Real-world data about treatment pattern and outcomes of patients with unresectable advanced or metastatic esophageal squamous cell carcinoma in France: results from the Fregat database

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Background

- Esophageal cancer is the seventh most common cancer and sixth leading cause of cancer death, worldwide, with approximately 600,000 new cases and over 540,000 deaths in 2020[1]. In France, more than half of esophageal cancers are unresectable at diagnosis, and most patients treated with curative intent eventually have a relapse[2].
- Squamous cell carcinoma accounts for approximately 60% of cases in Europe[3]. Patients with esophageal cancer that is metastatic or unresectable have a poor prognosis, especially in squamous cell carcinoma; median survival in clinical trials with chemotherapy has historically been <1 year[4]. Immune checkpoint inhibitors (ICI) have showed promising results for these patients[5,6] and nivolumab in combination with chemotherapy has been approved by the European Medicines Agency in April 2022 based on CheckMate 648 results for those patients with tumor cell PD-L1 ≥1%[6].

Objective

- The objective of this study is to better characterize "real-world" characteristics, treatment and outcomes (including overall survival [OS] and progression-free survival [PFS]) of French patients presenting with UnResectable Advanced, or Metastatic Esophageal Squamous-Cell Carcinoma (URAM-ESCC) from 2014 to 2019 before arrival of immune-checkpoint inhibitors (ICI)
- A secondary objective was to compare the profile and outcomes of the population enrolled in a phase III clinical trial with patients treated by ICI meeting the same selection criteria treated in a real-world setting

Method

Study design

- We conducted a retrospective cohort study to describe clinical and demographic characteristics, treatment and outcomes of patients within the FREGAT database which collected data for approximately 4,000 patients from 35 French centers[7]. Patients were identified to have URAM-ESCC at de novo diagnosis or during follow-up. OS and PFS were assessed using Kaplan-Meier method.
- A sub-group analysis was conducted on patients matching the inclusion criteria of CheckMate 648 evaluating nivolumab in combination with chemotherapy in this indication :
  - Subjects must have histologically confirmed squamous cell carcinoma or adeno-squamous cell carcinoma (predominant squamous differentiation) of esophagus.
  - Subjects must have unresectable advanced, recurrent, or metastatic ESCC.
  - Subjects must not be amenable to curative approaches such as definitive chemoradiation and/or surgery.
  - No prior systemic anticancer therapy given as primary therapy for advanced or metastatic disease. Prior adjuvant, neoadjuvant, or definitive, chemotherapy/ radiotherapy/ chemoradiotherapy for ESCC was permitted if given as part of curative intent regimen and completed before enrollment. A recurrence-free period is required for 24 weeks after completion of neoadjuvant or adjuvant chemotherapies, or after completion of multimodal therapies (chemotherapies and chemoradiotherapies) for locally advanced diseases.
  - ECOG Performance Status of 0 or 1.

Statistical analysis

- OS and PFS were defined from date of diagnosis of URAM-SCC or start of first-line therapy (index date) until death, recurrence/progression or last follow-up visit for those still alive at the end of study period. The Kaplan-Meier method was used to estimate survival rates. A Cox proportional hazards regression was performed to characterize relationships between patient characteristics (first-line treatment and clinical/tumor) and clinical outcomes.

Results

Population

Whole population

- The FREGAT database included a total number of 843 ESCC patients enrolled over the period 2014-2019. Among them 225 patients were diagnosed with URAM-ESCC as de novo in 137 (61%) and as recurrent in 86 (39%). Median age was 62 years, 77% were male. The performance status at inclusion (ECOG) were 0 in 56%, 1 in 35% and 2+ in 9%. The TNM metastatic was ≥ 1 in 47.5% and the grade was ≥ 2 in 51% of patients. Among these 225 patients, 216 (96%) received an active treatment which was chemotherapy in 174 (77%) and radiotherapy in 84 (23%).

