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COMMENTARY

Top advances of the year: Small cell lung cancer

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Abstract

Lung cancer remains the leading cause of cancer-related mortality in both men and women. Small cell lung cancer (SCLC) is notorious for its early metastatic spread, aggressive biology, and high frequency of disease relapse, resulting in inferior outcomes. In the last few years, immunotherapy for extensive-stage SCLC has offered a glimmer of hope by improving survival by approximately 2 months. In 2024, therapeutic breakthroughs for SCLC led to a meaningful impact for patients, offering potential for long-term survival. Here, the authors report the top advances from 2024, including the practice-changing implementation of consolidative durvalumab immunotherapy for limited-stage SCLC, lessons learned from the timing of immunotherapy with radiation using LU-005, how the delta-like ligand 3 bispecific T-cell engager tarlatamab affects the relapsed landscape, the addition of lurbinectedin to atezolizumab immunotherapy for extensive-stage SCLC, and the promising role of antibody–drug conjugates. In a forward-thinking approach, the authors discuss the feasibility of biomarker selection with the Southwest Oncology Group SWOG S1929 study and how precision medicine may inform consolidative treatments for extensive-stage SCLC through neuroendocrine subtyping with the Southwest Oncology Group SWOG S2409 (PRISM) trial. Finally, they conclude with the exciting role of advocacy with the newly formed advocacy group *Small Cell SMASHERS*, amplifying support for SCLC. In 2024, the *scientific revolution* for SCLC has arrived, spearheading a new *era of change* for this disease.

Plain Language Summary

- Immunotherapy can improve survival in both limited-stage and extensive-stage small cell lung cancer.
- Targeting surface proteins and new combinations can improve survival.
- Neuroendocrine subtypes may inform treatment for small cell lung cancer, and studies are underway.
- Advocacy is important in a disease that has historically faced nihilism and stigma.

KEYWORDS
advocacy, antibody–drug conjugates, bispecific T-cell engagers, breakthroughs, immunotherapy, neuroendocrine subtypes, scientific revolution, small cell lung cancer, Small Cell SMASHERS, transcriptomics

CURRENT LANDSCAPE: IMMUNOTHERAPY IN EXTENSIVE-STAGE SMALL CELL LUNG CANCER

In 2024, lung cancer remained the leading cause of cancer-related mortality in both men and women.[1] Small cell lung cancer (SCLC) accounts for approximately 13%–15% of all lung cancers.[2–4] Despite decades of clinical trials, the treatment for de novo SCLC with a platinum–etoposide chemotherapy backbone has remained unchanged.[5,6] The advent of immunotherapy with atezolizumab (IMpower133; ClinicalTrials.gov identifier NCT02763579) and durvalumab (CASPIAN; ClinicalTrials.gov identifier NCT03043872) to platinum–etoposide induction followed by immunotherapy maintenance in 2018 and 2019, respectively, led to the *lifting of the curve* for extensive-stage SCLC (ES-SCLC; Figure 1).[7,8] Immunotherapy for ES-SCLC offered a glimmer of hope in a notoriously detrimental disease by improving survival by approximately 2 months.[7,8] In 2023, the phase 3 IMbrellA extension study (ClinicalTrials.gov identifier NCT03148418) reported a median overall survival (OS) of 12% at 5 years, representing the first major improvement in long-term outcomes for SCLC.[9]

Despite harboring a high tumor mutational burden secondary to chronic tobacco exposure, SCLC is an immune-cold tumor with inherently defective mechanisms for antigen presentation and processing.[10] Candidate biomarkers to determine the minority of patients who will benefit from immunotherapy with ES-SCLC have been proposed, with inflamed signatures and subtypes that have intact antigen presentation and processing, including major histocompatibility complex class I, immune checkpoint molecules, and immune cell infiltration.[11,12] Notably, the addition of immunotherapy (anti–PD-L1) to chemotherapy was associated with a doubling of survival in patients identified within the *inflamed* (SCLC-I) subtype, based on two major phase 3 trials (IMpower133 and CASPIAN).[11,13] However, more effective approaches to enhance immune-mediated tumor cell targeting are needed for the majority of patients with SCLC.

