Original Study

Phase II Study of Arginine Deprivation Therapy With Pegargiminase in Patients With Relapsed Sensitive or Refractory Small-cell Lung Cancer

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Abstract

Recurrent small-cell lung cancer (SCLC) has limited chemotherapy options. Here, we report the outcome of the first trial of arginine-deprivation therapy (pegargiminase, ADI-PEG 20) in patients with relapsed/refractory SCLC. The best overall response to pegargiminase in SCLC was stable disease. Recent molecular stratification including MYC status and immune checkpoint blockade may leverage arginine-lowering therapy in SCLC going forward.

Background: Pre-clinical studies indicated that arginine-deprivation therapy using pegylated arginine deiminase (pegargiminase, ADI-PEG 20) may be effective in patients with argininosuccinate synthetase 1 (ASS1)-deficient small-cell lung cancer (SCLC). **Patients and Methods:** Patients were enrolled into either a 'sensitive' disease cohort ($\geq$ 90 days response to first-line chemotherapy) or a 'refractory' disease cohort (progression while on chemotherapy or $<$ 90 days afterwards or $\geq$ third-line treatment). Patients received weekly intramuscular pegargiminase, 320 IU/m^2 (36.8 mg/m^2), until unacceptable toxicity or disease progression. The primary endpoint was tumor response assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 with secondary endpoints including tolerability, pharmacodynamics, and immunogenicity. **Results:** Between January 2011 and January 2014, 22 patients were enrolled: 9 in the sensitive disease cohort and 13 in the refractory disease cohort. At a pre-planned interim analysis, the best overall response observed was stable disease in 2 patients in each cohort (18.2%). Owing to the lack of response and slow accrual in the sensitive disease cohort, the study was terminated early. Pegargiminase treatment was well-tolerated with no unexpected adverse events or discontinuations. **Conclusion:** Although pegargiminase monotherapy in SCLC failed to meet its primary endpoint of RECIST-confirmed responses, more recent molecular stratification, including MYC status, may provide new opportunities moving forward.

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Introduction

An estimated 1.6 million new lung cancers are diagnosed every year with small-cell lung cancer (SCLC) accounting for around 13% of cases.[1] Primary SCLC is associated with a cigarette-smoking history and derives from neuroendocrine precursor cells. SCLC is typified by a rapid proliferation rate together with a high response rate (~70%) to chemotherapy in the first-line setting.[1,2] However, the majority of patients with extensive SCLC will relapse with a median progression-free survival (PFS) of 5.5 months and a median overall survival of 9.6 months.[3] Response rates to second-line treatment are much poorer, being around 10% for patients with refractory disease ($<$ 3 months treatment-free interval) and 20% for patients with sensitive disease ($>$ 3 months).[1]

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Auxotrophy is the inability of an organism to synthesize an organic compound necessary for its growth.[4] At the cellular level, this has been exploited in the treatment of T-cell acute lymphoblastic leukemia (T-ALL) by the use of L-asparaginase. T-ALL cells are auxotrophic for asparagine owing to a lack of the enzyme asparagine synthetase, in contrast to normal cells.[5,6] Similarly, many tumor types have been found to be auxotrophic for arginine. Arginine is involved in the regulation of multiple cellular pathways, including proliferation via polyamines and mammalian target of rapamycin signaling, and as the precursor for nitric oxide involved in endothelial, immune, and neuronal cell biology.[7] Normal cells contain argininosuccinate synthetase 1 (ASS1), which converts citrulline to arginine, thereby providing an endogenous supply. However, many tumors downregulate ASS1, forcing them to be dependent on exogenous arginine (ie, arginine auxotrophic).[8-11] This has been studied most extensively in hepatocellular carcinoma (HCC) and melanoma, but has also been identified in a range of other tumor types.[7,12] An important mechanism of ASS1 downregulation is hypermethylation of the promoter, first identified in mesothelioma, although other mechanisms also play a role, including promoter repression by hypoxia-inducible factor-1α.[11,13] Downregulation of ASS1 leads to aspartate being shunted into increased pyrimidine synthesis and thereby tumor proliferation; thus bypassing the production of argininosuccinate and urea.[14] Notably, downregulation of ASS1 leads to a dependence on exogenous arginine that can be exploited therapeutically by catabolizing enzymes. One such approach is via arginine deiminase (ADI), which catalyzes the irreversible conversion of L-arginine to citrulline and an ammonium ion.[15] This was identified from Mycoplasma species and inhibited tumor growth in vitro.[16,17] However, in vivo, it is highly immunogenic with a short serum half-life, both of which were improved by conjugating ADI to polyethylene glycol (20,000 Da; ADI-PEG 20; pegargiminase).[18] The initial phase I/II trials were undertaken in HCC and melanoma owing to their high frequency of ASS1 loss.[19,20] Pharmacodynamic results showed that serum arginine was reduced to an undetectable level within 24 hours of the first ADI-PEG 20 injection and persisted for at least 7 days. The initial response rates in HCC and melanoma were promising, with no grade 3 or 4 toxicity observed from ADI-PEG 20.[19,20] Loss of ASS1 is a potential predictive biomarker to arginine deprivation therapy, with 53% of ASS1-deficient patients treated with ADI-PEG 20 having either a partial response or stable disease (SD) compared with 10% of ASS1-proficient patients with melanoma ($P = .041$).[10]

