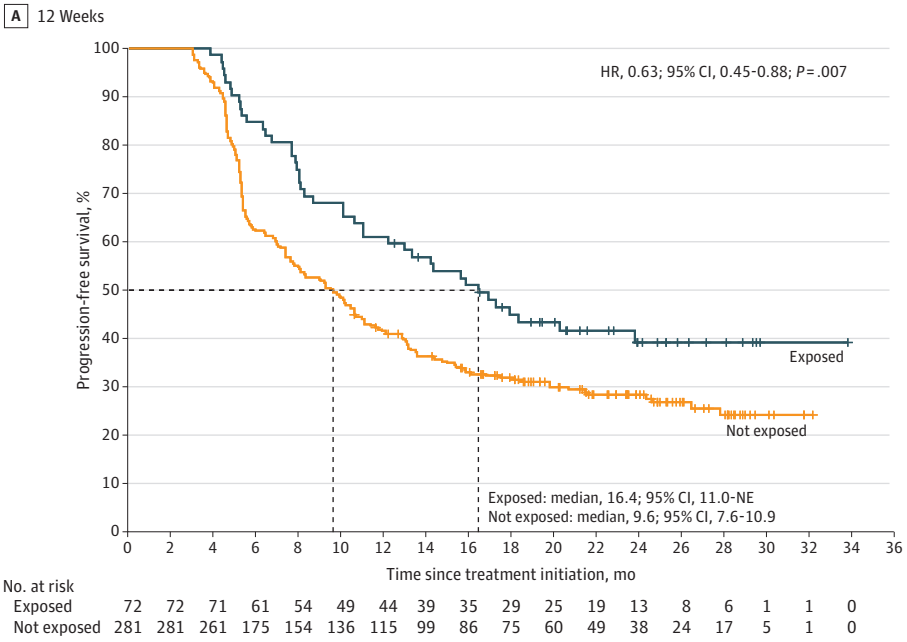
RESEARCH LETTER

Association of Corticosteroids With Survival Outcomes in Patients With Metastatic Renal Cell Carcinoma Treated With Nivolumab

