMed](#)]
33. Shirvani, S.M.; Juloori, A.; Allen, P.K.; Komaki, R.; Liao, Z.; Gomez, D.; O'Reilly, M.; Welsh, J.; Papadimitrakopoulou, V.; Cox, J.D.; et al. Comparison of 2 Common Radiation Therapy Techniques for Definitive Treatment of Small Cell Lung Cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2013**, *87*, 139–147. [[CrossRef](#)] [[PubMed](#)]
34. Rodríguez de Dios, N.; Couñago, F.; Murcia-Mejía, M.; Rico-Oses, M.; Calvo-Crespo, P.; Samper, P.; Vallejo, C.; Luna, J.; Trueba, I.; Sotoca, A.; et al. Randomized Phase III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECF-SEOR Study. *J. Clin. Oncol.* **2021**, *39*, 3118–3127. [[CrossRef](#)] [[PubMed](#)]
35. Amy, C.; Moreno, S.H.L. The Optimal Treatment Approaches for Stage I Small Cell Lung Cancer. *Transl. Lung Cancer Res.* **2019**, *8*, 88.
36. Timmerman, R.; Paulus, R.; Galvin, J.; Michalski, J.; Straube, W.; Bradley, J.; Fakiris, A.; Bezjak, A.; Videtic, G.; Johnstone, D.; et al. Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer. *JAMA* **2010**, *303*, 1070. [[CrossRef](#)] [[PubMed](#)]
37. Chang, J.Y.; Senan, S.; Paul, M.A.; Mehran, R.J.; Louie, A.V.; Balter, P.; Groen, H.J.M.; McRae, S.E.; Widder, J.; Feng, L.; et al. Stereotactic Ablative Radiotherapy versus Lobectomy for Operable Stage I Non-Small-Cell Lung Cancer: A Pooled Analysis of Two Randomised Trials. *Lancet Oncol.* **2015**, *16*, 630–637. [[CrossRef](#)]
38. Shioyama, Y.; Nakamura, K.; Sasaki, T.; Ohga, S.; Yoshitake, T.; Nonoshita, T.; Asai, K.; Terashima, K.; Matsumoto, K.; Hirata, H.; et al. Clinical Results of Stereotactic Body Radiotherapy for Stage I Small-Cell Lung Cancer: A Single Institutional Experience. *J. Radiat. Res.* **2013**, *54*, 108–112. [[CrossRef](#)]
39. Videtic, G.M.; Stephans, K.L.; Woody, N.M.; Pennell, N.A.; Shapiro, M.; Reddy, C.A.; Djemil, T. Stereotactic Body Radiation Therapy-Based Treatment Model for Stage I Medically Inoperable Small Cell Lung Cancer. *Pract. Radiat. Oncol.* **2013**, *3*, 301–306. [[CrossRef](#)]
40. Verma, V.; Simone, C.B., 2nd; Allen, P.K.; Lin, S.H. 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.e1. [[CrossRef](#)]
41. Guidelines Detail. Available online: <https://www.nccn.org/guidelines/guidelines-detail> (accessed on 4 October 2021).
42. Recommendations | Lung Cancer: Diagnosis and Management | Guidance | NICE. Available online: <https://www.nice.org.uk/guidance/ng122/chapter/recommendations> (accessed on 4 October 2021).
43. Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-Line Chemotherapy. Available online: <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/49411> (accessed on 27 October 2021).
44. Bradley, J.D.; Paulus, R.; Komaki, R.; Masters, G.; Blumenschein, G.; Schild, S.; Bogart, J.; Hu, C.; Forster, K.; Magliocco, A.; et al. Standard-Dose versus High-Dose Conformal Radiotherapy with Concurrent and Consolidation Carboplatin plus Paclitaxel with or without Cetuximab for Patients with Stage IIIA or IIIB Non-Small-Cell Lung Cancer (RTOG 0617): A Randomised, Two-by-Two Factorial Phase 3 Study. *Lancet Oncol.* **2015**, *16*, 187–199.