Pre-clinical data using SCLC cell lines and xenografts showed that 45% to 50% of tumors were negative for ASS1.[21] ADI-PEG 20 reduced the growth of $ASS1^-$, but not $ASS1^+$, cell lines in vitro. Similarly, arginine deprivation led to a dose-dependent reduction in the size of $ASS1^-$ xenografts in vivo, whereas $ASS1^+$ xenografts were resistant.[21] Therefore, the efficacy and safety of ADI-PEG 20 was examined in patients with ASS1-deficient SCLC.

Materials and Methods

Patients

Eligible patients were 18 years of age or older with histologically confirmed SCLC in which < 5% of tumor cells expressed ASS1 as determined by immunohistochemistry (0 or 1+ by ASS1 immunohistochemistry using mAb 195-21-1 from Polaris Pharmaceuticals, Inc, San Diego, CA). ASS1 levels were determined on archival tissue samples. Eligible patients must have had at least 1 previous line of chemotherapy prior to enrollment and have refractory/relapsed disease that was measurable by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[22] Patients had an Eastern Cooperative Oncology Group performance status of ≤ 2 as well as adequate hematologic, renal, and hepatic function. Exclusion criteria included metastatic disease to the central nervous system, unless treated and stable, as well as a history of seizures. Prior treatment with ADI-PEG 20 was not allowed.

Study Design

This was an open-label, 2-arm, non-randomized phase II study conducted across 8 centers in the United States, Taiwan, the United Kingdom, Germany, and Belgium. Cohort 1 enrolled patients with 'sensitive' disease who had maintained an appropriate response for 90 days or more after 1 previous line of chemotherapy. Cohort 2 enrolled patients with 'refractory' disease who had either progressed while on chemotherapy or within 90 days of completing treatment. Patients who required a third line of treatment, irrespective of the response duration to the initial 2 lines of chemotherapy (ie, sensitive or refractory), were also enrolled in Cohort 2. Each cohort was to be enrolled in 2 stages. In the first stage, 15 patients were to be enrolled in Cohort 1 and 12 patients in Cohort 2. If 3 or more patients met the primary endpoint (tumor response) in Cohort 1, then an additional 13 patients were to be accrued. If 2 or fewer patients met the primary endpoint in Cohort 1, then the study would be terminated and declared negative for this cohort. For Cohort 2, 1 or more patients had to meet the primary endpoint for an additional 4 patients to be accrued. If no patients achieved the primary endpoint in Cohort 2, then the study would be terminated and declared negative.

Treatment

Both cohorts received the same treatment regimen, consisting of 4 weekly intramuscular administrations of ADI-PEG 20, 320 IU/m^2 (36.8 mg/m^2) followed by a 1-week follow-up (1 cycle) as defined by earlier phase I/II studies.[19,20,23] No dose adjustment was allowed. If toxicity warranted a delay of 4 or more days, then the dose was omitted. Patients were withdrawn if 2 consecutive doses were omitted. Additional treatment cycles were permitted in the absence of disease progression requiring other therapeutic interventions.

End Points and Assessments

The primary endpoint for clinical efficacy was tumor response, defined as complete response (CR) or partial response (PR) as assessed by RECIST 1.1. Tumors could be assessed using any appropriate imaging. Tumor assessments could occur every 4 to 8 weeks, depending on local standard practice.