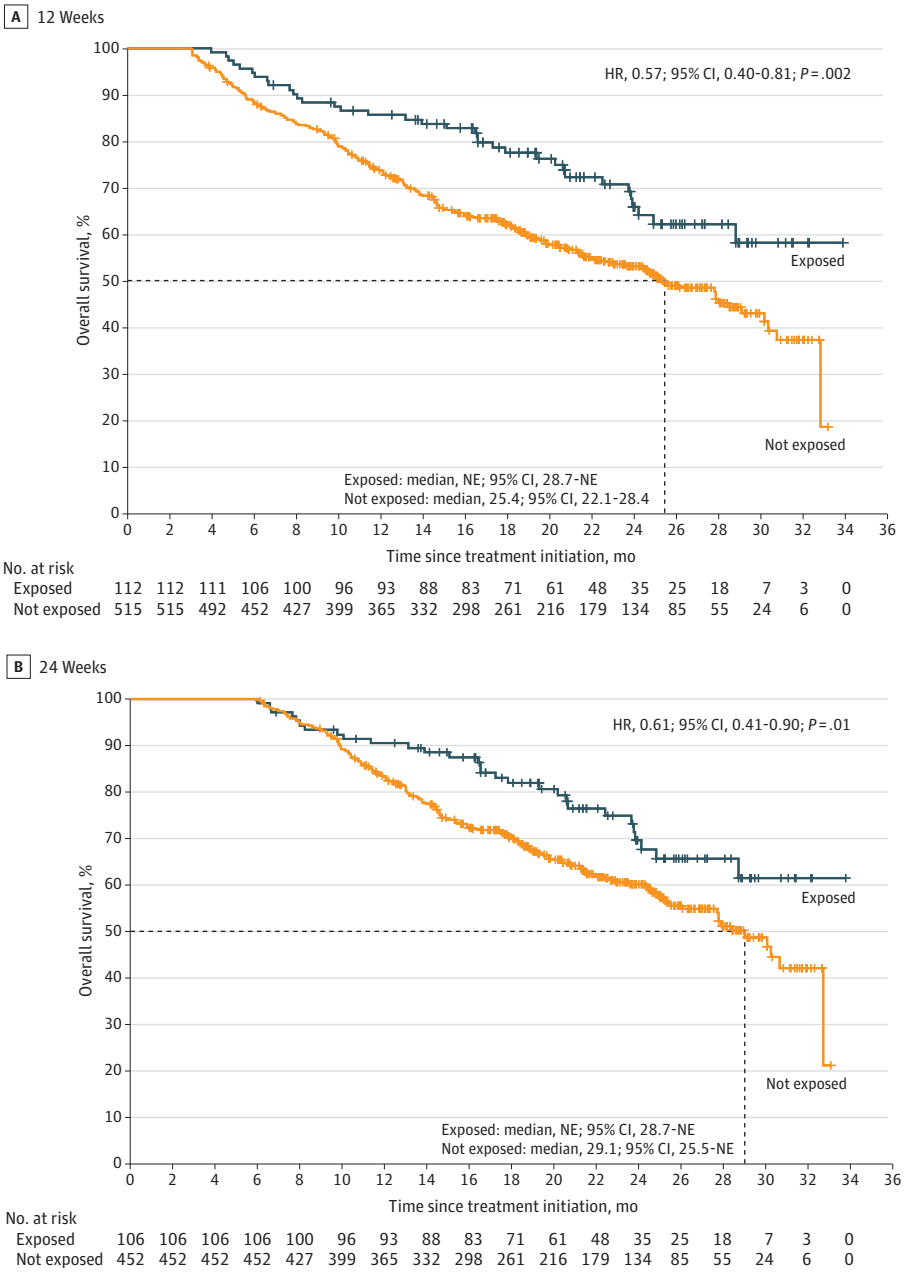
The immune checkpoint inhibitor (ICI) nivolumab is standard of care for patients with metastatic clear cell renal cell carcinoma (mccRCC). Corticosteroids are potent immunosuppressive drugs used to treat ICI-related adverse events (IrAEs). Concern is rising about the detrimental effect of such immunosuppression on ICI efficacy and patient survival. We evaluated the association of corticosteroids with survival outcomes during nivolumab treatment in patients with mccRCC.

Figure 1. Progression-Free Survival With 12- and 24-Week Landmark Analyses in Patients Exposed to Corticosteroids or Not



Crosses indicate censored patients, and dashed lines indicate median progression-free survival. NE indicates not estimable.

Figure 2. Overall Survival With 12- and 24-Week Landmark Analyses in Patients Exposed to Corticosteroids or Not



Crosses indicate censored patients, and dashed lines indicate median overall survival. NE indicates not estimable.

Methods | We conducted an ancillary study of the NIVOREN nonrandomized controlled trial (NCT03013335), a multicenter, single-arm, prospective, phase II safety study of nivolumab in mccRCC after progression on antiangiogenic treatment. Patients were included between February 12, 2016, and July 27, 2017. Nivolumab was given every 2 weeks until death, disease progression, or unacceptable toxicity.[1] Corticosteroid use was prospectively collected to identify patients exposed or not exposed to corticosteroids during nivolumab treatment. Patients receiving corticosteroids for progression were excluded. This study was approved by the Unicancer human research ethics committee. Patients provided written informed consent. The study followed the TREND reporting guideline.

Supplemental content

Since patients with longer survival are more likely to receive corticosteroids, overall survival (OS) and progression-free survival (PFS) were assessed using landmark analysis to overcome immortal time bias.[2] Hence, we excluded patients

who progressed or died before specified landmark time points at 12 and 24 weeks, as used previously.[3] We also evaluated the association of early exposure to corticosteroids (before 12 or 24 weeks) on survival outcomes. Data were analyzed between March 13, 2019, and March 19, 2020, using SAS, version 9.4 (SAS Institute Inc). A 2-sided $P < .05$ was considered significant by multivariable regression analysis.