ADRIATIC: ADVANCING IMMUNOTHERAPY INTO LIMITED-STAGE SCLC

In 2024, the phase 3 randomized, double-blind, placebo-controlled study ADRIATIC, investigating the role of durvalumab consolidation every 4 weeks for up to 2 years, with or without tremelimumab, after completion of standard-of-care, concurrent, platinum-based chemoradiation (CCRT) for limited-stage SCLC (LS-SCLC), was reported at the annual American Society of Clinical Oncology conference (ClinicalTrials.gov identifier NCT03703297; Table 1).[14-26] The ADRIATIC regimen containing durvalumab resulted an impressive improvement in median OS by 22.5 months (55.9 vs 33.4 months; hazard ratio [HR], 0.73; 98.321% confidence interval [CI], 0.54–0.98; $p = .01$).[14] The arm containing the addition of durvalumab with tremelimumab was not reported.[14] The regimen was well tolerated, with no significant increase in grade 3/4 pneumonitis with the addition of durvalumab compared with placebo (3.1% vs. 2.6%, respectively).[14]

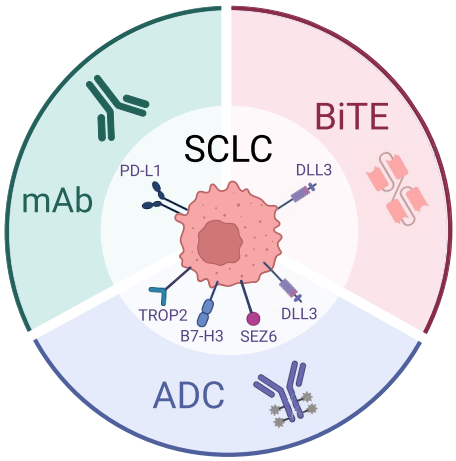

FIGURE 1 Depiction of the mechanism of action of novel agents in SCLC. ADC indicates antibody–drug conjugate; B7-H3, CD276; BiTE, bispecific T-cell engager; DLL3, delta-like ligand 3; mAb, monoclonal antibody; PD-L1, programmed death-ligand 1; SCLC, small cell lung cancer; SEZ6, seizure-related homolog 6; TROP2, tumor-associated calcium signal transducer 2.

The unprecedented shift in meaningful patient outcomes with the adjuvant use of durvalumab after CCRT in LS-SCLC quickly resulted in a practice-changing effect with implementation in national guidelines.[27] Durvalumab (Imfinzi; AstraZeneca) received US Food and Drug Administration (FDA) approval for this indication in LS-SCLC on December 4, 2024.[28]

LU-005: REFINING THE TIMING OF IMMUNOTHERAPY IN LS-SCLC

The timing of immunotherapy receipt in locally advanced lung cancer matters.[29,30] In 2024, the NRG Oncology/Alliance phase 3 study LU-005 (ClinicalTrials.gov identifier NCT03811002), exploring atezolizumab concurrently with CCRT followed by maintenance atezolizumab for 1 year in LS-SCLC, failed to make the same impact as ADRIATIC.[31] Unfortunately, the second planned interim analysis reported at the 2024 American Society for Radiation Oncology conference was statistically negative: atezolizumab did not improve its primary end point, and its addition to CCRT trended toward inferior outcomes (median OS, 33.1 vs. 39.5 months for atezolizumab plus CCRT and CCRT, respectively; HR, 1.11; 95% CI, 0.85–1.45).[31] No significant improvement was demonstrated in median progression-free survival (PFS) or distant metastasis-free survival with atezolizumab plus CCRT over CCRT.[31]

It is important to note that the design of ADRIATIC differed from LU-005, in that patients on ADRIATIC who had stable disease or a response to treatment were randomized to immunotherapy maintenance or placebo after completion of CCRT, whereas LU-005 enrolled patients who received one cycle of chemotherapy before registration on the study.[14,31] These differences in trial design also

TABLE 1 Top advances of the year for small cell lung cancer: Clinical trials with reported results.