Secondary endpoints were the safety and tolerability of ADI-PEG 20 (assessed using National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 4.0); to measure changes in the plasma arginine and citrulline levels associated with ADI-PEG 20 treatment; to investigate the association between plasma arginine and citrulline levels and the primary endpoint; to

investigate the immunogenicity of ADI-PEG 20 by measuring anti-ADI-PEG 20 antibodies over time; and to estimate overall survival (measured from initial date of treatment).

Statistical Analysis and Ethical Considerations

The sample size for each cohort was determined through a Simon 2-stage Minimax design with type I error and type II error set to 0.05 and 0.2, respectively.

In Cohort 1, patients with sensitive disease, a 15% response rate was considered not promising (based on a pooled analysis assessing the efficacy of current standard treatment, topotecan, that indicated a response rate of 18%), and a 35% response rate was considered promising. A minimum of 15 and a maximum of 28 subjects were to be enrolled in this cohort.

In Cohort 2, patients with refractory disease and any patient in need of third-line therapy, a 5% response rate was considered not promising (based on there being no established effective treatment for these patients), but a 25% response rate was considered promising. A minimum of 12 and a maximum of 16 patients were to be enrolled in this cohort.

All statistical analyses were performed using Statistical Analysis Software (SAS) Version 9.2 or higher for Windows.

The study was performed in accordance with good clinical practice and Institutional Review Board approval. All patients provided written informed consent. ClinicalTrials.gov number NCT01266018.

Results

Patients

Between January 2011 and January 2014, 22 patients were enrolled; 9 with sensitive disease and 13 with refractory disease, across 8 international sites. The age range was 49 to 83 years, with a median of 62.5 years (Table 1). Fourteen (64%) patients were male, and 11 (50%) were recruited from the United States, with 6 (27%) from Taiwan, 3 (14%) from the United Kingdom, and 1 (4%) each from Belgium and Germany. Eleven (50%) patients were negative for ASS1, and 11 (50%) had < 5% cells positive.

Table 1 Demographic Characteristics at Baseline

	All Patients (n = 22), n (%)
Age, y	
Median (range)	62.5 (49-83)
Gender	
Male	14 (64)
Female	8 (36)
Country	
United States	11 (50)
Taiwan	6 (27)
United Kingdom	3 (14)
Germany	1 (4.5)
Belgium	1 (4.5)
Race	
White	14 (64)
Asian	6 (27)
Black or African heritage	1 (4.5)
Unknown	1 (4.5)
ASS1 assay result	
Negative	11 (50)
<5% cells positive	11 (50)

Abbreviation: ASS1 = argininosuccinate synthetase 1

Tumor Response

No patient had a CR or PR as their best overall response. Two (22%) patients in the sensitive disease cohort and two (15%) in the refractory disease cohort had a best overall response of SD or 18.2% (4/22) overall. One patient with SD in the refractory disease cohort had a biochemical response as assessed by a drop in serum lactate dehydrogenase during the first month of ADI-PEG 20 therapy. The remainder had progressive disease. One patient was withdrawn from the sensitive disease cohort as it was determined that it was in the best medical interests of the patient by the investigator, and one was withdrawn from the refractory cohort owing to clinical evidence of disease progression. As such, both patients were non-evaluable with regard to the primary endpoint.

As no patient in the refractory cohort had a radiologic response to ADI-PEG 20, thereby failing to meet the pre-specified interim analysis criteria for further accrual, and there was poor recruitment to the sensitive disease cohort, the study was terminated early. Overall survival was not analyzed owing to the premature termination of the study.

Tolerability and Safety

The median treatment duration was 6.1 weeks in the sensitive cohort (range, 0.1-7.0 weeks) and 2.1 weeks (range, 0.1-15.1 weeks) in the refractory disease cohort. Similarly, the median number of doses received was 6.0 (range, 1-8) in the sensitive disease cohort and 3.0 (range, 1-16) in the refractory disease cohort. This is in line with expectations as the sensitive disease group, by definition, had responded to previous chemotherapy and therefore probably had less aggressive disease.

