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Atezolizumab (ATZ) plus Carboplatin (Cb) and Etoposide (Eto) in patients with untreated extensive-stage small-cell lung cancer (ES-SCLC): results from the Interim Analysis of MAURIS trial

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INTRODUCTION

- Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers and is characterised by early development of metastatic disease and hence poor prognosis[1].
- Atezolizumab (ATZ) is a humanized monoclonal anti–programmed death ligand 1 (PD-L1) antibody that inhibits PD-L1–programmed death 1 (PD-1) and PD-L1–B7-1 signaling and restores tumor-specific T-cell immunity[2].
- The results of the IMpower133 Phase III study showed that the addition of ATZ to 4 cycles of carboplatin (Cb) and etoposide (Eto) in extended stage (ES) SCLC was associated with significantly longer overall survival (OS) and progression-free survival (PFS) compared to chemotherapy alone, with a safety profile consistent with the defined toxic effects of the individual agents[3].

OBJECTIVES

MAURIS (Eudract No. 2019-001146-17) is a multicenter, open-label, single arm, phase IIIb trial conducted in 25 sites, aimed at evaluating the safety and efficacy of ATZ + Cb-Eto in patients with newly diagnosed ES-SCLC, including those not previously evaluated in the pivotal trial.

PATIENTS AND METHODS

- Main inclusion criteria
  - Histologically or cytologically confirmed ES SCLC, with measurable disease
  - Life expectancy > 12 weeks
  - ECOG Performance Status 0-2
  - Asymptomatic treated or untreated brain metastasis
  - No previous systemic treatment for ES-SCLC
  - Adequate hematologic and end-organ function

TREATMENT

Patients received ATZ 1200 mg + Cb-Eto every 3 weeks for 4–6 cycles in the induction phase (at the Investigator's discretion), followed by ATZ maintenance every 3 weeks up to disease progression, unacceptable toxicity or clinical deterioration.

STUDY ENDPOINTS

- Primary endpoints
  - Incidence of serious adverse events (SAEs)
  - Incidence of serious and non-serious immune-mediated adverse events (imAEs)
- Secondary endpoints
  - Survival rate at one year
  - Overall survival (OS)
  - Progression-free survival (PFS)
  - Overall response rate (ORR)

DATA ANALYSIS

Safety analyses were conducted in the Safety set, defined as all enrolled patients who had at least one administration of ATZ + Cb-Eto. The results of safety refer to the induction phase of the study. Efficacy analyses were conducted in the intent-to-treat (ITT) set, defined as all recruited patients. Data analysis was performed in overall patients and in subgroups based on the number of cycles of induction, i.e. in patients that performed ≤ 3 cycles, 4 cycles and 5-6 cycles.

RESULTS

- **Patient disposition and exposure**

A total of 155 patients were enrolled, 154 (99.4 %) were treated and 119 (76.8%) entered the maintenance phase: 139 patients (90.3%) discontinued treatment, 35 patients (22.6%) in the induction phase and 104 (67.1%) in the maintenance phase. At the cut-off date for the interim analysis (21 Oct 2021) at one year after the closure of enrolment, the median duration of follow-up was 10.5 months (range 0-2-24.3 months). In the safety set, 89 patients (57.8%) performed 5-6 cycles, 22 patients (14.3%) performed ≤ 3 cycles and 43 patients (27.9%) performed 4 cycles of induction. At a median follow-up of 10.5 months, the median number of ATZ administrations was 8.0 (range 1-35), the median number of administrations of Cb was 6.0 (range 1-6) and the median number of administrations of Eto was 18.0 (range 3-18). Overall, 14 patients receivedthoracic radiotherapy during the study and 15 patients received prophylactic cranial irradiation during the maintenance phase.

- **Baseline characteristics of patients**

Table 1 shows the baseline characteristics of patients overall and by subgroup.

Table 1. Summary of baseline characteristics of patients overall and by subgroup (ITT set)