45. Rwigema, J.-C.M.; Verma, V.; Lin, L.; Berman, A.T.; Levin, W.P.; Evans, T.L.; Aggarwal, C.; Rengan, R.; Langer, C.; Cohen, R.B.; et al. Prospective Study of Proton-Beam Radiation Therapy for Limited-Stage Small Cell Lung Cancer. *Cancer* **2017**, *123*, 4244–4251. [[CrossRef](#)] [[PubMed](#)]
46. Andrews, D.W.; Scott, C.B.; Sperduto, P.W.; Flanders, A.E.; Gaspar, L.E.; Schell, M.C.; Werner-Wasik, M.; Demas, W.; Ryu, J.; Bahary, J.P.; et al. Whole Brain Radiation Therapy with or without Stereotactic Radiosurgery Boost for Patients with One to Three Brain Metastases: Phase III Results of the RTOG 9508 Randomised Trial. *Lancet* **2004**, *363*, 1665–1672. [[CrossRef](#)]
47. Rusthoven, C.G.; Yamamoto, M.; Bernhardt, D.; Smith, D.E.; Gao, D.; Serizawa, T.; Yomo, S.; Aiyama, H.; Higuchi, Y.; Shuto, T.; et al. 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. [[CrossRef](#)]
48. Paez, J.G.; Jänne, P.A.; Lee, J.C.; Tracy, S.; Greulich, H.; Gabriel, S.; Herman, P.; Kaye, F.J.; Lindeman, N.; Boggon, T.J.; et al. EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy. *Science* **2004**, *304*, 1497–1500. [[CrossRef](#)]
49. Paez, J.G.; Kwak, E.L.; Bergethon, K.; Drilon, A.; Stephens, P.; Takahashi, T.; Sanchez-Cespedes, M.; Shapiro, G.I.; Singh, A.; Medina, P.P.; et al. Comprehensive Molecular Profiling of Lung Adenocarcinoma. *Nature* **2014**, *511*, 543–550.
50. Lynch, T.J.; Bell, D.W.; Sordella, R.; Gurubhagavatula, S.; Okimoto, R.A.; Brannigan, B.W.; Harris, P.L.; Haserlat, S.M.; Supko, J.G.; Haluska, F.G.; et al. Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib. *N. Engl. J. Med.* **2004**, *350*, 2129–2139. [[CrossRef](#)]
51. Piperdi, B.; Perez-Soler, R. Role of Erlotinib in the Treatment of Non-Small Cell Lung Cancer: Clinical Outcomes in Wild-Type Epidermal Growth Factor Receptor Patients. *Drugs* **2012**, *72* (Suppl. 1), 11–19. [[CrossRef](#)] [[PubMed](#)]
52. Maemondo, M.; Inoue, A.; Kobayashi, K.; Sugawara, S.; Oizumi, S.; Isobe, H.; Gemma, A.; Harada, M.; Yoshizawa, H.; Kinoshita, I.; et al. Gefitinib or Chemotherapy for Non-Small-Cell Lung Cancer with Mutated EGFR. *N. Engl. J. Med.* **2010**, *362*, 2380–2388. [[CrossRef](#)] [[PubMed](#)]
53. Shepherd, F.A.; Rodrigues, P.J.; Ciuleanu, T.; Tan, E.H.; Hirsh, V.; Thongprasert, S.; Campos, D.; Maoleekoonpiroj, S.; Smylie, M.; Martins, R.; et al. Erlotinib in Previously Treated Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2005**, *353*, 123–132. [[CrossRef](#)]
54. Mok, T.S.K. Personalized Medicine in Lung Cancer: What We Need to Know. *Nat. Rev. Clin. Oncol.* **2011**, *8*, 661–668. [[CrossRef](#)] [[PubMed](#)]
55. Thomas, A.; Liu, S.V.; Subramaniam, D.S.; Giaccone, G. Refining the Treatment of NSCLC according to Histological and Molecular Subtypes. *Nat. Rev. Clin. Oncol.* **2015**, *12*, 511–526. [[CrossRef](#)] [[PubMed](#)]