The administration of ADI-PEG 20 320 IU/m^2 to patients with SCLC was not associated with adverse events (AEs) or laboratory abnormalities that were unexpected (Table 2). AEs of any type were reported in 21 (95%) of the 22 patients with 6 (27%), 3 (14%), and 3 (14%) patients experiencing grade 3, 4, or 5 events, respectively. Ten (45%) patients experienced serious AEs. AEs were assessed as being treatment-related in 12 (54%) patients. Three (14%) patients had their treatment discontinued owing to AEs related to disease progression.

The most common AEs of any grade were fatigue (10 patients; 45%), decreased appetite (7 patients; 32%), and dyspnea (5 patients; 23%). Nine (41%) patients experienced at least 1 grade 3 to 4 AE. Of these AEs, 10 related to decreased blood cell counts (including febrile neutropenia) and were experienced by 3 (14%) patients. The remainder were dyspnea (4 patients; 18%), cough (1 patient; 4.5%), somnolence (1 patient; 4.5%), asthenia (1 patient; 4.5%), and non-cardiac chest pain (1 patient; 4.5%). The most common treatment-related AEs of any grade were fatigue (5 patients; 23%), leukopenia (3 patients; 14%), neutropenia (3 patients; 14%), injection site reaction (3 patients; 14%), decreased appetite (3 patients; 14%), and nausea (3 patients; 14%). Four (18%)

Table 2 Reported Adverse Events Based on the Common Terminology Criteria for Adverse Events (CTCAE 4.0)

Adverse Event	All Reported Events		Treatment-related Events	
	All Grades, n (%)	Grade 3-4, n (%)	All Grades, n (%)	Grade 3-4, n (%)
Any	21 (95)	9 (41)	12 (54)	4 (18)
Constipation	4 (18)	0 (0)	0 (0)	0 (0)
Nausea	4 (18)	0 (0)	3 (14)	0 (0)
Vomiting	4 (18)	0 (0)	2 (9)	0 (0)
Diarrhea	3 (14)	0 (0)	2 (9)	0 (0)
Fatigue	10 (45)	0 (0)	5 (23)	0 (0)
Asthenia	4 (18)	1 (4.5)	0 (0)	0 (0)
Neutropenia	3 (14)	3 (14)	3 (14)	3 (14)
Leukopenia	4 (18)	3 (14)	3 (14)	3 (14)
Lymphopenia	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)
Thrombocytopenia	3 (14)	2 (9)	2 (9)	2 (9)
Febrile neutropenia	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)
Decreased appetite	7 (32)	0 (0)	3 (14)	0 (0)
Dysgeusia	2 (9)	0 (0)	2 (9)	0 (0)
Dyspnea	5 (23)	4 (18)	0 (0)	0 (0)
Cough	4 (18)	1 (4.5)	0 (0)	0 (0)
Wheezing	3 (14)	3 (14)	0 (0)	0 (0)
Somnolence	1 (4.5)	1 (4.5)	0 (0)	0 (0)
Non-cardiac chest pain	1 (4.5)	1 (4.5)	0 (0)	0 (0)
Pruritis	2 (9)	0 (0)	2 (9)	0 (0)
Injection site reaction	3 (14)	0 (0)	3 (14)	0 (0)

patients had treatment-related AEs at a maximum grade of 3 or 4 (none had grade 5) that were all related to low blood cell counts, including 1 episode of febrile neutropenia. In 1 patient, hematologic toxicity was exacerbated by receiving 2 accidental overdoses of ADI-PEG 20. Injection-related AEs occurred in 3 (14%) patients and were all grade 1 in severity. Three (14%) patients, all in the refractory disease cohort, had the study drug withdrawn owing to disease progression. Three patients died within 30 days of the last administration of the study drug. The causes were reported as disease progression in 2 patients and cardiac arrest in 1 patient, with none assessed as being related to ADI-PEG 20.

Hematologic testing showed a tendency for neutrophil, lymphocyte, and white blood cell counts to mildly decrease (grade 1 or less) by cycle 1, day 15, and then to recover to their baseline levels by day 29. In previous clinical trials of ADI-PEG 20, increases in amylase, lipase, uric acid, and liver transaminases were seen. In this study, the number of patients tested at baseline for amylase (6 of 9 patients in the sensitive disease cohort) and lipase (5 patients in the sensitive disease cohort and 1 patient in the refractory disease cohort) were too small to draw any meaningful conclusion. No notable changes in any other clinical chemistry test, including uric acid, alanine aminotransferase, and aspartate aminotransferase, were seen apart from the decrease in serum lactate dehydrogenase described above, and identified as a treatment-related effect.

