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EDITORIAL

Tomić and Vranić: SCLC: Precision oncology era

Small cell lung cancer (SCLC): At the door of targeted therapies

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Small-cell lung cancer (SCLC) is a neuroendocrine lung neoplasm that is almost universally linked to tobacco exposure (1). It accounts for ~15% of all lung cancers, and ~150,000 new cases are diagnosed every year worldwide. For decades, SCLC has symbolized stagnation in thoracic oncology. In contrast to non-small-cell lung cancer (NSCLC), which underwent a metamorphosis with targeted and immune-based therapies that translated into prolonged survival, SCLC remained a therapeutic desert. The reasons are well known: rapid tumor growth, aggressive biology, and diagnosis at an extensive stage in most patients. Screening fails to enable early detection, and even in limited-stage SCLC (LS-SCLC), surgery is feasible in fewer than 5% of cases (2). Instead, most patients with LS-SCLC are treated with concurrent chemoradiotherapy, which remains the cornerstone of curative-intent management.

For decades, platinum-etoposide was the gold standard in first-line therapy for extensive-stage SCLC (ES-SCLC) with an overall survival (OS) of less than 12 months (2). This therapeutic stagnation earned SCLC the reputation of an orphan disease and a graveyard for drug development. The only incremental progress before immunotherapy came from radiotherapy in ES-SCLC and from prophylactic cranial irradiation (PCI) or MRI brain surveillance. Consolidative thoracic radiotherapy in ES-SCLC improved survival among patients who responded to chemotherapy (3). As more >50% of patients eventually develop intracranial metastases, PCI has been used to reduce the risk of symptomatic brain involvement (4). An active MRI surveillance offers an alternative strategy for patients who do not receive PCI (5).

The landscape of SCLC began to shift with two pivotal developments. First, the recognition of four molecular subtypes of SCLC, defined by transcriptional signatures, provided the foundation for a more personalized approach: SCLC-A (ASCL1/ASH1), SCLC-N (NEUROD1), SCLC-P (POU2F3), and the inflammatory subtype SCLC-I, which appears most likely to benefit from immunotherapy with immune checkpoint inhibitors (ICI) (6,7). Second, the introduction of ICI brought the first meaningful advance in more than three decades (Figure 1). The addition of atezolizumab or durvalumab to chemotherapy in ES-SCLC yielded only a modest median survival gain of about two months. Still, it critically revealed something unprecedented: a survival tail of

long-term responders (8,9). Building on this signal, subsequent studies suggested additional benefit in both ES-SCLC and, for the first time, in LS-SCLC. The IMforte study showed that the addition of lurbinectedin to atezolizumab as maintenance after chemoimmunotherapy in ES-SCLC improves OS (10). In contrast, the ADRIATIC study marked a true breakthrough in LS-SCLC, showing that durvalumab consolidation after concurrent chemoradiotherapy improved OS by an impressive 22 months (11).

Despite the remarkable chemosensitivity of SCLC, responses are transient, and relapse is nearly universal. Platinum rechallenges were an option for patients relapsing after ≥6 months, whereas those relapsing within 90 days faced an abysmal prognosis. In the second-line setting, topotecan and the CAV regimen (=cyclophosphamide, doxorubicin, and vincristine) were for a long time the only widely used standards. At the same time, newer agents such as lurbinectedin and amrubicin did not meaningfully improve OS.

Replacing a one-size-fits-all approach with a precise, targeted strategy requires first identifying a target that is highly expressed in SCLC and minimally present in normal cells. The best example of such a target is Delta-like ligand 3 (DLL3). DLL3 is an inhibitory Notch ligand that promotes cancer growth, invasion, and metastasis by influencing Notch signaling pathways, making it a promising therapeutic target (12). DLL3 is markedly overexpressed in various neuroendocrine cancers, particularly SCLC (13). Thus, high DLL3 expression on the surface of cancer cells was described in > 80% of SCLC cases, offering the first hint that target-directed therapy (antibody-drug conjugates/ADC/ and T-cell engagers) might be feasible (1,14,15). Tarlatamab, a bispecific T-cell engager (BiTE), recruits cytotoxic T cells to target DLL3-expressing tumor cells, thereby inducing cancer cell destruction. In the randomized phase 3 DeLLphi-304 study, tarlatamab extended median OS to 13.6 months compared with 8.3 months for standard-of-care chemotherapy in second-line ES-SCLC (HR 0.60, $p<0.001$) (16). Notably, DLL3 expression was not required for trial participation, and the study population included patients with platinum-resistant disease, brain metastases, and a majority (71%) with prior exposure to immunotherapy. The survival benefit was consistent across subgroups, including these high-risk groups. Toxicity was manageable,

