Identifying effect of a treatment from observational data in absence of contemporaneous control – Example of the TOSCA study, comparing the efficacy of cemiplimab vs. Historical Systemic Treatment in Cutaneous Squamous Cell Carcinoma in France

ID#: MSR145

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INTRODUCTION & OBJECTIVES

- Cemiplimab, an anti-programmed cell death receptor-1 (PD1) antibody, is approved and recommended by the European and US guidelines for the treatment of patients with locally advanced cutaneous squamous cell carcinoma (laCSCC) ineligible for curative surgery or radiation, or metastatic CSCC (mCSCC), based on a non comparative pivotal phase II study[1,2].
- Before cemiplimab, there was no approved systemic therapy for patients with advanced CSCC and treatment options had limited supporting evidence.
- In the absence of evidence from Randomized Controlled Trial, the TOSCA study aims to identify the effect of cemiplimab versus Historical Systemic Treatment (HST) from observational retrospective data.

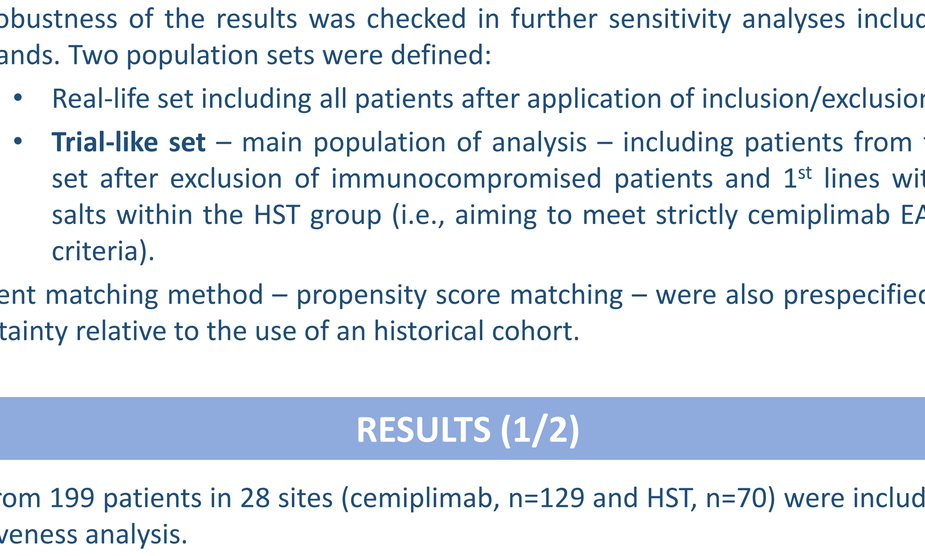
METHODS

- TOSCA is a retrospective, multicenter study (NCT05302297) in patients with advanced-CSCC treated with cemiplimab via the Early Access Program (EAP) (2018-2019) or with HST (2013-2018).
- Data was collected in 2022 in 28 centers in France.
- From the availability of cemiplimab in 2018, most patients eligible to cemiplimab received it; thus, contemporaneous control was not available.
- Primary endpoint was overall survival (OS).
- Secondary endpoints were progression-free survival (PFS), duration of response (DOR), overall response rate (ORR) and safety.
- Up to 3 lines of therapy could be extracted in the HST group. Since observation in the HST group could not be matched with observation in the cemiplimab group on the exact number of treatment line, a bootstrapping method was used to select the line of treatment of interest in the HST group objectively, making the number of treatment line of interest comparable between both groups.
- The main challenge was to control for imbalance in confounders between treatment groups.
    - Confounders – age, gender, known ongoing immunosuppression at advanced CSCC diagnosis, ongoing genodermatosis at advanced CSCC diagnosis, any multiple CSCC (>2) and type of advanced CSCC – were identified through systematic literature review and validated by a Scientific Committee.
    - Probability of treatment exposure (propensity score) was computed for each observation. **Inverse probability of treatment weighting (IPW)** approach was then used for emulating a pseudo-population in which the effect of cemiplimab vs. HST was assessed, corresponding to the main effectiveness analysis.
- The robustness of the results was checked in further sensitivity analyses including various estimands. Two population sets were defined:
    - Real-life set including all patients after application of inclusion/exclusion criteria;
    - **Trial-like set** – main population of analysis – including patients from the real-life set after exclusion of immunocompromised patients and 1st lines with platinum salts within the HST group (i.e., aiming to meet strictly cemiplimab EAP eligibility criteria).
- Different matching method – propensity score matching – were also prespecified to explore uncertainty relative to the use of an historical cohort.