Pharmacodynamics and Immunogenicity

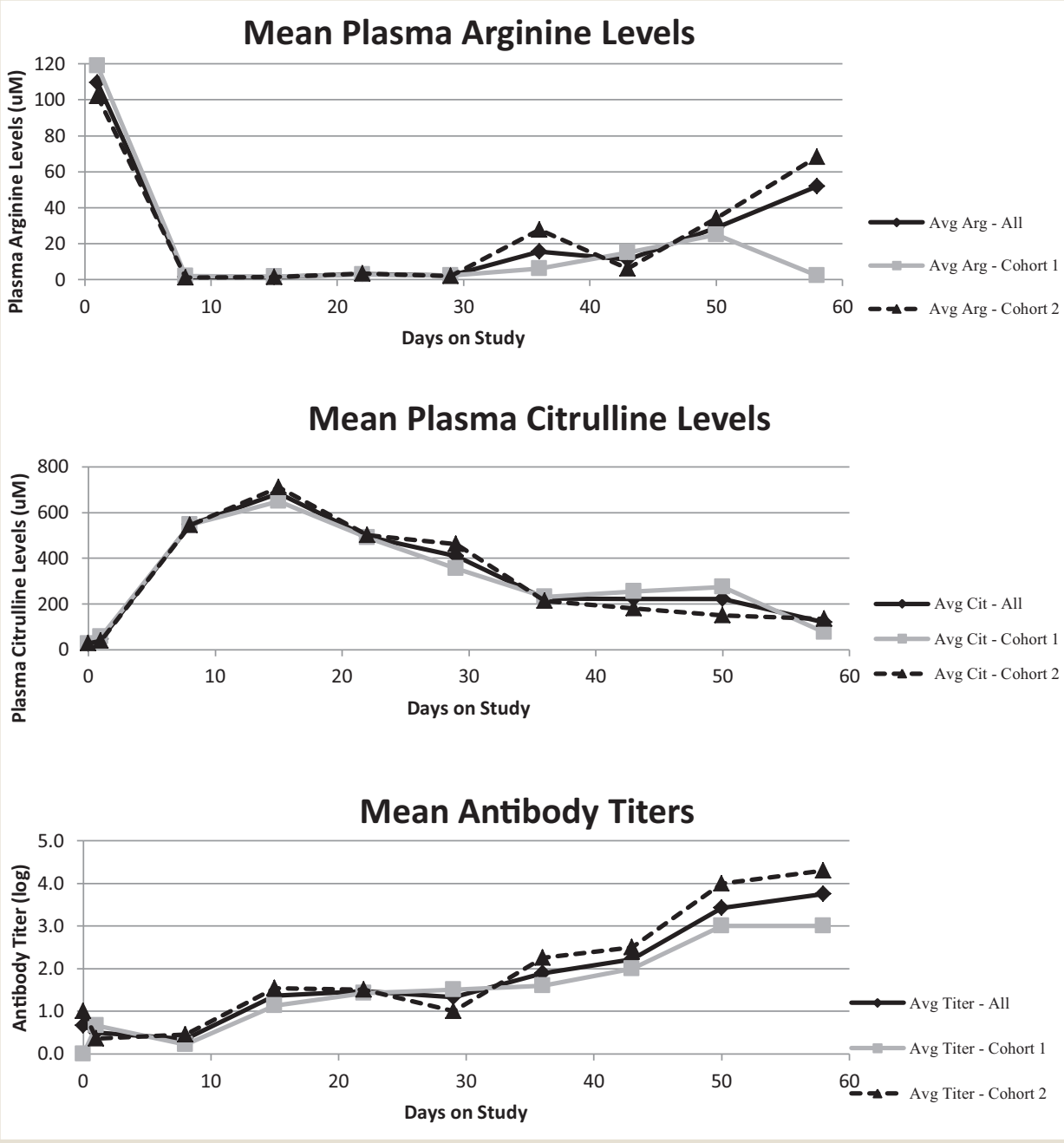
The arginine, citrulline, and anti-ADI-PEG 20 antibody levels were determined for 21 (95%) patients with available plasma samples. A total of 121 plasma samples were assessed. No significance difference in the pharmacodynamics was seen between the 2 cohorts (Figure 1). Weekly treatment with ADI-PEG 20 320 IU/m^2 (36.8 mg/m^2) was sufficient to reduce plasma arginine levels to $<$ 50% baseline for approximately 50 days, with a reciprocal rise in citrulline levels. However, by day 58 (the last day for which samples were analyzed), the mean arginine and citrulline levels were trending back towards their baseline levels. These changes correlated with the appearance of antibodies against ADI-PEG 20.

