Editorial Commentary

Aurora kinase B inhibition in small-cell lung cancer: BCL-2 as a potential therapeutic biomarker and combination target

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Small-cell lung cancer (SCLC): the need for new treatments and biomarkers

Lung cancer is the leading cause of cancer-related deaths worldwide (1). SCLC accounts for approximately 15% of all lung cancers and is characterized by a high proliferation rate, strong predisposition for early metastases, and poor prognosis. In general, SCLC is more sensitive to cytotoxic chemotherapy and radiation therapy than non-small cell lung cancer (NSCLC). Recently, notable advancements have been made in combining a cytotoxic agent and an immune checkpoint inhibitor as a first-line treatment for extended-stage (ES)-SCLC, showing that 60–68% of patients achieved an objective response (2,3). However, many patients eventually develop resistance to these therapies after a relatively short median response duration of 4.2–5.1 months. NSCLC therapeutic landscape has been enriched by remarkable achievements especially for targeted therapies in case of gene alterations. Unfortunately, such advancements have not been observed in SCLC, despite significant efforts in this direction. Therefore, new SCLC treatment strategies are urgently needed, especially targeted therapies for subpopulations identified by specific biomarkers.

Recently, molecular profiling of SCLC specimens with a primarily unsupervised approach led to the widely-approved classification of SCLC subtypes: ASCL1, NeuroD1, YAP1, and POU2F3 (4). These subtypes have been observed in several independent profiling studies. However, the biological meanings are unknown, or whether these subtypes reflect the cells of origin, oncogenic pathways, or metastatic ability, etc. Moreover, whether these subtypes reflect the susceptibility to specific therapies remains unknown.

In this editorial commentary, we consolidate the surrounding issues regarding the therapeutic approaches and utility of predictive biomarkers, based on a study by Ramkumar *et al.* (published in August 2023) (5) that elucidates the role of B-cell/CLL lymphoma 2 (BCL-2) expression as a new biomarker for AURKB inhibition in SCLC.

Aurora kinase B (AURKB): a potential target for SCLC

As a novel approached to treatment, numerous potential therapeutic targets in SCLC are actively under investigation, such as vascular endothelial growth factors (VEGFs), poly(ADP-ribose) polymerase, delta-like protein 3, and aurora kinases (6). Aurora kinases are protein serine/threonine kinases that comprise three gene family members: aurora kinase A (AURKA), AURKB, and aurora kinase C (AURKC). AURKs are vital cell cycle regulators; AURKA and AURKB are crucial for mitosis, while AURKC predominantly affects gametogenesis. AURKA and AURKB are widely overexpressed in numerous malignancies (7), and inhibiting them is a key focus of many clinical trials. However, based on preclinical gene knockout studies, selectively inhibiting AURKB may offer distinct

Table 1 Clinical trials considering selective aurora kinase B inhibitor in extended-stage small-cell lung cancer patients. Trials were searched in the clinicaltrials.gov website on October 30, 2023 and data were extracted from the database

Study	Drug	Line of treatment	Phase	Status	Status in detail
NCT03366675 (SUKSES-N3)	AZD2811	2 or 3	II	Terminated	Early detection of the purpose of the study
NCT04525391 (SUKSES-N5)	AZD2811 + durvalumab	2 or 3	II	Terminated	Terminated due to adverse events occurring in other clinical trials conducted with the same drug
NCT04745689 (TAZMAN)	AZD2811 + durvalumab	1	II	Active, not recruiting	–
NCT03216343 (CAR105)	Chiauranib	≥3	Ib/II	Completed	No results posted
NCT05271292 (CAR107)	Chiauranib	≥3 (phase II part)	Ib/II	Recruiting	–
NCT04830813 (CAR302)	Chiauranib	≥3	III	Recruiting	–

advantages. The functionality of AURKB when knocked out could potentially be compensated for by AURKC in the early embryonic phases (8), unlike AURKA, which is indispensable for normal development (9). Therefore, targeting AURKB inhibition emerges as a promising approach for cancer therapy.

