2SMALL phase I part. Lurbinectedin (LUR) in combination with Atezolizumab (ATZ) for second line Extensive Stage Small Cell Lung Cancer (ES-SCLC) patients

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BACKGROUND

Current front-line treatment for ES-SCLC includes chemotherapy plus a PD-L1 inhibitor. FDA has recently approved LUR for pretreated patients with SCLC [1,2]

2SMALL is a two-part phase 1/2 study assessing the safety, tolerability and efficacy of LUR in combination with ATZ as second line treatment for ES-SCLC. Here is reported data from phase I part of the 2SMALL trial with data cut-off 14-July-2021

METHODS

2SMALL phase I was an open-label, single arm, dose exploration trial.

Eligible patients had confirmed ES-SCLC, who progressed to first line platinum-based treatment, ECOG performance status score 0-1, adequate organ function and with signed informed consent. Prior exposure to immunotherapy was not allowed.

During dose finding phase pts received increasing doses of LUR 2.5 mg /m2 - 3.2 mg /m2 on day 1 plus a fixed dose of ATZ (1200 mg) every 3 weeks following a standard 3+3 dose escalation design.

MTD was defined as the lowest dose level explored during dose escalation at which more than one third of evaluable patients experience a Dose Limiting Toxicity (DLT) during Cycle 1.

The RD was defined as the highest dose level explored during dose escalation at which less than one third of evaluable patients experience a DLT during Cycle 1.

OBJECTIVES

The primary objective of Phase I part was to determine the safety profile, the maximum tolerated dose (MTD) and the recommended dose (RD) for phase II studies of LUR in combination with ATZ in advanced SCLC patients progressing after platinum double chemotherapy.

Additional efficacy objectives included the Overall Response Rate (ORR) and the Progression Free Survival (PFS) analysis.

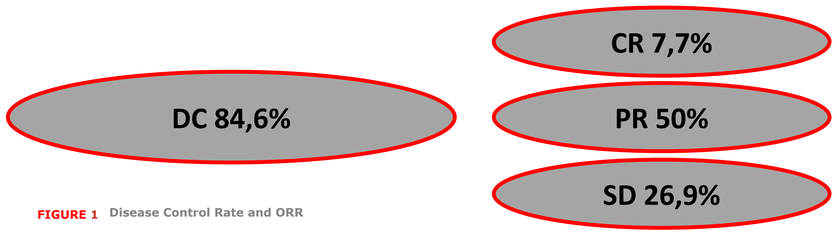

FIGURE 1 Disease Control Rate and ORR

References:
1.- Subbiah V, Paz-Ares L, Besse B, et al. Antitumor activity of lurbinectedin in second-line small cell lung cancer patients who are candidates for re-challenge with the first-line treatment. Lung Cancer 2020; 150:90-96.

2.- Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol 2020; 21(5):645-654.

RESULTS

A total of **26 patients** were treated, including male 14 pts (53.8%) and female 12 pts (46.2%) with median age 60.6 years

Five pts received LUR 2.5 mg/m2 + ATZ 1200 mg, and 3 pts were evaluable without DLT.

Out of the 21 pts who received LUR 3.2 mg/m2+ ATZ 1200 mg (6 pts with primary G-CSF), 5 pts (20.8%) developed DTLs:

- 2 pts G3 febrile neutropenia (9.5%) (1 pt with G4 thrombocytopenia)
- 2 pts G4 neutropenia lasting more than 72 hours (9.5%)
- 1 pt G4 thrombocytopenia (4.8%).

Most frequent hematological adverse events ≥ grade 2 (21 pts) in DL2 cohort were:

- 9 pts neutropenia (42.9%)
- 6 pts thrombocytopenia (28.6%)
- 4 pts anemia (19.1%)
- 1 pt lymphopenia (4.8%)
- 1 pt febrile neutropenia (4.8%)

The most common non-hematological treatment related adverse events ≥ grade 2 was asthenia 30.8 % (8 pts), **Table 1**. No treatment-related deaths were reported.

As the proportion of patients that experienced a DLT was less than a third (20.8%), the MTD could not be calculated.