Discussion

This phase II study of arginine deprivation by ADI-PEG 20 in patients with relapsed or refractory SCLC failed to meet its primary endpoint, with no objective responses to treatment seen. This, coupled with slow accrual in the sensitive disease cohort, led to the trial being terminated early. The AEs seen in this study were expected for the study population and ADI-PEG 20 therapy. No patients discontinued owing to treatment-related AEs, and no deaths were attributable to the study drug. Fatigue, decreased appetite, and leucopenia were the most common treatment-related AEs, in line with the findings of other studies.[24,25]

The lack of objective responses is consistent with recent trials using ADI-PEG 20 monotherapy in other tumor types. Although a small-scale phase I/II trial with 19 patients suggested a meaningful response rate in HCC, this was not borne out in larger phase II and III trials with objective response rates of 0.5% to 3%.[19,25,26] Similarly, a randomized phase II study in ASS1-deficient malignant pleural mesothelioma (MPM) failed to record any objective responses.[24] However, an improvement in PFS of 1.2 months was seen in ADI-PEG 20-treated patients with mesothelioma compared with best supportive care alone (P = .03), highlighting that

Figure 1 Pharmacodynamics and Immunogenicity Studies. The Mean Arginine Levels (Top), Citrulline Levels (Middle), and Serum Levels of anti-ADI-PEG 20 (Bottom) for Patients Treated With ADI-PEG 20 in the Sensitive Disease Cohort (Cohort 1), the Refractory Disease Cohort (Cohort 2) and Both Cohorts Combined (All) are Shown by Day on Study



Abbreviations: ADI-PEG 20 = pegylated arginine deiminase (pegargiminase); Arg = arginine; Avg = average; Cit = citrulline.

response rate alone may be insensitive in measuring the activity of arginine-depleting agents. Moreover, post-hoc analysis revealed that the PFS improvement was proportional to the degree of ASS1 deficiency, with > 75% loss being associated with the best survival outcomes compared with > 50% to 75% deficiency.[24] This SCLC study required > 95% loss of ASS1 expression, indicating that this is unlikely to be the reason for the negative outcome.

Furthermore, the duration of arginine deprivation has been linked to overall survival, with prolonged arginine deprivation beyond 4 weeks linked to better outcomes across studies in melanoma, HCC, and MPM.[10,23,27] In this small study, the duration patients spent on pegargiminase therapy varied most notably in the refractory SCLC disease cohort (up to 16 weeks). This may indicate that there is a subgroup of ASS1-deficient patients with SCLC who

derive more benefit from pegargiminase and warrant further investigation. Indeed, one possibility is that these represent the MYC-driven variant SCLC subgroup characterized recently as exquisitely sensitive to ADI-PEG 20 using patient-derived xenografts of SCLC.[28] In contrast, cells of the more common classic or MYCL-driven subtype were resistant to arginine deprivation.[28] Unfortunately, owing to limited material from patients enrolled in this study, retrospectively testing for MYC status was not feasible. However, future studies of pegargiminase, at least potentially for monotherapy, would require SCLC molecular subtyping rather than ASS1 status alone in patient selection.[29]