AURKB inhibition can induce apoptosis in both blood and solid malignant cells (10,11). AURKB is a promising therapeutic target, particularly in SCLC, which shows almost global inactivation of RB1, resulting in mitotic abnormalities and increased sensitivity to AURKB inhibition (12). Clinical trials assessing the efficacy and safety of selective AURKB inhibitors for patients with SCLC are summarized in *Table 1*, including trials of AZD2811 and chiauranib. AZD2811 is a selective AURKB inhibitor that has been investigated in three phase II trials; NCT03366675 (SUKSES-N3) and NCT04525391 (SUKSES-N5) are part of a multi-arm phase II trial examining second or third-line treatments for recurrent SCLC patients, allocated as biomarker non-selected arms (13). In SUKSES-N3, which evaluated the single-agent AZD2811, 15 patients were enrolled. This trial showed limited clinical efficacy of the drug as a monotherapy, with no objective response and a median progression-free survival of 1.6 months [95% confidence interval (CI): 0.9–1.7]. SUKSES-N5, examining the combination of AZD2811 and the anti-programmed death-ligand 1 (PD-L1) antibody durvalumab, had four patients allocated but was recommended for termination owing to suspected unexpected serious adverse reactions (SUSARs) in another trial using the same drugs. NCT04745689 (TAZMAN) is being conducted with a regimen similar to SUKSES-N5. It is a single-arm phase II trial that evaluates the safety and efficacy of combining AZD2811 with the standard maintenance therapy of durvalumab. This trial targets patients who did not progress after induction therapy with platinum + etoposide + durvalumab, which is one of the current standard first-line treatments. To date, nine patients have received the combination therapy of durvalumab and AZD2811, and the results have not yet been posted yet. It is crucial to note that the latter two trials (SUKSES-N5 and TAZMAN) are combination studies with immune checkpoint inhibitors, not monotherapy trials of AZD2811. Furthermore, it is important to note that the last trial examines combination therapy in first-line treatment; this differs from the other trials, which focus on recurrent SCLC. These distinctions in the treatment setting should be carefully considered. Chiauranib, or CS2164, is a potent multi-kinase inhibitor of AURKB, VEGFRs, and colony-stimulating factor-1 receptor (14). Tree trials are currently investigating chiauranib; NCT03216343 (CAR105) and NCT05271292 (CAR107) are single-group trials administering chiauranib monotherapy to patients with recurrent SCLC. CAR105 is a phase Ib/II trial examining the safety and efficacy of a regimen involving a daily oral dose of 50 mg chiauranib capsules. In the phase II part, 28 patients were enrolled. Of these, 17.9% (95% CI: 6.1–36.9%) achieved an objective response and the median progression-free survival was 3.6 months. The regimen was well tolerated, although grade 3–4 adverse events (AEs) including hypertension (25%) and hyponatremia (14%) were observed (15). CAR107 consists of a phase Ib part to determine the optimal dose of chiauranib capsules for solid tumors (between 35 and 65 mg/day), and a phase II to assess the safety and efficacy of the determined dose in recurrent SCLC. Results, including patient enrollment numbers, have not yet been published. Planned in response to promising results suggested in CAR105, NCT04830813 (CAR302) is a randomized, double-blind, placebo-

controlled, multi-center phase III clinical trial to verify the effect of chiauranib monotherapy in patients with recurrent SCLC. It is currently in the recruiting stage. Among the aforementioned trials, it is noteworthy that only CAR302 is designed as a placebo-controlled comparative study, in contrast to the others which are designed as single-arm trials.

AZD1152 and its improved product, AZD2811NP (frequently referred to as "AZD2811"), are the most widely investigated AURKB inhibitors in clinical trials conducted on malignancies (16). AZD1152, also known as barasertib, is a water-soluble ATP-competitive selective AURKB inhibitor; it shows 1,000-fold more selectivity for AURKB than AURKA (10). Despite the promising clinical efficacy of AZD1152 in malignancies, such as acute myeloid leukemia, its clinical utility was limited by the requirement for an infusion period of 7 continuous days; development was discontinued due to the toxicity and inconvenience of clinical application (17). During development, AZD1152 was known as a prodrug and quickly converted to the active drug AZD2811 (previously known as AZD1152-hQPA) in plasma, which shows almost no solubility in water thus not suitable for clinical application. However, AZD2811NP, a recently developed nanoparticle-encapsulated AZD2811 with extended drug release and a favorable toxicity-efficacy profile in preclinical models, has been developed and may be considered as an AURKB inhibitor, suitable for clinical study (18,19).

To refine the clinical application of AURKB inhibitors, biomarkers that predict the efficacy of AURKB inhibition are needed to ensure that treatment is given to patients who are predicted to respond, thereby maximizing efficacy and minimizing exposure to unnecessary toxicity. AURKB activity is known to be enhanced by the oncogene c-MYC, which also benefits from AURKB by helping to stabilize the c-MYC protein (20). This interdependence suggests that cancers with high levels of c-MYC might be particularly sensitive to AURKB inhibitors. In support of this, research using AZD1152, an AURKB inhibitor, showed that tumors with c-MYC amplification were more likely to respond to treatment, as evidenced by reduced tumor growth in animal models of SCLC (21).