Class of drug	Target	Investigational agent	Phase	Stage	Indication	ORR, %	PFS, months	OS, months	Study name	ClinicalTrials.gov identifier	Status
Immunotherapy	PD-L1 ± CTLA-4	Durvalumab (D) ± tremelimumab (Tr) vs. placebo (P) [Chen 2024[14] Spigel 2024[15]]	3	LS-SCLC	Consolidation after chemoradiation for up to 2 years	D vs. P: Median, 30.3 (95% CI, 23.6–37.7) vs. 32.0 (95% CI, 25.0–o 39.6)	D vs. P: Median, 16.6 (95% CI, 10.2–28.2) vs. 9.2 (95% CI, 7.4–12.9)	D vs. P: Median, 55.9 (95% CI, 37.3 to NR) vs. 33.4 (95% CI, 35.5–39.9)	ADRIATIC	NCT03703297	Active, not recruiting
						Tr: Not reported	Tr: Not reported	Tr: Not reported			
Bispecific T-cell engager	DLL3	Tarlatamab, dose finding [Amgen 2024[16]]	1	ES-SCLC	Relapsed/refractory	Median, 23.4 (95% CI, 15.7–32.5)	Median, 3.7 (95% CI, 2.1–5.4)	Median, 13.2 (95% CI, 10.5 to NR)	DeLLphi-300	NCT03319940	Active, not recruiting
		Tarlatamab, 10 vs. 100 mg [Ahn 2023[17]]	2	ES-SCLC	Relapsed/refractory	10 vs. 100 mg: Median, 55.0 vs. 57.0	10 vs. 100 mg: Median, 4.9 (95%, 2.9–6.7) vs. 3.9 (95% CI, 2.6–4.4)	Median, 9; OS: 10 vs. 100 mg, 68.0% vs. 66.0%	DeLLphi-301	NCT05060016	Active, not recruiting
		Tarlatamab 10 mg after carboplatin, etoposide, and PD-L1 inhibitor atezolizumab (A) or durvalumab (D) [Lau 2024[18]]	1b	ES-SCLC	First-line maintenance	NA	Landmark with first-line maintenance: A vs. D: 5.6 (3.5–8.5) vs. 5.3 (3.5 to NE)	Median, 9; OS, A vs. D: Median, 86.7% (95% CI, 70.3%–94.4%) vs. 91.8% (95% CI, 76.6%–97.3%)	DeLLphi-303	NCT05361395	Active, not recruiting
		BI 764532/obrixtamig in SCLC and other neuroendocrine neoplasms (NENs) expressing DLL3 [Wermke 2023,[19] 2024[20]]	1	ES-SCLC	Relapsed/refractory	SCLC, 50.0%; extrapulmonary neuroendocrine carcinomas (NECs), 56.0%; 70% large cell NECs, 70.0%	Median, 1.5 (95% CI, 1.4–2.4)	NA	NA	NCT04429087	Active, not recruiting
Trispecific T-cell activating construct		HPN328 in advanced cancers with DLL3 expression [Johnson 2022[21]]	1/2	ES-SCLC	Relapsed/refractory	Doses >1.215 mg: 50%	NA	NA	HPN328-4001	NCT04471727	Recruiting
Chemotherapy	RNA polymerase II, TME	Lurbinectedin/PM01183 + atezolizumab vs. atezolizumab alone after carboplatin, etoposide, and atezolizumab [Paz-Ares 20221,[22] Jazz Pharmaceuticals 2024[23]]	3	ES-SCLC	First-line maintenance	NA	Statistically positive (press release)	Statistically positive (press release)	IMforte	NCT05091567	Active, not recruiting
Antibody–drug conjugate	B7-H3	Ifinatamab deruxtecan [Johnson 2023[24]]	2	ES-SCLC	Relapsed/refractory	Median 52.4 (95% CI, 29.8–74.3)	Median, 5.6 (95% CI, 3.9–8.1)	Median, 12.2 (95% CI, 6.4 to NR)	IDeate-Lung01	NCT05280470	Active, not recruiting

(Continues)

TABLE 1 (Continued)

Class of drug	Target	Investigational agent	Phase	Stage	Indication	ORR, %	PFS, months	OS, months	Study name	ClinicalTrials.gov identifier	Status
	SEZ6	ABBV-706 ± budigalimab/ABBV-181, carboplatin, or cisplatin in SCLC or NECs [Chandana 2024[25]]	1	ES-SCLC	Relapsed/refractory	SCLC cohort: Median, 73.0 (40.0 confirmed, 33.0 unconfirmed)	NA	NA	NA	NCT05599984	Recruiting
	TROP2	Sacituzumab govitecan/IMMU-132 in metastatic solid tumors [Dowlati 2024[26]]	2	ES-SCLC	Second-line	Median, 41.9 (95% CI, 27.0–57.9)	Median, 4.4 (95% CI, 3.81–6.11)	Median, 13.6 (95% CI, 6.57–14.78)	TROPiCS-03	NCT03964727	Active, not recruiting