Antibodies to ADI-PEG 20 appeared by day 50, consistent with prior monotherapy ADI-PEG 20 studies.[23,26,30,31] These may act to limit the efficacy of ADI-PEG 20. Other resistance mechanisms have been described, including re-expression of ASS1 via hypoxia-inducible factor-1α as well as autophagy.[13,21] Increased autophagy has been observed in SCLC cells in vitro in response to ADI-PEG 20 treatment and may provide a means of supplying arginine when exogenous levels are low.[21] Similarly, the tumor microenvironment has been implicated in supplying amino acids when exogenous levels are low, either through micropinocytosis or stromal cells.[12,32,33] Therefore, multiple mechanisms exist to maintain arginine homeostasis when plasma levels are low, and consequently pegargiminase alone, as with asparaginase monotherapy for T-ALL, will be limiting as a single agent. This is supported by the first phase III study of ADI-PEG 20 monotherapy in second-line treatment of advanced HCC that did not show a PFS or overall survival advantage versus placebo.[25]

There is a biochemical rationale for combining ADI-PEG 20 with chemotherapy. ASS1 positivity is associated with sensitivity to platinum chemotherapy, whereas ASS1 loss is a predictor of resistance.[34-36] Loss of ASS1 correlates with increased levels of thymidylate synthase (TS) and dihydrofolate reductase, target enzymes of pemetrexed chemotherapy.[12] High levels of TS have been associated with resistance to pemetrexed.[37,38] ADI-PEG 20 has been demonstrated to suppress TS and dihydrofolate reductase and thereby potentiate the effect of pemetrexed chemotherapy.[12] Therefore, given the heterogeneity of $ASS1^{+}$ and $ASS1^{-}$ cells in most tumors, a triplet combination of platinum plus pemetrexed and ADI-PEG 20 may prove more effective than either doublet chemotherapy or ADI-PEG 20 monotherapy.[39] This approach has shown promise in non–small-cell lung cancer, MPM, and relapsed glioblastoma, with larger scale trials ongoing.[40,41] Finally, with the recent incremental survival benefit of combining programmed death-ligand 1 blockade with carboplatin and etoposide as front-line therapy for extensive SCLC, there are additional avenues that merit further study.[42,43] Specifically, pegargiminase has been shown to induce programmed death-ligand 1 expression in tumor cell lines and promote a T cell infiltrate in syngeneic tumour models.[44] Moreover, urea cycle-deficient cancers, including functional loss of ASS1, may be more tractable to immunometabolic strategies in general.[45] Indeed, a phase I/II study is underway of a bioengineered form of human arginase 1, pegzilarginase, combined with pembrolizumab specifically in patients with relapsed SCLC (ClinicalTrials.Gov Identifier: NCT03371979).[46] In summary, combination studies will be critical in defining the role of depleting arginine as a novel anti-metabolite strategy for SCLC.

Conclusion

In conclusion, the use of pegargiminase monotherapy in patients with relapsed or refractory SCLC failed to meet its primary endpoint, with no tumor responses seen in either cohort. Four (18%) patients (2 in each cohort) had a best response of SD. The study was therefore terminated early. The treatment was well-tolerated with no unexpected AEs or discontinuations.

Clinical Practice Points

- SCLC is an aggressive form of lung cancer with limited effective treatment options after first-line chemotherapy.
- Many tumors, including 45% to 50% of SCLC, are auxotrophic for arginine, usually via downregulation of ASS1. As such, these tumors are unable to produce endogenous arginine and are dependent on an exogenous supply.
- This can be exploited therapeutically using ADI-PEG 20 (pegargminase), which showed efficacy in preclinical studies involving ASS1-deficient SCLC xenografts.
- This paper reports the first trial of ADI-PEG 20 in patients with relapsed/refractory SCLC, recruited into a 'sensitive' disease cohort ($\geq$ 90 days response to first-line chemotherapy; 9 patients) or a 'refractory' disease cohort (progression while on chemotherapy or $<$ 90 days afterwards or $\geq$ third-line treatment; 13 patients). The primary end point was tumor response rate by RECIST 1.1.
- At a pre-planned interim analysis, the best overall response observed was SD in 2 (18.2%) patients in each cohort. Owing to the lack of objective response and to slow accrual in the sensitive disease cohort, the study was terminated early.
- The outcome of this trial indicates that pegargiminase monotherapy is unlikely to be an effective treatment for recurrent/refractory SCLC. However, recent preclinical work has indicated that MYC status may identify a subpopulation of patients with SCLC who are sensitive to arginine deprivation monotherapy, and further combination trials are planned employing this stratification biomarker.
- Additionally, arginine-lowering agents combined with immune checkpoint blockade are being tested in the clinic, including in SCLC, based on preclinical immunometabolic cooperation.

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