	Total n=155	≤3 cycles n=23	4 cycles n=43	5-6 cycles n=89
Age (years), mean (SD)	65.1 (9.05)	67.2 (7.48)	67.2 (9.90)	63.6 (8.77)
Gender, n (%)				
Females	60 (38.7%)	5 (21.7%)	15 (34.9%)	40 (44.9%)
Males	95 (61.3%)	18 (78.3%)	28 (65.1%)	49 (55.1%)
ECOG PS, n (%)				
0	68 (44.2%)	5 (21.7%)	19 (44.2%)	44 (50.0%)
1	80 (51.9%)	16 (69.6%)	23 (53.5%)	41 (46.6%)
2	6 (3.9%)	2 (8.7%)	1 (2.3%)	3 (3.4%)
Smoking status, n (%)				
Never smoked	8 (5.2%)	1 (4.3%)	2 (4.7%)	5 (5.6%)
Current smoker	59 (38.1%)	9 (39.1%)	17 (39.5%)	33 (37.1%)
Former smoker	88 (56.8%)	13 (56.5%)	24 (55.8%)	51 (57.3%)
Previous diagnosis of limited stage SCLC, n (%)	14 (9.0%)	2 (8.7%)	8 (18.6%)	4 (4.5%)
Brain metastases at baseline, n (%)	19 (12.3%)	5 (21.7%)	3 (7.0%)	11 (12.4%)
Untreated brain metastases at baseline, n (%)	13 (8.4%)	2 (8.7%)	2 (4.7%)	9 (10.1%)
Longest diameter of target lesions (mm), mean (SD)	49.0 (32.1)	37.3 (28.3)	35.4 (21.3)	38.8 (23.8)

- **Results of efficacy**

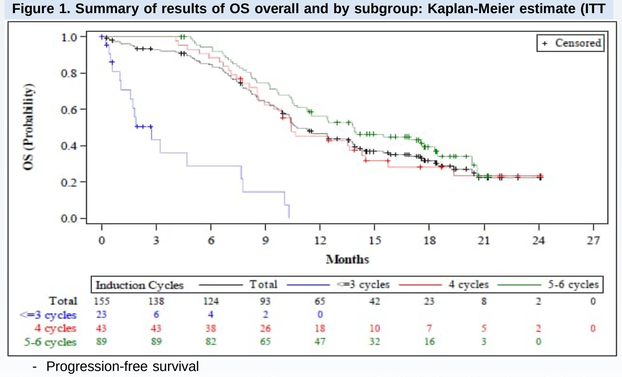
- Survival rate at one year

In the overall ITT population, 65 patients (41.9%; 95% CI, 34.5% to 49.8%) were alive at 1 year. The number of patients alive at 1 year was 18 (27.3%; 95% CI, 18.0% to 39.0%) in those who performed 4 induction cycles and 47 (52.8%; 95% CI, 42.5% to 62.8%) in those who performed 5-6 induction cycles. None of the 23 patients that performed ≤ 3 cycles was alive at 1 year.

- Overall survival (OS)

The median OS in the overall ITT population was 10.7 months (95% CI, 9.9 to 13.7 months). Figure 1 shows the results of OS by subgroup (number of cycles of induction). The median OS was longer in patients who performed 5-6 induction cycles (13.8 months, 95% CI, 10.7 to 18.2 months) than in those who performed 4 cycles (10.4 months, 95% CI, 8.6 to 14.2 months) or ≤ 3 cycles (2.7 months, 95% CI, 1.0 to 7.6 months).

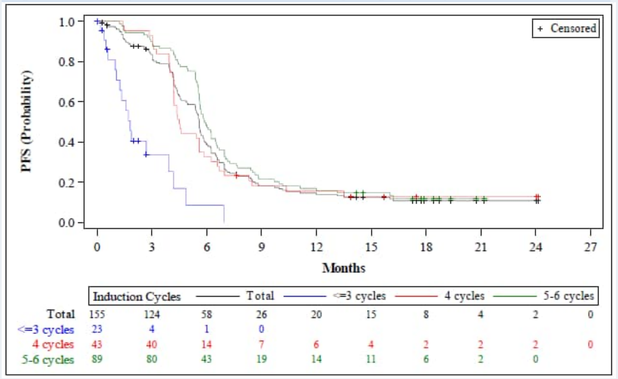
Figure 1. Summary of results of OS overall and by subgroup: Kaplan-Meier estimate (ITT



- Progression-free survival

The median PFS in the overall ITT population was 5.5 months (95% CI, 5.3 to 5.8 months). Figure 2 shows the results of PFS by subgroup (number of cycles of induction). The median PFS was longer in patients who performed 5-6 induction cycles (5.8 months, 95% CI, 5.5 to 6.5 months) than in those who performed 4 cycles (4.5 months, 95% CI, 4.1 to 5.5 months) or ≤ 3 cycles (1.8 months, 95% CI, 1.0 to 3.9 months).