Results | Among 665 evaluable patients (mean [SD] age, 63.4 [10.4] years; female, 151 [22.7%]; male, 514 [77.3%]) with a median follow-up of 23.9 months (95% CI, 23.0-24.7 months), 113 (17%) received corticosteroids during nivolumab treatment. Corticosteroid median starting dose was 60 mg (IQR, 40-80 mg) prednisone equivalents, and median time between nivolumab initiation and corticosteroid use was 21.6 weeks (IQR, 7.6-40 weeks). Eighty-three patients (73.5%) received corticosteroids for IrAEs (47 [41.6%] for grade ≥3). Other main reasons for corticosteroids were radiotherapy AEs (3 patients [2.7%]), infections (17 [15.0%]), and chronic obstructive pulmonary disease (2 [1.8%]). With a landmark analysis at 12 weeks, OS rates at 12 months were 85.6% and 73.5% in patients exposed or not to corticosteroids, respectively (hazard ratio [HR], 0.57; 95% CI, 0.40-0.81; $P = .002$). The PFS rates at 12 months were 61.1% and 41.6%, respectively (HR, 0.63; 95% CI, 0.45-0.88; $P = .007$). Landmark analyses at 24 weeks showed similar results for OS but no difference for PFS (**Figure 1** and **Figure 2**). In multivariable analysis, corticosteroid exposure adjusted for age, number of previous treatments, Eastern Cooperative Oncology Group, prior treatment, International mRCC Database Consortium prognostic group, history of brain metastases, and kidney clearance before progression was associated with longer OS (HR, 0.55 [95% CI, 0.37-0.81; $P = .002$] and 0.61 [95% CI, 0.40-0.94; $P = .02$]) at 12 and 24 weeks, respectively. In the population receiving corticosteroids only before 12 or 24 weeks, no differences in PFS or OS were observed compared with patients not receiving corticosteroids.

Discussion | In this large study assessing the outcomes of corticosteroids given during immunotherapy, patients exposed to corticosteroids did not have a shorter OS or PFS than patients who were not, which is consistent with previous work.[4] Possible persistent immortal time bias and the variety of indications for corticosteroid use limit the interpretation of the results. We found that patients receiving corticosteroids had a longer PFS and OS than patients who did not. Patients required corticosteroids mainly for IrAEs, which may have selected the AEs associated with a stronger immune response and, thus, a greater antitumoral activity, as suspected in previous studies.[5,6] This difference may also be due to a persistent significant immortal time bias. Both hypotheses are not inconsistent with one another and need further investigation.

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Author Contributions: Prof Albiges had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Lefort, Chabaud, Escudier, Albiges.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lefort, Chabaud, Albiges.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Dalban, Chabaud.
Obtained funding: Escudier, Albiges.
Supervision: Lefort, Laguerre, Escudier, Albiges.

Conflict of Interest Disclosures: Dr Lefort reported receiving personal fees from MSD, Eisai, and Merck outside the submitted work. Dr Gross-Goupil reported receiving advisory board fees from Bristol Myers Squibb and MSD; travel honoraria from Pfizer; and receiving honoraria from Eisai, AstraZeneca, and Ipsen outside the submitted work. Dr Laguerre reported receiving personal fees from Pfizer, Ipsen, MSD, Eisai, Astellas Pharma, and Janssen and nonfinancial support from Pfizer, Bristol Myers Squibb, and MSD outside the submitted work. Dr Chabaud reported receiving grants from CLB Academic during the conduct of the study. Dr Escudier reported receiving grants from Bristol Myers Squibb during the conduct of the study. Prof Albiges reported receiving consulting fees paid to his institution from Bristol Myers Squibb, Astellas Pharma, Ipsen, Janssen, MSD, Merck, Pfizer, Eisai, and Roche and travel support from Ipsen, MSD, and Bristol Myers Squibb outside the submitted work. No other disclosures were reported.

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