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Tarlatamab and the Future of Immunotherapy: A New Approach to Small Cell Lung Cancer

On May 16, 2024, the US Food and Drug Administration–approved tarlatamab[a] for patients with advanced-stage small cell lung cancer (SCLC) that has advanced after platinum-based chemotherapy. Imdelltra is given via intravenous infusion, first weekly for 3 doses and then every 2 weeks.

Small cell lung cancer is an intense malignancy with kinetic characteristics such as rapid growth, early metastasis, therapeutically acquired resistance and poor survival profile.[1] Small cell lung cancer constitutes about 15% of all lung malignancies. Limited-stage is diagnosed in only one-third of patients.[2] According to the Surveillance, Epidemiology, and End Results (SEER) database research, females account for a lesser proportion of SCLC instances, with only 14.9% of patients being women.[3] The Notch pathway inhibitory ligand delta-like ligand 3 (DLL3) is involved in tumor growth and metastasis, and it is related with increased levels in SCLC. Because of its sparing in normal tissues and its abundance in tumors, this protein is a promising biomarker for targeted therapy of SCLC.[4] When treating limited-stage SCLC, the gold standard is early concomitant chemo-radiation. Cisplatin or carboplatin, with atezolizumab administration being the standard, is the main premise of first-line treatment for etoposide-treated advanced stage-SCLC. The majority of SCLCs respond to treatment at first, but they almost always relapse.[5] Neoadjuvant immunochemotherapy is a novel method for treating SCLC, with a particular emphasis on combination type SCLC. This approach decreased the stage of the tumor to allow for radical resection, thereby underlining the necessity that immunotherapy provide a solution for improving resectability and dealing with complex histologic characteristics in aggressive SCLC.[6] Immune therapy particularly immune check point inhibitors has transformed treatment strategies for extensive stage SCLC to have higher survival more than conventional therapy. The current treatments prove ineffective because tissues develop intrinsic resistance mechanisms including; ineffective antigen presentation and poor penetration of T cells.[7] Tarlatamab fills the gap by providing anticancer activity, sustained clinical responses, and favorable survival outcomes in patients with SCLC who have been previously treated. However, it does not identify any new safety concerns.[8]

Delta-like ligand 3 is a protein that is upregulated in the SCLC cells and preferentially expressed in SCLC-A subtype. Although the DLL3 protein is rarely found in normal cells at a high level, it is highly upregulated in SCLC cancer cells.[9] Since DLL3 is a promising target to kill the cancerous cells, tarlatamab binds to DLL3 on SCLC cells and to CD3 on T cells to create a cytolytic synapse that triggers T cell-mediated tumor cell death.[10] In the Phase I trial, tarlatamab indicated promising efficacy and tolerable safety in strongly pretreated patients. The trial included 107 patients, with the majority having undergone at least 2 prior lines of therapy. There were 107 patients in the study, and most of them had tried 2 different treatments before. Doses of tarlatamab as low as 0.003 mg and as high as 100 mg produced reactions; however, the rates of response were highest at doses higher than 3 mg. With 2 full and 23 partial replies, the study achieved an objective response rate of 23.4%. The median response time was 12.3 months. Median overall survival was 13.2 months, median progression-free survival was 3.7 months, and disease control rate was 51.4%. All suggested that the efficacy was primarily positive. All the statistical analysis is shown in Figures 1 and 2. The most prevalent treatment-related adverse reaction was cytokine release syndrome (CRS), which affected 52% of patients but was often minor. Neutropenia was observed in 16% patients. Cognitive dysfunction were observed in 70.1% of patients, and 11.2% of patients were seen with grade 3 or above.[11]

In the Phase II trial, 220 people with SCLC who had already received treatment took part. Both 10 and 100 mg dosages of tarlatamab were given to individuals. The objective response rate for the 10 mg group was 40.0%, whereas for the 100 mg dose it was 31.8%. With 10 mg doses, the results demonstrate a median overall survival of 14.3 months; however, the 100 mg level has not been reached yet. Hundred milligram dose resulted in a 4-month median progression-free survival, whereas 10-mg dose resulted in 5.0 months. The statistical analysis is shown in Figure 3.[12]