with grade ≥3 adverse events being less frequent than with chemotherapy. Importantly, new immune-mediated toxicities were observed: cytokine release syndrome in 56% of patients (predominantly grade 1–2) and immune effector cell–associated neurotoxicity syndrome (ICANS) in ~6%. Based on these practice-changing results, tarlatamab is now considered a new standard of care in the second-line treatment of ES-SCLC.

Another promising and attractive target in the treatment of SCLC is B7-H3 (CD276), a member of the B7 family of immune checkpoint regulators. B7-H3 is a protein that plays a key role in promoting tumor growth, metastasis, immune evasion, and resistance to therapies (17). Its expression has been described in many cancers, including SCLC (18,19). Consequently, B7-H3 has emerged as a promising therapeutic target in SCLC. High expression of B7-H3 is associated with poor prognosis, and unlike DLL3, whose expression varies across molecular subtypes, it is consistently and uniformly overexpressed across all four SCLC subtypes (20). This biology provides a compelling rationale for a high response rate to B7-H3-directed therapies. This rationale was strongly supported by the phase 2 IDeate-Lung01 study, in which the ADC ifinatamab deruxtecan (I-DXd) demonstrated unprecedented efficacy in heavily pretreated ES-SCLC (21). Among patients who had received at least two prior lines of therapy (76% of whom had prior immunotherapy), the 12 mg/kg dose cohort achieved a confirmed objective response rate (ORR) of 54.8%, a median progression-free survival (PFS) of 5.5 months, and a median OS of 11.8 months. I-DXd also achieved clinically relevant responses in patients with brain metastases, a subgroup historically characterized by poor outcomes. Based on these landmark results, the U.S. Food and Drug Administration (FDA) granted I-DXd breakthrough therapy designation for heavily pretreated patients with ES-SCLC (22).

Responses to both tarlatamab and I-DXd were observed irrespective of DLL3 and B7-H3 expression levels (16,23). In contrast, when considering predictors of chemoimmunotherapy benefit, DLL3 expression did not correlate with response, whereas B7-H3 did (24). High B7-H3 expression appears to be associated with shorter survival and impaired $CD8^+$ T-cell function, underscoring its dual role as both a therapeutic target and a potential prognostic biomarker.

Taken together, these recent advances are substantially reshaping the therapeutic landscape of SCLC. DLL3- and B7-H3–directed therapies represent complementary breakthroughs, demonstrating unprecedented efficacy in the second and later-line therapy for ES-SCLC. Beyond these, ADC targeting the transmembrane glycoprotein (Trop2) and seizure protein 6 (SEZ6) are in development, suggesting that the long barren pipeline of SCLC may finally be filling with active drugs (Figure 1). However, key challenges remain, including optimizing sequencing and combinations to overcome rapid resistance and expanding these approaches into the first-line setting. Equally important are strategies to manage the unique toxicities of BiTEs and the development of predictive biomarkers for better patient selection. Yet, the trajectory has shifted. After decades of futility, relapsed SCLC is witnessing a double breakthrough: the field is finally transitioning from uniform chemotherapy toward a precision medicine paradigm (Figure 1). For the first time, the story of SCLC no longer feels defined by despair but by cautious optimism.

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REFERENCES

1. Krpina K, Vranić S, Tomić K, Samaržija M, Batičić L. Small Cell Lung Carcinoma: Current Diagnosis, Biomarkers, and Treatment Options with Future Perspectives. Biomedicines. 2023 July 13;11(7):1982.

2. National Comprehensive Cancer Network. Small Cell Lung Cancer. Version 1.2026. Available from: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf.