Sub-population meeting inclusion criteria of CheckMate 648 study

- A total of 120 (69%) patients met the selection criteria of the randomized Phase-III trial CheckMate 648 and received a first-line active systemic treatment. Median age was 62.4 years and 77% were male. The Performance status at diagnosis of URAM-SCC (ECOG) were 0 in 57%, and 1 in 43%. The TNM metastatic was ≥ 1 in 41% and the grade was ≥ 2 in 64% of patients.

Treatment pattern

Whole population

- Among the 174 patients who received a first-line chemotherapy, it was most frequently with 5FU+Oxaliplatin+leucovorin (n=115 ; 66%) or 5FU+Cisplatin (n=12 ; 7%) or 5FU+Oxaliplatin (n=9 ; 5.2%) followed by a high diversity of other regimens. Among patients receiving first-line chemotherapy, 44 (25%) received second-line chemotherapy, most frequently Paclitaxel (n=10 ; 23%) or FOLFIRI (n=8 ; 18%).

Table 1. Treatment received in whole URAM-ESCC population

First-line regimen	N (%)
FOLFOX : folinic acid + 5FU + Oxaliplatin	115 (66.1)
5FU + Cisplatin	12 (6.9)
5FU + Oxaliplatin	9 (5.2)
LV5FU2 : folinic acid + 5FU	8 (4.6)
Carboplatin + Paclitaxel	7 (4.0)
DCF : Docetaxel + Cisplatine + 5FU	4 (2.3)
FOLFIRI : folinic acid + 5FU + Irinotecan	4 (2.3)
Other	15 (1.1)

Sub-population meeting inclusion criteria of CheckMate 648 study

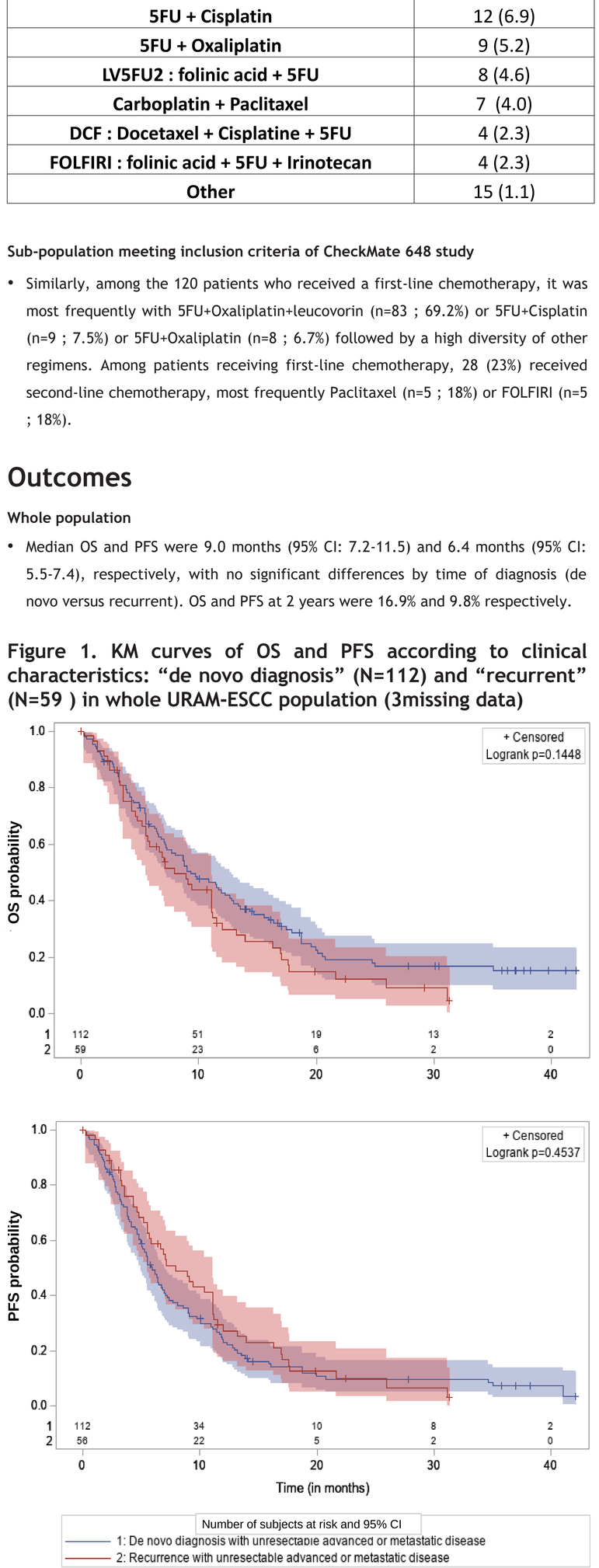
- Similarly, among the 120 patients who received a first-line chemotherapy, it was most frequently with 5FU+Oxaliplatin+leucovorin (n=83 ; 69.2%) or 5FU+Cisplatin (n=9 ; 7.5%) or 5FU+Oxaliplatin (n=8 ; 6.7%) followed by a high diversity of other regimens. Among patients receiving first-line chemotherapy, 28 (23%) received second-line chemotherapy, most frequently Paclitaxel (n=5 ; 18%) or FOLFIRI (n=5 ; 18%).