56. Reck, M.; Rodríguez-Abreu, D.; Robinson, A.G.; Hui, R.; Csőszi, T.; Fülöp, A.; Gottfried, M.; Peled, N.; Tafreshi, A.; Cuffe, S.; et al. Five-Year Outcomes with Pembrolizumab versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer with PD-L1 Tumor Proportion Score $\geq 50\%$. *J. Clin. Oncol.* **2021**, *39*, 2339–2349. [[CrossRef](#)]
57. Carbone, D.P.; Reck, M.; Paz-Ares, L.; Creelan, B.; Horn, L.; Steins, M.; Felip, E.; van den Heuvel, M.M.; Ciuleanu, T.-E.; Badin, F.; et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2017**, *376*, 2415. [[CrossRef](#)] [[PubMed](#)]
58. Herbst, R.S.; Giaccone, G.; de Marinis, F.; Reinmuth, N.; Vergnenegre, A.; Barrios, C.H.; Morise, M.; Felip, E.; Andric, Z.; Geater, S.; et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. *N. Engl. J. Med.* **2020**, *383*, 1328–1339. [[CrossRef](#)] [[PubMed](#)]
59. Grant, M.J.; Herbst, R.S.; Goldberg, S.B. Selecting the Optimal Immunotherapy Regimen in Driver-Negative Metastatic NSCLC. *Nat. Rev. Clin. Oncol.* **2021**, *18*, 625–644. [[CrossRef](#)] [[PubMed](#)]
60. Taniguchi, H.; Sen, T.; Rudin, C.M. Targeted Therapies and Biomarkers in Small Cell Lung Cancer. *Front. Oncol.* **2020**, *10*, 741. [[CrossRef](#)] [[PubMed](#)]
61. Byers, L.A.; Wang, J.; Nilsson, M.B.; Fujimoto, J.; Saintigny, P.; Yordy, J.; Giri, U.; Peyton, M.; Fan, Y.H.; Diao, L.; et al. Proteomic Profiling Identifies Dysregulated Pathways in Small Cell Lung Cancer and Novel Therapeutic Targets Including PARP1. *Cancer Discov.* **2012**, *2*, 798. [[CrossRef](#)] [[PubMed](#)]
62. Lok, B.H.; Gardner, E.E.; Schneeberger, V.E.; Ni, A.; Desmeules, P.; Rekhman, N.; de Stanchina, E.; Teicher, B.A.; Riaz, N.; Powell, S.N.; et al. PARP Inhibitor Activity Correlates with SLFN11 Expression and Demonstrates Synergy with Temozolomide in Small Cell Lung Cancer. *Clin. Cancer Res.* **2017**, *23*, 523–535. [[CrossRef](#)]
63. Cardnell, R.J.; Feng, Y.; Mukherjee, S.; Diao, L.; Tong, P.; Stewart, C.A.; Masrourpour, F.; Fan, Y.; Nilsson, M.; Shen, Y.; et al. Activation of the PI3K/mTOR Pathway Following PARP Inhibition in Small Cell Lung Cancer. *PLoS ONE* **2016**, *11*, e0152584. [[CrossRef](#)]
64. Gardner, E.E.; Lok, B.H.; Schneeberger, V.E.; Desmeules, P.; Miles, L.A.; Arnold, P.K.; Ni, A.; Khodos, I.; de Stanchina, E.; Nguyen, T.; et al. Chemosensitive Relapse in Small Cell Lung Cancer Proceeds through an EZH2-SLFN11 Axis. *Cancer Cell* **2017**, *31*, 286–299. [[CrossRef](#)] [[PubMed](#)]
65. Allison Stewart, C.; Tong, P.; Cardnell, R.J.; Sen, T.; Li, L.; Gay, C.M.; Masrourpour, F.; Fan, Y.; Bara, R.O.; Feng, Y.; et al. Dynamic Variations in Epithelial-to-Mesenchymal Transition (EMT), ATM, and SLFN11 Govern Response to PARP Inhibitors and Cisplatin in Small Cell Lung Cancer. *Oncotarget* **2017**, *8*, 28575–28587. [[CrossRef](#)] [[PubMed](#)]
66. Murai, J.; Feng, Y.; Yu, G.K.; Ru, Y.; Tang, S.-W.; Shen, Y.; Pommier, Y. Resistance to PARP Inhibitors by SLFN11 Inactivation Can Be Overcome by ATR Inhibition. *Oncotarget* **2016**, *7*, 76534–76550. [[CrossRef](#)] [[PubMed](#)]