Figure 2. Summary of results of PFS overall and by subgroup: Kaplan-Meier estimate (ITT



- Overall response rate (ORR)

In the overall ITT population, 111 patients (71.6%; 95% CI, 64.1% to 78.1%) had response and 44 (28.4%; 95% CI, 21.9% to 35.9%) did not respond to treatment. The proportion of responder patients was higher in those who performed 5-6 cycles (75 patients, 84.3%) than in those who performed 4 cycles (31 patients, 72.1%) or ≤ 3 cycles (5 patients, 21.7%).

- **Results of safety in the induction phase**

Table 2 shows the overall summary of results of safety overall and by subgroup.

Table 2. Overall summary of results of safety in the induction phase (safety set)

	Total n=154	≤3 cycles n=22	4 cycles n=43	5-6 cycles n=89
TEAEs	139 (90.3%)	21 (95.5%)	41 (95.3%)	77 (86.5%)
Treatment-related TEAEs	117 (76.0%)	13 (59.1%)	35 (81.4%)	69 (77.5%)
Grade 3-4 TEAEs	80 (51.9%)	13 (59.1%)	23 (53.5%)	44 (49.4%)
Grade 3-4 treatment-related TEAEs	73 (47.4%)	10 (45.5%)	22 (51.2%)	41 (46.1%)
SAEs	46 (29.9%)	14 (63.6%)	15 (34.9%)	17 (19.1%)
Treatment-related SAEs	28 (18.2%)	6 (27.3%)	12 (27.9%)	10 (11.2%)
Treatment discontinuations due to TEAEs	9 (5.8%)	5 (22.7%)	1 (2.3%)	3 (3.4%)
Ate discontinuations due to TEAEs	7 (4.5%)	5 (22.7%)	1 (2.3%)	1 (1.1%)
CB discontinuations due to TEAEs	7 (4.5%)	4 (18.2%)	0 (0.0%)	3 (3.4%)
Eto discontinuations due to TEAEs	7 (4.5%)	4 (18.2%)	0 (0.0%)	3 (3.4%)
TEAEs leading to death	7 (4.5%)	6 (27.3%)	0 (0.0%)	1 (1.1%)
Treatment-related TEAEs leading to death	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Adverse events of special interest (AESI)	15 (9.7%)	4 (18.2%)	3 (7.0%)	8 (9.0%)
Infusion/injection site reactions	10 (6.5%)	2 (9.1%)	1 (2.3%)	7 (7.9%)
Im-TEAEs	23 (14.9%)	4 (18.2%)	5 (11.6%)	14 (15.7%)
Im-SAEs	4 (2.6%)	1 (4.5%)	2 (4.7%)	1 (1.1%)

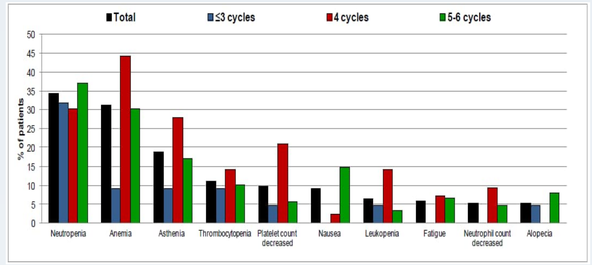
TEAEs: treatment-emergent adverse events

The most common imTEAEs by preferred term (PT) in the overall Safety set were: hypothyroidism, diarrhea, asthenia and pruritus, all with 3 events in 3 patients (1.9%). The four serious imTEAEs consisted of (PT) diarrhoea, platelet count decreased, encephalitis autoimmune and pruritus.

- **Results of safety**

Figure 3 shows the most common treatment-related (to any component) TEAEs by PT.

Figure 3. Most common (i.e. reported in ≥ 5% of patients overall) treatment-related (any component) TEAEs by PT



CONCLUSIONS

- The results of safety in the induction phase of the MAURIS study are in line with the known safety profile of ATZ, CB and Eto.
- More than half of the patients continued the induction up to 5-6 cycles, according to the Investigator's choice based on safety and efficacy evaluation.
- The longer benefit for patients receiving 5-6 cycles of chemotherapy in comparison with those ≤4 deserves further investigation
- There was no evidence of an increase in the risk of toxicity with an increased number of cycles in the induction phase of the study (however, a minority of patients performed ≤ 3 cycles).
- The results of efficacy observed up to the cut-off date (median follow-up 10.5 months) seems to be in line with those observed in the pivotal trial. The median OS was slightly shorter than that of the IMpower133 study, possibly due to the inclusion of patients with a worse prognosis. Instead mPFS and ORR were comparable.
- The final analysis of the MAURIS study will provide more data on the safety and efficacy of ATZ in combination with CB plus Eto for the treatment of ES SCLC patients managed in Italy.

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