RESULTS (1/2)

- Data from 199 patients in 28 sites (cemiplimab, n=129 and HST, n=70) were included in main effectiveness analysis.
- Effective Sample Size (ESS) was estimated according to Philippo & al. at 173. After weighting, patient characteristics were balanced between the two groups including similar age, gender, metastatic status, ECOG performance status, multiple localization, ongoing genodermatosis but the number of pretreated patients remained higher in the cemiplimab arm.
- After controlling for confounding using IPW, the median OS of 21 months [95% CI, 15–26] in the cemiplimab group (median follow-up of 20 months) was higher than the one of 10 months [95% CI, 6–13] in the HST group (median follow-up of 10 months) with an hazard ratio of death of 0.57 [95%CI]: [0.45-0.73] (P-value <0.0001) (*Figure 1*).

Figure 1 – OS using the Kaplan-Meier method (trial-like set – IPW method)

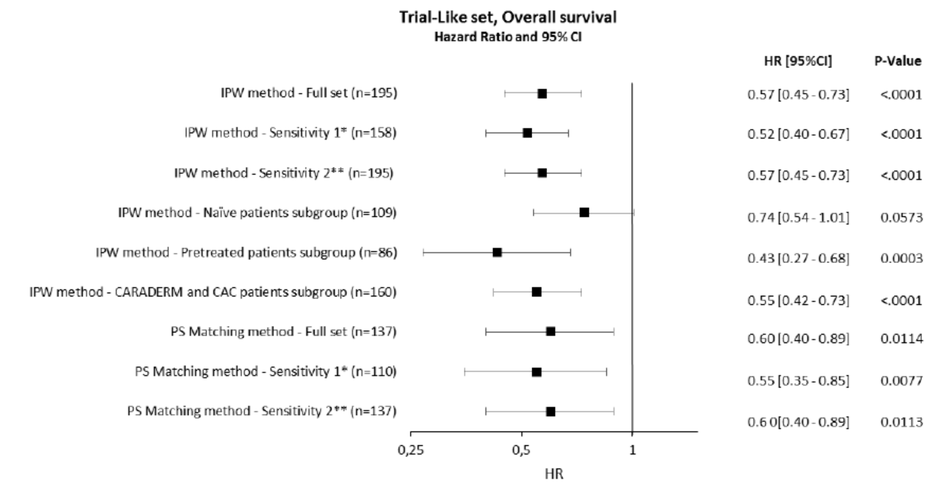


Notes:
199 patients in the population but 195 patients with non-missing time to event (126 in the cemiplimab group and 69 in the control group).
The cemiplimab curve was shorter than the control curve because the time interval for data collection was larger for the control group than for the cemiplimab group.

RESULTS (2/2)

- Sensitivity analyses were consistent with the main results (*Figure 2*).