Note: Top advances in small cell lung cancer (SCLC) with reported results are outlined by class of drug, drug target, phase of the study, stage of SCLC, indication for use, objective response rate, median progression-free survival (PFS), median overall survival (OS), study name, national clinical trial (NCT) ClinicalTrials.gov identifier, and study status (data cutoff, December 1, 2024).

Abbreviations: ±, with or without; AE, adverse event; B7-H3, CD276; CI, confidence interval; DLL3, delta-like ligand 3; DLT, dose-limiting toxicity; ES-SCLC, extensive-stage SCLC; LS-SCLC, limited-stage SCLC; MTD, maximum tolerated dose; NA, not available; NE, not evaluable; NR, not reached; PK/PD, pharmacokinetics/pharmacodynamics; SEZ6, seizure-related homolog protein 6; TME, tumor microenvironment; TROP2, tumor-associated calcium signal transducer 2.

may have contributed as variables in assessing the effect of immunotherapy on this patient population.

One key takeaway from LU-005 is the schedule of radiotherapy and its effect on survival for LS-SCLC. Indeed, patients who received twice-daily radiation (RT), regardless of whether they received atezolizumab, had improved OS compared with those who received daily RT (median OS, 35.4 months [95% CI, 32.3 months to not reached] vs. 28.3 months [95% CI, 21.7–40.6 months]; HR, 1.44; 95% CI, 1.10–1.89). These findings suggest that the timing of RT (i.e., once vs. twice daily) is effective, and twice-daily RT should be considered when prescribing curative-intent radiotherapy for LS-SCLC, as recapitulated in previous studies,[32,33] although it may not be feasible for all patients because of scheduling or the risk of RT-induced esophagitis.

TARLATAMAB: RESHAPING MANAGEMENT OF RELAPSE IN ES-SCLC

Despite breakthroughs from anti–PD-L1 therapy as first-line treatment for ES-SCLC, relapse of SCLC occurs in most patients (approximately 80%–90%).[7–9,34] Novel treatments with unique mechanisms of action are desperately needed (Figure 1). Outside of a clinical trial, therapies for relapsed SCLC before 2024 have included platinum-rechallenge (typically reserved for patients with platinum-sensitive disease who have a chemotherapy-free interval ≥6 months), topotecan, irinotecan, taxanes, temozolomide, and, most recently, lurbinectedin.[27]

The phase 2 study DeLLphi-301 (ClinicalTrials.gov identifier NCT05060016) assessed the role of tarlatamab, a delta-like ligand (DLL3) and CD3 bispecific T-cell engager (BiTE), at two doses (10 and 100 mg) intravenously every 2 weeks in 220 patients with ES-SCLC, with a median of two lines of prior therapy (Table 1).[17] In 2023, results of the phase 2 study were reported from 99 evaluable patients, with an objective response rate (ORR) of 40% (97.5% CI, 29%–52%) in the 10-mg group and 32% (97.5% CI, 21%–44%) in the 100-mg group.[17] Thee median OS was 14.3 months.[17] Among tarlatamab responders, the duration of response was ≥6 months in 40 of 68 patients (59%).[17] Reported toxicities with >20% frequency on the DLL3 BiTE therapy included: cytokine release syndrome (CRS; 55%), fatigue (51%), dysgeusia (36%), pyrexia (36%), decreased appetite (34%), musculoskeletal pain (30%), constipation (30%), anemia (27%), and nausea (22%).[16,17] CRS onset was typically within the first two doses (43% and 29%, respectively) and was low grade (1 or 2) in severity, with a median time to onset of all-grade CRS of 13.5 hours (range, 1–268 hours).[16,17] Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in up to 47% of patients who received tarlatamab, including 10% grade 3, with a median time to onset of all-grade ICANS of 29.5 days (range, 1–154 days).[16,17]