BCL-2: biomarker and combination target with AZD2811

Recently, Ramkumar *et al.* investigated the therapeutic efficacy of AZD2811 (*in vitro*) and AZD2811NP (*in vivo*) and showed that efficacy could be predicted by low BCL-2 expression rather than MYC expression (5). Moreover, the combination of AZD2811/AZD2811NP and BCL-2 inhibition by both genetic knockdown and pharmacological inhibition showed superior efficacy in a subset of preclinical models stratified by higher BCL-2 expression. The number of AZD2811NP and BCL-2 inhibitor doses could be decreased to achieve similar treatment efficacy. Accordingly, they provided specific evidence for combining AURKB and BCL2 inhibition as a novel therapeutic strategy for SCLC, especially in patients with high-BCL2 SCLC.

Interestingly in this study, preclinical models using cell lines and xenografts showed that high BCL-2 expression levels have been correlated to AURKB inhibitors lower efficacy (5). Although AURKB and c-MYC have a close mechanistic relationship, leading to the original hypothesis of the utility of c-MYC as a therapeutic biomarker for AURKB inhibition, the expected correlation between high c-MYC expression (estimated from proteomic expression profiling and genomic amplification) and high AURKB inhibitor sensitivity was not observed in the cell line study. Contrary to expectations, it was low BCL-2 expression that emerged as a predictive marker for treatment efficacy. In this study, proteomic expression profiling was performed to examine the levels of BCL-2 family proteins within the cell lines. It was found that cell lines with low levels of BCL-2 protein expression were more sensitive to AURKB inhibitors. BCL-2 is a member of the BCL-2 protein family, and it is pivotal in regulating apoptosis. Members of this family can be pro-apoptotic (e.g., BAX, BAK, and BH3-only proteins, such as BIM and BAD) or anti-apoptotic (e.g., BCL-2 and BCL-XL), and their interactions determine a cell's fate, that is, survival or apoptosis. Aberrant BCL-2 protein expression is implicated in various malignancies, making them attractive therapeutic targets. For example, the BCL-2 inhibitor venetoclax is approved for treating certain leukemias, which highlights the clinical relevance of targeting this pathway (22). Preclinical studies show that targeting the BCL-2 family and using these proteins as biomarkers in SCLC are promising (21,23,24).

Although Ramkumar *et al.* did not find a direct mechanistic relevance for combining BCL-2 targeting with AURKB inhibition, they managed to enhance the therapeutic efficacy by targeting BCL-2. This discovery somewhat aligns with prior findings that demonstrated the effectiveness of a combination therapy involving AURKB inhibition and BCL-xL inhibition (another member of the BCL-2 protein family) in treating other malignancies (25).

However, distinctively, Ramkumar *et al.* identified BCL-2, rather than BCL-xL, as both a biomarker and a therapeutic target in the context of AURKB inhibition for SCLC.

Inducing apoptosis in SCLC cells remains a promising treatment strategy and a combination of different classes of apoptosis-related proteins as treatment targets or biomarkers is reasonable. These findings underscore the potential of a stratified therapeutic approach, wherein the combination of distinct classes of apoptosis-related proteins, such as aurora kinases and BCL-2 family proteins, could be explored as treatment targets or biomarkers to optimize SCLC therapeutic outcomes.

A further finding of this study was the suggestion that both AURKB and BCL-2 inhibitor doses could be decreased to mitigate toxicity and achieve a similar efficacy (5). As already mentioned, combined chemo-immunotherapy is the standard of care in the first-line treatment of ES-SCLC, and a phase II study is considering the combination of AZD2811NP and immunotherapy. As combination therapies could be considered actively, it is essential to explore administration methods that balance efficacy and reduce toxicities.

Conclusions

Overall, Ramkumar *et al.* uncovered a new treatment strategy and a biomarker for SCLC using convincing preclinical evidence. Low BCL-2 expression levels can predict the efficacy of AZD2811/AZD2811NP treatment against SCLC cells and a combination of AZD2811/AZD2811NP and BCL-2 inhibition could be a novel combined treatment approach. The dosage of this combination treatment can be adjusted to mitigate AEs.

The results of ongoing clinical trials using AURKB inhibitors and further biomarker studies using clinical specimens are eagerly awaited. Moreover, further preclinical investigations are still needed to develop new treatment strategies, including stratification through biomarkers.

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