67. Owonikoko, T.K.; Niu, H.; Nackaerts, K.; Csoszi, T.; Ostoros, G.; Mark, Z.; Baik, C.; Joy, A.A.; Chouaid, C.; Jaime, J.C.; et al. Randomized Phase II Study of Paclitaxel plus Alisertib versus Paclitaxel plus Placebo as Second-Line Therapy for SCLC: Primary and Correlative Biomarker Analyses. *J. Thorac. Oncol.* **2020**, *15*, 274–287. [[CrossRef](#)] [[PubMed](#)]
68. Mollaoglu, G.; Guthrie, M.R.; Böhm, S.; Brägelmann, J.; Can, I.; Ballieu, P.M.; Marx, A.; George, J.; Heinen, C.; Chalisehar, M.D.; et al. MYC Drives Progression of Small Cell Lung Cancer to a Variant Neuroendocrine Subtype with Vulnerability to Aurora Kinase Inhibition. *Cancer Cell* **2017**, *31*, 270–285. [[CrossRef](#)] [[PubMed](#)]
69. Patel, S.; Petty, W.J.; Sands, J.M. An Overview of Lurbinectedin as a New Second-Line Treatment Option for Small Cell Lung Cancer. *Ther. Adv. Med. Oncol.* **2021**, *13*, 17588359211020529. [[CrossRef](#)]
70. Eckardt, J.R.; von Pawel, J.; Pujol, J.-L.; Papai, Z.; Quoix, E.; Ardizzoni, A.; Poulin, R.; Preston, A.J.; Dane, G.; Ross, G. Phase III Study of Oral Compared with Intravenous Topotecan as Second-Line Therapy in Small-Cell Lung Cancer. *J. Clin. Oncol.* **2007**, *25*, 2086–2092. [[CrossRef](#)] [[PubMed](#)]
71. O'Brien, M.E.R.; Ciuleanu, T.-E.; Tsekov, H.; Shparyk, Y.; Cuceviá, B.; Juhasz, G.; Thatcher, N.; Ross, G.A.; Dane, G.C.; 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. [[CrossRef](#)]
72. von Pawel, J.; Schiller, J.H.; Shepherd, F.A.; Fields, S.Z.; Kleisbauer, J.P.; Chrysson, N.G.; Stewart, D.J.; Clark, P.I.; Palmer, M.C.; Depierre, A.; et al. Topotecan versus Cyclophosphamide, Doxorubicin, and Vincristine for the Treatment of Recurrent Small-Cell Lung Cancer. *J. Clin. Oncol.* **1999**, *17*, 658–667. [[CrossRef](#)]
73. Trigo, J.; Subbiah, V.; Besse, B.; Moreno, V.; López, R.; Sala, M.A.; Peters, S.; Ponce, S.; Fernández, C.; Alfaro, V.; et al. Lurbinectedin as Second-Line Treatment for Patients with Small-Cell Lung Cancer: A Single-Arm, Open-Label, Phase 2 Basket Trial. *Lancet Oncol.* **2020**, *21*, 645–654. [[CrossRef](#)]
74. Elez, M.E.; Tabernero, J.; Geary, D.; Macarulla, T.; Kang, S.P.; Kahatt, C.; Pita, A.S.-M.; Teruel, C.F.; Siguero, M.; Cullell-Young, M.; et al. First-in-Human Phase I Study of Lurbinectedin (PM01183) in Patients with Advanced Solid Tumors. *Clin. Cancer Res.* **2014**, *20*, 2205–2214. [[CrossRef](#)]
75. George, J.; Lim, J.S.; Jang, S.J.; Cun, Y.; Ozretić, L.; Kong, G.; Leenders, F.; Lu, X.; Fernández-Cuesta, L.; Bosco, G.; et al. Comprehensive Genomic Profiles of Small Cell Lung Cancer. *Nature* **2015**, *524*, 47–53. [[CrossRef](#)] [[PubMed](#)]
76. Saunders, L.R.; Bankovich, A.J.; Anderson, W.C.; Aujay, M.A.; Bheddah, S.; Black, K.; Desai, R.; Escarpe, P.A.; Hampl, J.; Laysang, A.; et al. A DLL3-Targeted Antibody-Drug Conjugate Eradicates High-Grade Pulmonary Neuroendocrine Tumor-Initiating Cells In Vivo. *Sci. Transl. Med.* **2015**, *7*, 302ra136. [[CrossRef](#)] [[PubMed](#)]