On May 16, 2024, the FDA issued an accelerated approval of tarlatamab (Imdelltra, tarlatamab-dlle; Amgen, Inc.) for ES-SCLC after progression on or after platinum-based chemotherapy.[35] The confirmatory phase 3 study DeLLphi-304 (ClinicalTrials.gov identifier

NCT05740566) is ongoing (Table 2). Given the boxed warning for prescribing tarlatamab for CRS and ICANS, monitoring for 22–24 hours on cycle 1 day 1 and on cycle 1 day 8 after tarlatamab in an appropriate health care setting is recommended. This recommendation allows for prompt administration of supportive care, including antipyretics and fluids, dexamethasone, and/or an anti–IL-6 receptor monoclonal antibody (tocilizumab), as indicated after appropriate CRS and ICANS grading and expectant management if a higher level of care is necessary.[16] Predictive biomarkers to better understand who will experience high-grade CRS and/or ICANS are needed. Potential surrogates include a high burden of disease, heavily pretreated disease, and comorbidities that may impair baseline function (i.e., severe chronic obstructive pulmonary disease).

TABLE 2 Top advances of the year for small cell lung cancer: Active trials.

Class of drug	Target	Investigational agent	Phase	Stage	Indication	Study name	Primary endpoint	ClinicalTrials.gov identifier	Status
Bispecific T-cell engager	DLL3	Tarlatamab vs. standard of care (lurbinectedin, topotecan, or amrubicin)	3	ES-SCLC	Second line	DeLLphi-304	OS	NCT05740566	Active, not recruiting
		Tarlatamab and durvalumab vs. durvalumab alone after platinum, etoposide, durvalumab	3	ES-SCLC	First-line maintenance	DeLLphi-305	OS	NCT06211036	Recruiting
		Tarlatamab	3	LS-SCLC	Consolidation after chemoradiation for up to 2 years	DeLLphi-306	PFS by BICR	NCT06117774	Recruiting
		BI 764532 monotherapy in SCLC and other NENs (dose group 1 vs. group 2)	2	ES-SCLC	Relapsed/refractory	DAREON-5	ORR, TEAEs	NCT05882058	Active, not recruiting
		BI 764532 (obrixtamig) with platinum and etoposide in neuroendocrine carcinomas (NECs)	1	NECs	First-line	DAREON-7	MTD, DLTs	NCT06132113	Recruiting
		BI 764532 with platinum, etoposide, and anti–PD-L1 in SCLC	1	ES-SCLC	First-line	DAREON-8	MTD, DLTs	NCT06077500	Recruiting
		BI 764532 (dose escalation) with single-agent chemotherapy in SCLC	1	ES-SCLC	Relapsed/refractory	DAREON-9	MTD, DLTs, AEs	NCT05990738	Recruiting
Chemotherapy	RNA polymerase II, TME	Lurbinectedin ± irinotecan vs. topotecan or irinotecan	3	SCLC	Relapsed/refractory	LAGOON	OS	NCT05153239	Recruiting
Antibody–drug conjugate	B7-H3	I-DXd vs. standard of care (lurbinectedin, topotecan, or amrubicin)	3	ES-SCLC	Relapsed/refractory	IDeate-Lung02	OS, ORR	NCT06203210	Recruiting
		I-DXd + atezolizumab ± carboplatin	1b/2	ES-SCLC	First-line induction or maintenance	IDeate-Lung03	DLT	NCT06362252	Recruiting
	SEZ6	ABBV-706 ± budigalimab (ABBV-181), carboplatin, or cisplatin in SCLC or NECs	1	ES-SCLC	Relapsed/refractory	NA	PFS, OS, DOR, PK/PD, correlatives	NCT05599984	Recruiting

Note: Top advances in small cell lung cancer (SCLC) for 2024 with active studies are outlined by class of drug, drug target, phase of the study, stage of SCLC, indication for use, study name, primary end point, national clinical trial (NCT) ClinicalTrials.gov identifier, and study status (data cutoff, December 1, 2024).

Abbreviations: ±, with or without; AE, adverse event; B7-H3, CD276; BICR, blinded, independent central review; DLL3, delta-like ligand 3; DLTs, dose-limiting toxicities; DOR, duration of response; ES-SCLC, extensive-stage SCLC; I-DXd, ifinatamab deruxtecan; LS-SCLC, limited-stage SCLC; MTD, maximum tolerated dose; NA, not available; NENs, neuroendocrine neoplasms; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics; SEZ6, seizure-related homolog protein 6; TEAEs, treatment-emergent adverse events; TEM, tumor microenvironment.