Outcomes

Whole population

- Median OS and PFS were 9.0 months (95% CI: 7.2-11.5) and 6.4 months (95% CI: 5.5-7.4), respectively, with no significant differences by time of diagnosis (de novo versus recurrent). OS and PFS at 2 years were 16.9% and 9.8% respectively.

Figure 1. KM curves of OS and PFS according to clinical characteristics: "de novo diagnosis" (N=112) and "recurrent" (N=59) in whole URAM-ESCC population (3missing data)



Sub-population meeting inclusion criteria of CheckMate 648 study

- In the population of patients meeting the strict selection criteria of randomized Phase-III CheckMate 648, median OS and PFS were 9.0 months (95% CI 7.1 – 12.2) and 6.3 months (95% CI 5.3– 7.7), respectively.
- In Table 2, are presented a summary of OS and PFS results for whole URAM-ESCC population, sub-populations according to URAM diagnosis and sub-population meeting the inclusion criteria of CheckMate 648 study and the corresponding results from the trial.
- For sub-population meeting CheckMate 648 criteria of inclusion, OS and PFS had no significant differences according to the regimens used in first-line. Note that patients with tumor cell PD-L1 expression of ≥1% could not be document yet in the FREGAT database.

Table 2. Survival outcomes according to populations, clinical characteristics and first-line treatment

Clinical characteristics	Median OS months (95%CI)	Median PFS months (95%CI)
Whole URAM-ESCC population from FREGAT database		
De novo diagnosis (N=112)	9.3 (7.2-12.8)	5.9 (4.9-7.1)
Recurrent diagnosis (N=59)	8.9 (5.6-11.2)	8.0 (5.5-11.1)
URAM-ESCC sub-population meeting inclusion criteria of CheckMate 648 study from FREGAT database		
Overall (N=120)	9.0 (7.1 – 12.2)	6.3 (5.3 – 7.7)
Treated with Fp+Pt±lv (N=100)	9.0 (6.8 – 12.8)	6.2 (5.2 – 7.7)
Treated with FOLFOX (N=83)	9.1 (7.1 – 13.0)	6.3 (5.3 – 8.6)
Population from Phase-III CheckMate 648 study		
Overall population (control arm*)	10.7 (9.4–11.9)	5.6 (4.3–5.9)
Patients with tumor cell PD-L1 ≥1% (control arm*)	9.1 (7.7–10.0)	4.4 (2.9–5.8)

Fp+Pt±lv = FOLFOX or 5FU+Cisplatin or 5FU+Oxaliplatin

*CheckMate 648 control arm = FOLFOX or XELOX first-line chemotherapy

Conclusion

- This study offers insights into treatments options in current practice and outcomes in unselected French patients diagnosed with URAM-ESCC between 2014 and 2019 before arrival of immunotherapy.
- In the context where majority of patients receive different first-line chemotherapy regimen, outcomes confirm the high burden of this cancer and the need of more efficient therapeutic options.
- These results were consistent with outcomes in the CheckMate 648 control arm and suggested that results from CheckMate 648 clinical trial were transferable to a real-world French population.

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