3. Slotman BJ, van Tinteren H, Praag JO, Knegjens JL, El Sharouni SY, Hatton M, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet Lond Engl. 2015 Jan 3;385(9962):36–42.

4. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med. 2007 Aug 16;357(7):664–72.

5. Takahashi T, Yamanaka T, Seto T, Harada H, Nokihara H, Saka H, 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 May;18(5):663–71.

6. Gay CM, Stewart CA, Park EM, Diao L, Groves SM, Heeke S, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell. 2021 Mar 8;39(3):346-360.e7.

7. Rudin CM, Poirier JT, Byers LA, Dive C, Dowlati A, George J, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. Nat Rev Cancer. 2019 May;19(5):289–97.

8. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018 Dec 6;379(23):2220–9.

9. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, 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 Lond Engl. 2019 Nov 23;394(10212):1929–39.

10. Paz-Ares L, Borghaei H, Liu SV, Peters S, Herbst RS, Stencel K, et al. Efficacy and safety of first-line maintenance therapy with lurbinectedin plus atezolizumab in extensive-stage small-cell lung cancer (IMforte): a randomised, multicentre, open-label, phase 3 trial. Lancet Lond Engl. 2025 June 14;405(10495):2129–43.

11. Cheng Y, Spigel DR, Cho BC, Laktionov KK, Fang J, Chen Y, et al. Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. N Engl J Med. 2024 Oct 10;391(14):1313–27.

12. Furuta M, Kikuchi H, Shoji T, Takashima Y, Kikuchi E, Kikuchi J, et al. DLL3 regulates the migration and invasion of small cell lung cancer by modulating Snail. Cancer Sci. 2019 May;110(5):1599–608.

13. Lozada JR, Elliott A, Evans MG, Wacker J, Storey KM, Egusa EA, et al. Expression Patterns of DLL3 across Neuroendocrine and Non-neuroendocrine Neoplasms Reveal Broad Opportunities for Therapeutic Targeting. Cancer Res Commun. 2025 Feb 1;5(2):318–26.

14. Huang RSP, Holmes BF, Powell C, Marati RV, Tyree D, Admire B, et al. Delta-like Protein 3 Prevalence in Small Cell Lung Cancer and DLL3 (SP347) Assay Characteristics. Arch Pathol Lab Med. 2019 Nov;143(11):1373–7.

15. Rojo F, Corassa M, Mavroudis D, Öz AB, Biesma B, Brcic L, et al. International real-world study of DLL3 expression in patients with small cell lung cancer. Lung Cancer Amst Neth. 2020 Sept;147:237–43.

16. Mountzios G, Sun L, Cho BC, Demirci U, Baka S, Gümüş M, et al. Tarlatamab in Small-Cell Lung Cancer after Platinum-Based Chemotherapy. N Engl J Med. 2025 July 24;393(4):349–61.

17. Getu AA, Tigabu A, Zhou M, Lu J, Fodstad Ø, Tan M. New frontiers in immune checkpoint B7-H3 (CD276) research and drug development. Mol Cancer. 2023 Mar 2;22(1):43.

18. Carvajal-Hausdorf D, Altan M, Velcheti V, Gettinger SN, Herbst RS, Rimm DL, et al. Expression and clinical significance of PD-L1, B7-H3, B7-H4 and TILs in human small cell lung Cancer (SCLC). J Immunother Cancer. 2019 Mar 8;7(1):65.

19. Qiu MJ, Xia Q, Chen YB, Fang XF, Li QT, Zhu LS, et al. The Expression of Three Negative Co-Stimulatory B7 Family Molecules in Small Cell Lung Cancer and Their Effect on Prognosis. Front Oncol. 2021;11:600238.

20. Gay CM, Owonikoko TK, Byers LA, Choudhury NJ, Ahmed S, Cain Z, et al. Multidimensional Analysis of B7 Homolog 3 RNA Expression in Small Cell Lung Cancer Molecular Subtypes. Clin Cancer Res Off J Am Assoc Cancer Res. 2025 Aug 14;31(16):3476–82.