The most common adverse event in clinical trials, with 51% of participants reporting it, was CRS. The percentage of patients at 100 mg is 60.9%, which is quite high compared with just 1% at 10 mg. Most of the CRS were grade 1 or 2, and most of them were observed during the first cycle of treatment. Grade 3 was uncommon, affecting 0.8% of the participants at 10 mg and 5.7% at 100 mg. Most importantly, incidence of grade 4 and 5 were 0%, which shows a potentially fatal CRS incident. The rates of discontinuation for treatment-emergent adverse events in the 10 mg and the 100 mg groups were almost identical, which were 3% and 3.4%, respectively.[12]

In conclusion, after the approval of tarlatamab by US Food and Drug Administration, the analyzed data prove that tarlatamab has moderate and significant clinical benefit, as well as an acceptable level of safety for patients with SCLC who have undergone numerous prior treatments. It complements the existing treatments and offers opportunities to highly-susceptible patients, who have few treatment options.

[a] Trademark: Imdelltra™ (Amgen), Thousand Oaks, CA, USA.

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Tumor Response to Tarlatamab According to Investigator Assessment

Response	Interim Efficacy Analysis Set[a] (N = 107)
ORR, % (95% CI)	
Confirmed	23 (15.7 to 32.5)
Confirmed and unconfirmed	25 (17.3 to 34.6)
Disease control rate, % (95% CI)	51 (41.5 to 61.2)
Best overall response, No. (%)	
Confirmed complete response	2 (2)
Confirmed partial response	23 (22)
Stable disease	30 (28)
Progressive disease	9 (8)
Could not be evaluated[b]	34 (32)
No assessment[c]	9 (8)
TTR, months, median (IQR)	1.81 (1.68-1.91)
Duration of objective response months, median (95% CI)	12.3 (6.6 to 14.9)

Fig. 1. Tumor response to tarlatamab according to investigator assessment.[11] IQR = interquartile range; ORR = objective response rate; TTR = time to response. Superscript 'b' and 'c' indicate statistical significance and subgroup analysis, respectively.