TABLE 1 | **Treatment related adverse events with CTCAE grade higher than 1 (NCI-CTCAE v.5)**

Adverse event description – MedDRA PT term	DL1 N (%) (N=5)	DL2 N (%) (N=21)	TOTAL N (%) (N=26)
Neutropenia	3 (60)	9 (42.9)	12 (46.2)
Asthenia	1 (20)	7 (33.3)	8 (30.8)
Decreased apetite	1 (20)	5 (23.8)	6 (23.1)
Thrombocytopenia	0 (0)	5 (23.8)	5 (19.2)
Anaemia	0 (0)	4 (19.1)	4 (15.4)
Alanine aminotransferase increased	0 (0)	3 (14.3)	3 (11.5)
Haemoglobin decreased	0 (0)	2 (9.5)	2 (7.7)
Aspartate aminotransferase increased	0 (0)	1 (4.8)	1 (3.9)
Back pain	0 (0)	1 (4.8)	1 (3.9)
Blood creatinine increased	0 (0)	1 (4.8)	1 (3.9)
Diarrhoea	0 (0)	1 (4.8)	1 (3.9)
Dyspnoea	0 (0)	1 (4.8)	1 (3.9)
Fatigue	0 (0)	1 (4.8)	1 (3.9)
Febrile neutropenia	0 (0)	1 (4.8)	1 (3.9)
Hepatitis	1 (20)	0 (0)	1 (3.9)
Hypomagnesaemia	0 (0)	1 (4.8)	1 (3.9)
Lymphopenia	1 (20)	1 (4.8)	2 (7.7)
Myalgia	0 (0)	1 (4.8)	1 (3.9)
Nausea	0 (0)	1 (4.8)	1 (3.9)

RESULTS

Objective responses (ORR) were observed in 15 pts (57.7%), including complete responses (CR) in 2 pts (7.7%), partial response (PR) in 13 pts (50%). Stable disease (SD) was observed in 7 pts (26.9%) and 3 pts (11.54%) were in progressive disease (PD). Disease control rate (DC) was 84.61%, **Figure 1**.

With 8 pts censored for progression, median PFS was 4.93 months (range 3.37 - 7.47 months) and patient duration of response for each patient was as follow, **Figure 2.**

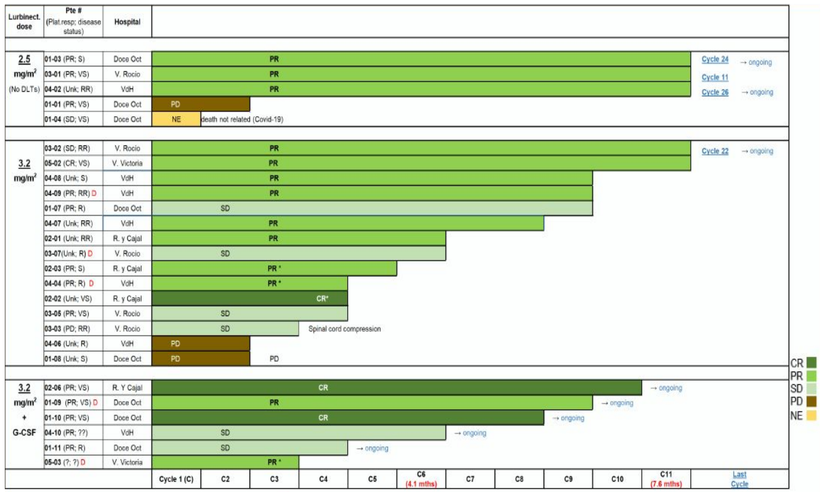

FIGURE 2 Patient status of treatment (S sensitive; VS very sentitive; R resistant; RR refractory; D DLT)

CONCLUSION

- The combination of LUR plus ATZ was well tolerated, without unexpected toxicities
- Transient hematological toxicity was dose limiting
- The RD for further studies is LUR 3.2 mg/m2 on Day 1 + ATZ 1200 mg Day 1 with G-CSF
- Preliminary anti-tumor activity is remarkable
- 2SMALL trial part II is ongoing and will provide further data regarding efficacy and safety of the regimen for second line SCLC.

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