The implementation of tarlatamab in real-world practice over the third and fourth quarters of 2024 has unveiled potential disparities and inequities for patients with SCLC. Specifically, access to tarlatamab may be limited or not yet available for those who live in rural areas and may not have proximity to major health centers with hospital privileges. Alternatively, patients who receive care at local centers who have limited experience with BiTE therapies may have had slower activation of the medication at their site because of hesitancy and need for additional staffing. Recent data demonstrated safety in outpatient monitoring for 6–8 hours after tarlatamab administration (DeLLphi-300; part F cohort; ClinicalTrials.gov identifier NCT03319940) without an increase in safety outcomes compared with the inpatient group, highlighting a potential opportunity for tarlatamab administration in the future to overcome these disparities in access.[36] Alternative indications for tarlatamab as well as other DLL3-targeting agents (e.g., BI 764532), alone or in combination with other agents, are actively being investigated (Tables 1, Table 2).[18–21]

LURBINECTEDIN: IS EARLIER BETTER FOR ES-SCLC?

In 2020, lurbinectedin received accelerated approval by the FDA after a phase 2, single-arm basket trial of 105 patients demonstrated an ORR of 35.2% (95% CI, 26.2%–45.2%) in patients with relapsed ES-SCLC (ClinicalTrials.gov identifier NCT02454972).[37,38] The confirmatory phase 3 study LAGOON investigating lurbinectedin either as a single agent or in combination with irinotecan versus irinotecan or topotecan in relapsed ES-SCLC is anticipated to complete in 2026 (ClinicalTrials.gov identifier NCT05153239).

The phase 1/2 single-arm study 2SMALL investigated the safety, tolerability, and efficacy of atezolizumab with lurbinectedin in patients who progressed after first-line platinum-based chemotherapy with ES-SCLC (ClinicalTrials.gov identifier NCT04253145).[39] In that study, the ORR was 57.69% in 26 patients, including two complete responses (7.69%), 13 partial responses (50%), and a median PFS of 4.93 months (range, 3.37–7.67 months), with eight patients censured for progression.[39]

The phase 3 trial IMforte compares the role of consolidative atezolizumab with lurbinectedin versus atezolizumab alone in patients with ES-SCLC who were randomized after the receipt of induction chemoimmunotherapy and had an ongoing response or stable disease (ClinicalTrials.gov identifier NCT05091567).[22] In 2024, a press release of the IMforte trial enthusiastically reported a significant improvement in the co-primary end points PFS and OS (Table 1).[23] One hypothesis for the significant impact of IMforte is that the early introduction of lurbinectedin after CCRT prevents the emergence of extrachromosomal *MYC* amplification and subclones of relapsed SCLC that are associated with chemoresistance.[40,41] Results of IMforte are anticipated in 2025.

MOVING THE NEEDLE: NEUROENDOCRINE SUBTYPING TO DEFINE TREATMENT

SCLC is a transcriptionally regulated disease defined by its dominant neuroendocrine (NE) subtype, including achaete-scute homologue 1 (*ASCL1*; SCLC-A), neurogenic differentiation factor 1 (*NEUROD1*; SCLC-N), POU class 2 homeobox 3 (*POU2F3*; SCLC-P), and SCLC-I, with near-ubiquitous loss of function of tumor suppressors *TP53* and *RB1* (Figure 2).[11,42] These transcription factors serve as master regulators to promote proliferation and metastatic spread, and they are not directly actionable. However, each NE subtype has specific targets and/or vulnerabilities based on their expression profile or preclinical responses to certain therapeutics.[43]

The phase 2 SWOG S1929 study represents the first biomarker-selected SCLC trial that assessed the role of adding the poly(adenosine diphosphate-ribose) polymerase inhibitor talazoparib to maintenance atezolizumab, compared with atezolizumab alone, in patients who had Schlafen-11 (SLFN11)-positive disease, with an improvement