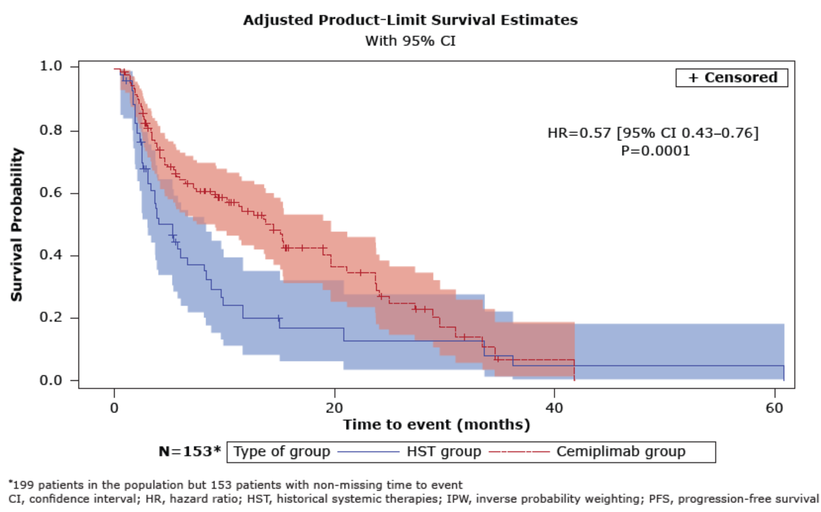
Figure 2 – Global forest plot for overall survival using Cox regression model estimation (trial-like set)



CAC, Center Against Cancer; CI, Confidence Interval; HR, Hazard Ratio; IPW, Inverse Probability Weighting; PS, Propensity Score.
Notes:
* The time to event is defined as the time between diagnosis and death.
** The follow-up for the control group was censored as the longest follow-up duration of the treated group.
Source: Modified figure based on Figures 14.4.1.1.19 and 14.4.1.2.10 (TFL, V1.0 dated 08-FEB-2023).

- Secondary endpoints results showed median PFS of 14 [95% CI, 9–20] months in the cemiplimab group higher than the one of in the HST group of 5 [95% CI, 3–8] months with an HR of progression or death of 0.57 [95% CI]: [0.43–0.76] (P-value = 0.0001) (*Figure 3*).

Figure 3 – PFS using the Kaplan-Meier method (trial-like set – IPW method)



*199 patients in the population but 153 patients with non-missing time to event
CI, confidence interval; HR, hazard ratio; HST, historical systemic therapies; IPW, inverse probability weighting; PFS, progression-free survival

- All grades adverse drug reaction were also collected in the TOSCA study and no new safety signal was identified.

DISCUSSION

- An appropriate methodology was used to ensure robustness of the findings. However, some bias and limitations are inherent to the retrospective observational design of the TOSCA study:
    - The use of an historical comparative control group could induce selection bias. The IPW method was successful for balancing in measured confounders. In addition, for accounting for potential evolution of the therapeutic strategy between the two periods, various estimands in terms of population set were used in sensitivity analyses which showed the consistency of the results.
    - Missing data were more frequent in the control arm, leading to a higher proportion of excluded patients. These missing data are expected to be randomly distributed, thus without impact on the results.
    - Pre-treatment was more frequent in the cemiplimab arm leading to potential underestimation of cemiplimab effect (conservative approach).
    - In absence of randomization, residual confounding could not be ruled out.
- Furthermore, all sensitivity analysis were coherent and suggested superiority of cemiplimab. The ESS close to the actual number of recruited patients showed that the results were not significantly impacted by extreme weights. Elaboration of the study relied on a Scientific Committee comprising both clinicians and methodologist.

Finally, the TOSCA study results must be interpreted considering both the risk of biases and the large and robust effect size.

To that extent and thanks to an appropriate methodology, the TOSCA study shows cemiplimab superiority versus HST with confident size of effect.

CONCLUSION

TOSCA study showed longer survival in patients treated with cemiplimab versus HST. Use of an appropriate methodology was required for limiting bias and ensuring robustness of the study given the absence of contemporaneous control. Further sensitivity analyses were used to ensure validity of the results and confirm the robustness of TOSCA results.

REFERENCES

1. Stratigos AJ, et al. Eur J Cancer. 2023;193:113252.
2. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Squamous Cell Skin Cancer (Version 1.2023).

DISCLOSURES

Presenting author is a Sanofi employee and may hold shares and/or stock options in the company.

FUNDING

This study was sponsored by Sanofi.

Presented at ISPOR Europe 2023; November 12-15, 2023; Copenhagen, Denmark, and virtual.