21. Rudin CM, Ahn MJ, Johnson M, Hann CL, Girard N, Nishio M, et al. Ifinatamab deruxtecan (I-DXd) in extensive-stage small cell lung cancer (ES-SCLC): Interim analysis of IDEATE-Lung01. J Thorac Oncol. 2024;19(10 Suppl):S15-S16.

22. Ifinatamab deruxtecan granted breakthrough therapy designation by U.S. FDA for patients with pretreated extensive-stage small cell lung cancer. News release. Merck. August 18, 2025. Accessed August 18, 2025. https://www.merck.com/news/ifinatamab-deruxtecan-granted-breakthrough-therapy-designation-by-u-s-fda-for-patients-with-pretreated-extensive-stage-small-cell-lung-cancer/.

23. Johnson M, Awad M, Koyama T, Gutierrez M, Falchook GS, Piha-Paul SA, et al. OA05.05 Ifinatamab Deruxtecan (I-DXd; DS-7300) in Patients with Refractory SCLC: A Subgroup Analysis of a Phase 1/2 Study. J Thorac Oncol. 2023 Nov;18(11):S54–5.

24. Kurosaki T, Kanemura H, Otani T, Kawanaka Y, Fukuda Y, Kudo K, et al. Impact of B7-H3 and DLL3 expression on the efficacy of PD-L1 blockade therapy in extensive-stage small cell lung cancer. Lung Cancer. 2025 Sept;207:108723.

FIGURE WITH LEGEND

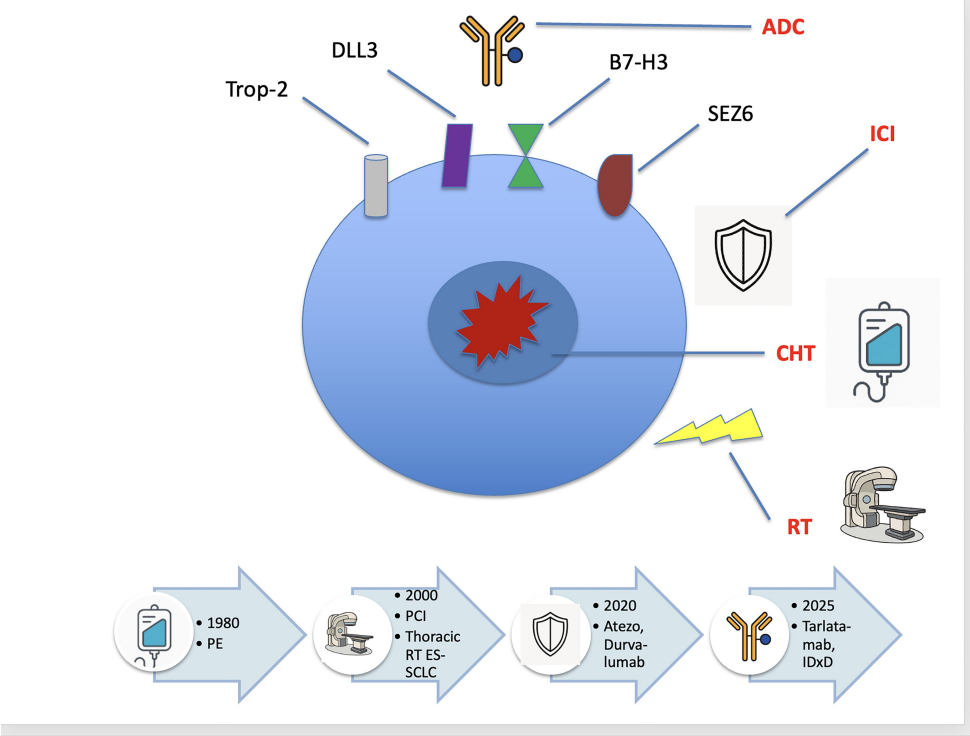

Figure 1. Therapeutic evolution in small cell lung cancer (SCLC) from 1980 until mid-2025.

Abbreviations: ADC, antibody–drug conjugates; Atezo – atezolizumab; ICI, immune checkpoint inhibitors; CHT, chemotherapy; RT, radiotherapy; PE, cisplatin/etoposide; PCI, prophylactic cranial irradiation; ES-SCLC, extensive stage small cell lung cancer; IDxD, ifinatamab deruxtecan.