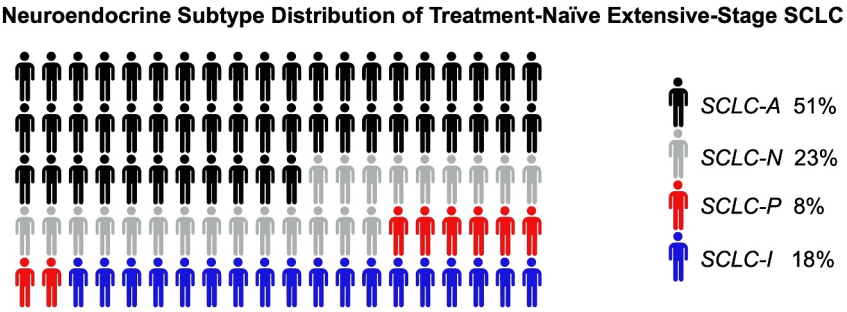

FIGURE 2 The prevalence of neuroendocrine subtypes in treatment-naive ES-SCLC from the IMpower133 trial. This is a graphical representation of the percentage of patients with ES-SCLC in the four neuroendocrine subtypes, as identified by transcriptomics in the IMpower133 trial ($n = 276$), including (A) 51% with the ASCL1 subtype (SCLC-A; black), 23% with the NEOROD1 subtype (SCLC-N; gray), 8% with the PUR2F3 subtype (SCLC-P; red), and 18% with the inflamed subtype (SCLC-I; blue). ASCL1 indicates achaete-scute homologue 1; ES-SCLC, extensive-stage small cell lung cancer; NEUROD1, neurogenic differentiation factor 1; POU2F3, POU class 2 homeobox 3; SCLC, small cell lung cancer.

in PFS but not in OS (ClinicalTrials.gov identifier NCT04334941).[44] That study, which enrolled ahead of schedule despite a global pandemic, achieved a turnaround time for biomarker results of <7 days and demonstrated the feasibility of using biomarker-guided approaches to match patients to specific therapies.[44]

The next step will be to personalize therapy based on SCLC subtypes and other biomarkers (Figure 3). Toward this goal, SWOG S2409 (PRISM) is the first-of-its-kind trial that ushers in an era of precision medicine based on distinct SCLC subtypes centered on two biomarker features—first, the tumor messenger RNA profile (using a robust, Clinical Laboratory Improvement Amendments–validated, multigene signature to determine subtype) and SLFN11 status (using immunohistochemistry). PRISM incorporates the benefits from immunotherapy established by IMpower133 and CASPIAN, with the identification of SCLC subtypes and their potential therapeutic vulnerabilities in a randomized design.[7,8] The design allows all patients who are screened to enroll in the appropriate study and uses our most invaluable resources (e.g., patients and their tissue samples) in an efficient way.

During first-line chemoimmunotherapy, tissue from approximately 900 patients will be tested to determine their eligibility into three cohorts based on NE subtype and SLFN11 status. In each cohort (e.g., cohorts A, B, and C), the primary objective is to compare PFS in participants with ES-SCLC randomized to receive immunotherapy with or without the respective biomarker-directed agent as novel maintenance therapy (Figure 3). Secondary objectives include evaluating safety, toxicity, and OS. PRISM is anticipated to start in 2025.

USHERING IN A TROJAN HORSE: ANTIBODY–DRUG CONJUGATES

Since 2023, several clinical trials with antibody–drug conjugates (ADCs) have reported unprecedentedly high ORRs (range, 41.9%–73%) for the treatment of relapsed/refractory ES-SCLC (Table 1).[24–26,45] These ADCs act as a trojan horse by using surface-some targets in SCLC (i.e., B7-H3 [CD276], SEZ6 90 [seizure-related homolog 6], TROP2 [tumor-associated calcium signal transducer 2]) to deliver a chemotherapy payload (Figure 1).[45] Breakthrough designations are anticipated given the high response rates and promising durability in patients with heavily pretreated, relapsed/refractory SCLC (Table 1).[24–26,45] Novel combinations of ADCs with DLL3-targeting agents or immunotherapy to exploit the vulnerabilities of SCLC in a multifactorial fashion are underway (Table 2).