77. Rudin, C.M.; Pietanza, M.C.; Bauer, T.M.; Ready, N.; Morgensztern, D.; Glisson, B.S.; Byers, L.A.; Johnson, M.L.; Burris, H.A.; Robert, F.; et al. 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. [[CrossRef](#)]
78. Morgensztern, D.; Besse, B.; Greillier, L.; Santana-Davila, R.; Ready, N.; Hann, C.L.; Glisson, B.S.; Farago, A.F.; Dowlati, A.; Rudin, C.M.; et al. Efficacy and Safety of Rovalpituzumab Tesirine in Third-Line and Beyond Patients with DLL3-Expressing, Relapsed/Refractory Small-Cell Lung Cancer: Results from the Phase II TRINITY Study. *Clin. Cancer Res.* **2019**, *25*, 6958–6966. [[CrossRef](#)] [[PubMed](#)]
79. Blackhall, F.; Jao, K.; Greillier, L.; Cho, B.C.; Penkov, K.; Reguart, N.; Majem, M.; Nackaerts, K.; Syrigos, K.; Hansen, K.; et al. Efficacy and Safety of Rovalpituzumab Tesirine Compared with Topotecan as Second-Line Therapy in DLL3-High SCLC: Results from the Phase 3 TAOHE Study. *J. Thorac. Oncol.* **2021**, *16*, 1547–1558. [[CrossRef](#)] [[PubMed](#)]
80. Malhotra, J.; Nikolinakos, P.; Leal, T.; Lehman, J.; Morgensztern, D.; Patel, J.D.; Wrangle, J.M.; Curigliano, G.; Greillier, L.; Johnson, M.L.; et al. A Phase 1–2 Study of Rovalpituzumab Tesirine in Combination with Nivolumab Plus or Minus Ipilimumab in Patients with Previously Treated Extensive-Stage SCLC. *J. Thorac. Oncol.* **2021**, *16*, 1559–1569. [[CrossRef](#)] [[PubMed](#)]
81. Hann, C.L.; Burns, T.F.; Dowlati, A.; Morgensztern, D.; Ward, P.J.; Koch, M.M.; Chen, C.; Ludwig, C.; Patel, M.; Nimeiri, H.; et al. A Phase 1 Study Evaluating Rovalpituzumab Tesirine in Frontline Treatment of Patients WITH Extensive-Stage SCLC. *J. Thorac. Oncol.* **2021**, *16*, 1582–1588. [[CrossRef](#)]
82. Johnson, M.L.; Zvirbule, Z.; Laktionov, K.; Helland, A.; Cho, B.C.; Gutierrez, V.; Colinet, B.; Lena, H.; Wolf, M.; Gottfried, M.; et al. Rovalpituzumab Tesirine as a Maintenance Therapy after First-Line Platinum-Based Chemotherapy in Patients with Extensive-Stage-SCLC: Results from the Phase 3 MERU Study. *J. Thorac. Oncol.* **2021**, *16*, 1570–1581. [[CrossRef](#)]
83. Owonikoko, T.K.; Champiat, S.; Johnson, M.L.; Govindan, R.; Izumi, H.; Victoria Victoria Lai, W.; Borghaei, H.; Boyer, M.J.; Boosman, R.J.; Hummel, H.-D.; et al. Updated Results from a Phase 1 Study of AMG 757, a Half-Life Extended Bispecific T-Cell Engager (BiTE) Immuno-Oncology Therapy against Delta-like Ligand 3 (DLL3), in Small Cell Lung Cancer (SCLC). *J. Clin. Oncol.* **2021**, *39*, 8510. [[CrossRef](#)]
84. Esposito, G.; Palumbo, G.; Carillio, G.; Manzo, A.; Montanino, A.; Sforza, V.; Costanzo, R.; Sandomenico, C.; La Manna, C.; Martucci, N.; et al. Immunotherapy in Small Cell Lung Cancer. *Cancers* **2020**, *12*, 2522. [[CrossRef](#)]
85. Iams, W.T.; Porter, J.; Horn, L. Immunotherapeutic Approaches for Small-Cell Lung Cancer. *Nat. Rev. Clin. Oncol.* **2020**, *17*, 300–312. [[CrossRef](#)] [[PubMed](#)]