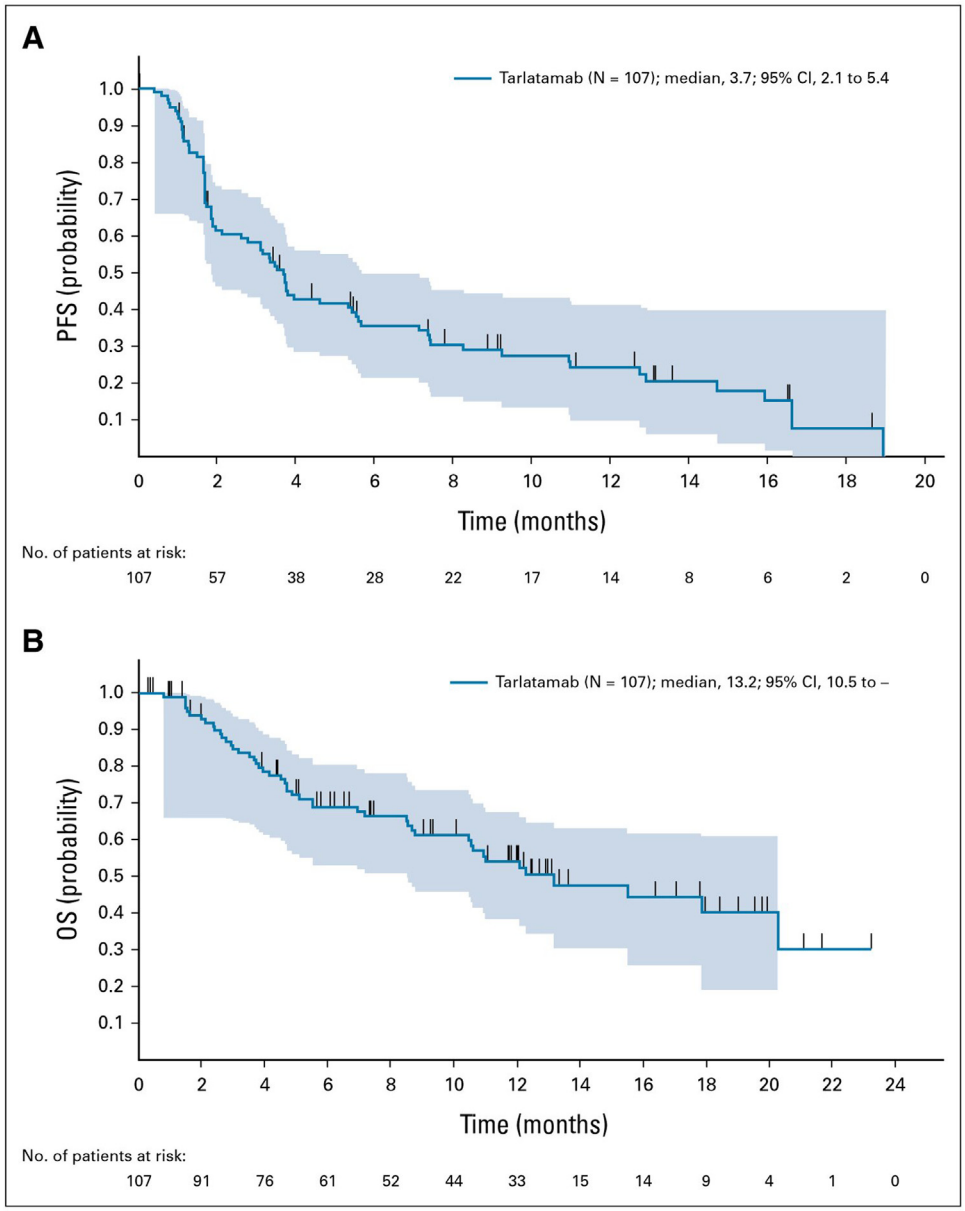

Fig. 2. Efficacy of tarlatamab in patients with small cell lung cancer.[11] (A) Kaplan–Meier curve of progression-free survival (PFS) for patients whose data cutoff date is at least 9 weeks after the first dose date (N = 107). (B) Kaplan–Meier curve of overall survival (OS) for patients whose data cutoff date is at least 9 weeks after the first dose date (N = 107).

	10 mg (n = 100)*	100 mg (n = 88)*
ORR, % (97.5% CI)	40.0 (29.1—51.7)	31.8 (21.1—44.1)
Complete response, n (%)	1 (1.0)	7 (8.0)
Partial response, n (%)	39 (39.0)	21 (23.9)
Stable disease, n (%)	30 (30.0)	27 (30.7)
Progressive disease, n (%)	20 (20.0)	13 (14.8)
Not evaluable, n (%)	2 (2.0)	4 (4.5)
Death before post-baseline scan, n (%)	6 (6.0)	13 (14.8)
No post-baseline scan, n (%)	2 (2.0)	3 (3.4)
mDoR, mo (95% CI)	NE (5.9—NE)	NE (6.6—NE)
Disease control rate % (95% CI)	70.0 (60.0, 78.8)	62.5 (51.5, 72.6)
mOS, mo (95% CI)	14.3 (10.8—NE)	NE (12.4—NE)
mPFS, mo (95% CI)	4.9 (2.9—6.7)	3.9 (2.6—4.4)

Fig. 3. Efficacy analysis set per intention-to-treat analysis (patients in safety substudy [n = 34] not included as data immature). mOS = median overall survival; mPFS = median progression-free survival; NE = not estimable; ORR = objective response rate .
Asterisk indicates p-value < 0.05; mDoR stands for median Duration of Response.

Author Contributions

Raza Ur Rehman conceived the study, designed the study protocol, and performed data analysis and interpretation literature review, data collection, and manuscript writing. Ahmad Furqan Anjum made critical revisions of the manuscript, gave final approval of the version to be published, supervised the study, and provided administrative support. Rida Fatima performed data analysis and interpretation literature review, data collection, and manuscript writing.

Declaration of competing interest

None.

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Raza Ur Rehman, MBBS*
Ahmad Furqan Anjum, MBBS
Rida Fatima, MBBS
Shaikh Khalifa Bin Zayed Al-Nahyan Medical and Dental College, Lahore, Punjab, Pakistan
*Address correspondence to: Shaikh Khalifa Bin Zayed Al-Nahyan Medical and Dental College, Lahore.
E-mail address: ranaraza7262@gmail.com (R.U. Rehman)