ADVOCACY IN SMALL CELL: WHY YOUR VOICE MATTERS

In 2024, an advocacy group focused exclusively for SCLC was formed to address the nihilism, stigma, and isolation that patients with SCLC have historically faced. The group *Small Cell SMASHERS* was founded in partnership with Lungevity Foundation and physician scientist Misty D. Shields to support patients and their care partners in their journey with SCLC—through community, providing hope while

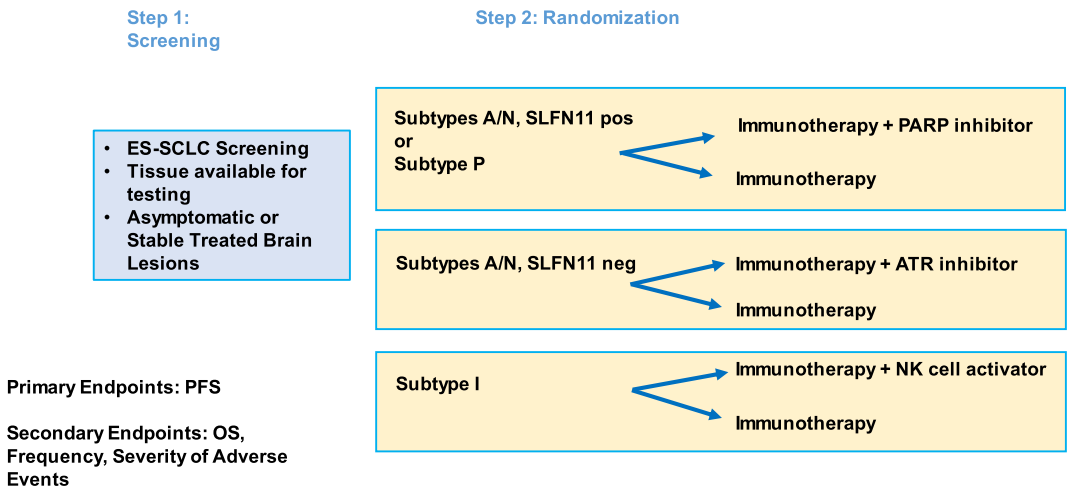

FIGURE 3 The SWOG S2409 PRISM study schema. S2409 permits the screening of patients diagnosed with ES-SCLC during induction chemoimmunotherapy. The study randomizes patients to maintenance immunotherapy with or without a subtype biomarker-directed, novel agent by neuroendocrine subtype. Specifically, neuroendocrine subtypes ASCL1 (SCLC-A) and NEUROD1 (SCLC-N) are further categorized by SLFN11-positive or SLFN11-negative status to randomize patients to maintenance therapy with a PARP inhibitor versus an ATR inhibitor, respectively, targeting the characteristic biology of those subtypes. It has been demonstrated that SLFN11-positive SCLC is sensitive to PARP inhibitors, as is SCLC with subtype POU2F3 (SCLC-P). In SLFN11-negative SCLC, the ATR inhibitor acts as a synthetic, lethal vulnerability and will be targeted in this cohort. In patients with the inflamed subtype (SCLC-I), the addition of an NK cell activator may promote activation of the immune tumor microenvironment. A/N indicates achaete-scute homologue 1/neurogenic differentiation factor 1 subtypes; ASCL2, achaete-scute homologue 1; ATR, ataxia telangiectasia and RAD3-related kinase; ES-SCLC, extensive-stage small cell lung cancer; neg, negative; NEUROD1, neurogenic differentiation factor 1; NK cell, natural killer cell; OS, overall survival; PARP, poly(adenosine diphosphate-ribose) polymerase; PFS, progression-free survival; pos, positive; POU2F3, POU class 2 homeobox 3; SCLC, small cell lung cancer; SLFN11, Schlafen-11; SWOG, Southwest Oncology Group.

amplifying research and voices for advocacy. More information on the Small Cell SMASHERS can be found at https://sclc.lungevity.org.

THE ERA OF SCIENTIFIC REVOLUTION: LOOKING FORWARD

We declare that the year 2024 marks the beginning of the *scientific revolution* for SCLC.[5] Dramatic advancements to understand the molecular underpinnings of SCLC, coupled with exploiting therapeutic vulnerabilities of the disease with novel agents while maximizing support for patients with SCLC, have spearheaded a new *era of change*. This *breath of hope* is the beginning of "light at the end of the tunnel" to ultimately end this recalcitrant disease.[5]

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CONFLICT OF INTEREST STATEMENT

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