86. Arriola, E.; Wheeler, M.; Galea, I.; Cross, N.; Maishman, T.; Hamid, D.; Stanton, L.; Cave, J.; Geldart, T.; Mulatero, C.; et al. Outcome and Biomarker Analysis from a Multicenter Phase 2 Study of Ipilimumab in Combination with Carboplatin and Etoposide as First-Line Therapy for Extensive-Stage SCLC. *J. Thorac. Oncol.* **2016**, *11*, 1511–1521. [[CrossRef](#)]

87. Reck, M.; Luft, A.; Szczesna, A.; Havel, L.; Kim, S.-W.; Akerley, W.; Pietanza, M.C.; Wu, Y.-L.; Zielinski, C.; Thomas, M.; et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. *J. Clin. Oncol.* **2016**, *34*, 3740–3748. [[CrossRef](#)] [[PubMed](#)]
88. Horn, L.; Mansfield, A.S.; Szczesna, A.; Havel, L.; Krzakowski, M.; Hochmair, M.J.; Huemer, F.; Losonczy, G.; Johnson, M.L.; Nishio, M.; et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N. Engl. J. Med.* **2018**, *379*, 2220–2229. [[CrossRef](#)] [[PubMed](#)]
89. Glisson, B.; Besse, B.; Dols, M.C.; Dubey, S.; Schupp, M.; Jain, R.; Jiang, Y.; Menon, H.; Nackaerts, K.; Orlov, S.; et al. A Randomized, Placebo-Controlled, Phase 1b/2 Study of Rilatumumab or Ganitumab in Combination with Platinum-Based Chemotherapy as First-Line Treatment for Extensive-Stage Small-Cell Lung Cancer. *Clin. Lung Cancer* **2017**, *18*, 615–625.e8. [[CrossRef](#)] [[PubMed](#)]
90. Paz-Ares, L.; Dvorkin, M.; Chen, Y.; Reinmuth, N.; Hotta, K.; Trukhin, D.; Statsenko, G.; Hochmair, M.J.; Özgüroğlu, M.; Ji, J.H.; et al. Durvalumab plus Platinum-Etoposide versus Platinum-Etoposide in First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer (CASPIAN): A Randomised, Controlled, Open-Label, Phase 3 Trial. *Lancet* **2019**, *394*, 1929–1939. [[CrossRef](#)]
91. Rudin, C.M.; Awad, M.M.; Navarro, A.; Gottfried, M.; Peters, S.; Csösz, T.; Cheema, P.K.; Rodriguez-Abreu, D.; Wollner, M.; Yang, J.C.-H.; et al. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. *J. Clin. Oncol.* **2020**, *38*, 2369–2379. [[CrossRef](#)] [[PubMed](#)]
92. Gay, C.M.; Stewart, C.A.; Park, E.M.; Diao, L.; Groves, S.M.; Heeke, S.; Nabet, B.Y.; Fujimoto, J.; Solis, L.M.; Lu, W.; et al. Patterns of Transcription Factor Programs and Immune Pathway Activation Define Four Major Subtypes of SCLC with Distinct Therapeutic Vulnerabilities. *Cancer Cell* **2021**, *39*, 346–360.e7. [[CrossRef](#)]
93. Welsh, J.W.; Heymach, J.V.; Guo, C.; Menon, H.; Klein, K.; Cushman, T.R.; Verma, V.; Hess, K.R.; Shroff, G.; Tang, C.; et al. Phase 1/2 Trial of Pembrolizumab and Concurrent Chemoradiation Therapy for Limited-Stage SCLC. *J. Thorac. Oncol.* **2020**, *15*, 1919–1927. [[CrossRef](#)]
94. Peters, S.; Pujol, J.-L.; Dafni, U.; Dómine, M.; Popat, S.; Reck, M.; Andrade, J.; Becker, A.; Moro-Sibilot, D.; Curioni-Fontecedro, A.; et al. Consolidation Nivolumab and Ipilimumab versus Observation in Limited-Disease Small Cell Lung Cancer after Chemo-Radiotherapy - Results from the Randomised Phase II ETOP/IFCT 4-12 STIMULI Trial. *Ann. Oncol.* **2021**, in press. [[CrossRef](#)] [[PubMed](#)]
95. Senan, S.; Shire, N.; Mak, G.; Yao, W.; Jiang, H. ADRIATIC: A Phase III Trial of Durvalumab ± Tremelimumab after Concurrent Chemoradiation for Patients with Limited Stage Small Cell Lung Cancer. *Ann. Oncol.* **2019**, *30*, ii25. [[CrossRef](#)]
96. Ross, H.J.; Hu, C.; Higgins, K.A.; Jabbour, S.K.; Kozono, D.E.; Owonikoko, T.K.; Movsas, B.; Solberg, T.; Xiao, C.; Williams, T.M.; et al. NRG Oncology/Alliance LU005: A Phase II/III Randomized Clinical Trial of Chemoradiation versus Chemoradiation plus Atezolizumab in Limited Stage Small Cell Lung Cancer. *J. Clin. Oncol.* **2020**, *38*, TPS9082. [[CrossRef](#)]
97. Simpson, K.L.; Stoney, R.; Frese, K.K.; Simms, N.; Rowe, W.; Pearce, S.P.; Humphrey, S.; Booth, L.; Morgan, D.; Dynowski, M.; et al. A Biobank of Small Cell Lung Cancer CDX Models Elucidates Inter- and Intratumoral Phenotypic Heterogeneity. *Nat. Cancer* **2020**, *1*, 437–451. [[CrossRef](#)]
98. Rudin, C.M.; Poirier, J.T.; Byers, L.A.; Dive, C.; Dowlati, A.; George, J.; Heymach, J.V.; Johnson, J.E.; Lehman, J.M.; MacPherson, D.; et al. Molecular Subtypes of Small Cell Lung Cancer: A Synthesis of Human and Mouse Model Data. *Nat. Rev. Cancer* **2019**, *19*, 289–297. [[CrossRef](#)]
99. Iorio, F.; Knijnenburg, T.A.; Vis, D.J.; Bignell, G.R.; Menden, M.P.; Schubert, M.; Aben, N.; Gonçalves, E.; Barthorpe, S.; Lightfoot, H.; et al. A Landscape of Pharmacogenomic Interactions in Cancer. *Cell* **2016**, *166*, 740–754. [[CrossRef](#)] [[PubMed](#)]
100. Barretina, J.; Caponigro, G.; Stransky, N.; Venkatesan, K.; Margolin, A.A.; Kim, S.; Wilson, C.J.; Lehár, J.; Kryukov, G.V.; Sonkin, D.; et al. The Cancer Cell Line Encyclopedia Enables Predictive Modelling of Anticancer Drug Sensitivity. *Nature* **2012**, *483*, 603–607. [[CrossRef](#)]
101. Trapnell, C. Defining Cell Types and States with Single-Cell Genomics. *Genome Res.* **2015**, *25*, 1491–1498. [[CrossRef](#)]
102. Kolodziejczyk, A.A.; Kim, J.K.; Svensson, V.; Marion, J.C.; Teichmann, S.A. The Technology and Biology of Single-Cell RNA Sequencing. *Mol. Cell* **2015**, *58*, 610–620. [[CrossRef](#)]
103. Rozenblatt-Rosen, O.; Regev, A.; Oberdoerffer, P.; Nawy, T.; Hupalowska, A.; Rood, J.E.; Ashenberg, O.; Cerami, E.; Coffey, R.J.; Demir, E.; et al. The Human Tumor Atlas Network: Charting Tumor Transitions across Space and Time at Single-Cell Resolution. *Cell* **2020**, *181*, 236–249. [[CrossRef](#)]
104. Ireland, A.S.; Micinski, A.M.; Kastner, D.W.; Guo, B.; Wait, S.J.; Spainhower, K.B.; Conley, C.C.; Chen, O.S.; Guthrie, M.R.; Soltero, D.; et al. MYC Drives Temporal Evolution of Small Cell Lung Cancer Subtypes by Reprogramming Neuroendocrine Fate. *Cancer Cell* **2020**, *38*, 60–78.e12. [[CrossRef](#)] [[PubMed](#)]
105. Stewart, C.A.; Gay, C.M.; Xi, Y.; Sivajothi, S.; Sivakamasundari, V.; Fujimoto, J.; Bolisetty, M.; Hartsfield, P.M.; Balasubramanian, V.; Chalise, M.D.; et al. Single-Cell Analyses Reveal Increased Intratumoral Heterogeneity after the Onset of Therapy Resistance in Small-Cell Lung Cancer. *Nat. Cancer* **2020**, *1*, 423–436. [[CrossRef](#)] [[PubMed](#)]