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Comparison of Adverse Event Costs of Nivolumab Plus Ipilimumab Versus Sunitinib for Previously Untreated Intermediate/Poor-Risk Advanced Renal Cell Carcinoma in Switzerland

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Introduction

- Renal cell carcinoma (RCC) is a common urological malignancy that represents 85% of all kidney cancers. In Switzerland, the incidence of kidney cancer in men and women represents 12.7 and 5.0 cases per 100,000, respectively[1]
- Approximately one-third of affected patients present with advanced or metastatic RCC (aRCC) at diagnosis, and an additional 20% of patients will go on to develop aRCC after surgery.[2] Despite various available first-line treatments, 5-year survival is only approximately 12% in patients with distant metastases, indicating an unmet need for a treatment to extend patient survival[3]
- On July 26, 2018, nivolumab plus ipilimumab (NIVO+IPI) was approved by Swissmedic for the treatment of patients with previously untreated International Metastatic Renal Cell Carcinoma Database Consortium intermediate/poor-risk aRCC based on the results of the phase 3, open-label, randomized CheckMate 214 trial (NCT02231749)[4]
- In CheckMate 214, NIVO+IPI showed superior efficacy over sunitinib (SUN) in patients with previously untreated intermediate-risk or poor-risk aRCC, with longer overall survival (median not reached vs 26.6 months; hazard ratio, 0.66; $P < 0.0001$) and higher objective response rates (42% vs 29%; $P = 0.0001$). In addition, NIVO+IPI was associated with a lower incidence of treatment-related grade 3–4 adverse events (AEs) than SUN (47% vs 64%, respectively)[5,6]
- Grade 3–4 treatment-related AEs, which generally require hospitalization and immediate intervention, are associated with significant costs in RCC. Thus, understanding the AE profile and the associated economic burden for any new treatment is crucial to inform treatment decision making for payers and healthcare providers[7–9]

Objective

- The objective of this study was to assess the financial burden of grade 3–4 AEs associated with NIVO+IPI combination therapy and SUN monotherapy in patients with previously untreated aRCC in Switzerland

Methods

Data sources

- Treatment-related and all-cause grade 3–4 AE frequencies associated with NIVO+IPI and SUN were estimated using individual patient-level data for 839 treated intermediate/poor-risk patients (NIVO+IPI, N = 423; SUN, N = 416) from CheckMate 214 (database lock date, August 3, 2018; minimum follow-up, 30 months)
- For unit costs of grade 3–4 AEs, the Swiss inpatient tariff system (SwissDRG) was considered. A mean value for the base rate of 8 large hospitals from the canton of Zurich (UniversitätsSpital Zürich, Kantonsspital Winterthur, Stadtspital Triemli, GZO Spital Wetzikon, Spital Uster, Spital Limmattal, Klinik Hirslanden, and Spital Bülach) was used to calculate the fixed rate per case[7,10]

AE cost calculations

- The total cost for a given grade 3–4 AE was calculated by multiplying the unit cost by its frequency within the designated study period
  - Frequencies (total number) of treatment-related and all-cause grade 3–4 AEs that occurred over 1, 2, and 3 years were calculated for each treatment arm based on the patient-level data
- Per-patient costs of treatment-related grade 3–4 AEs (main analysis) and all-cause grade 3–4 AEs (sensitivity analysis) over 1, 2, and 3 years post treatment initiation were calculated by dividing the total treatment-related AE costs (all-cause AE costs in sensitivity analysis) by the number of patients in each treatment arm for each assessment period
- All costs were inflated and are presented in 2019 CHF

Results

Main analysis

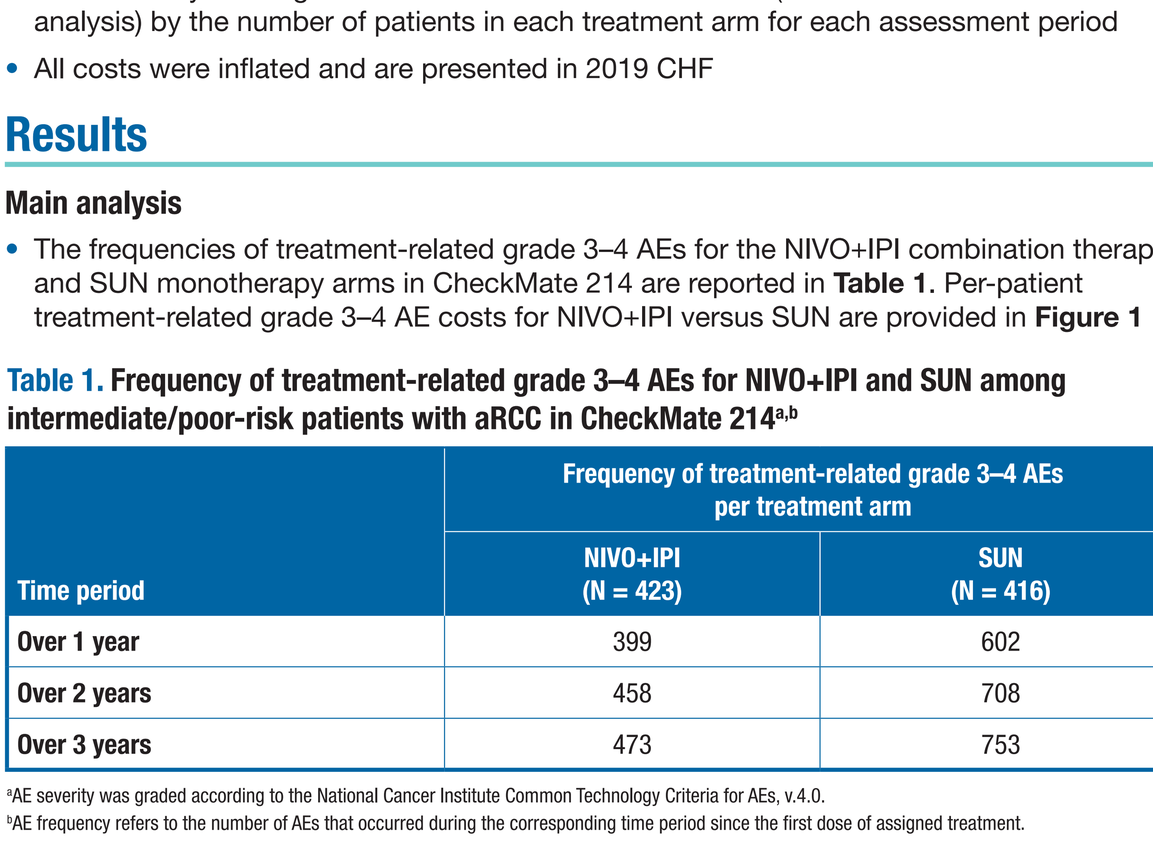
- The frequencies of treatment-related grade 3–4 AEs for the NIVO+IPI combination therapy and SUN monotherapy arms in CheckMate 214 are reported in **Table 1**. Per-patient treatment-related grade 3–4 AE costs for NIVO+IPI versus SUN are provided in **Figure 1**

Table 1. Frequency of treatment-related grade 3–4 AEs for NIVO+IPI and SUN among intermediate/poor-risk patients with aRCC in CheckMate 214[a,b]

Time period	Frequency of treatment-related grade 3–4 AEs per treatment arm	
	NIVO+IPI (N = 423)	SUN (N = 416)
Over 1 year	399	602
Over 2 years	458	708
Over 3 years	473	753

[a]AE severity was graded according to the National Cancer Institute Common Technology Criteria for AEs, v.4.0.
[b]AE frequency refers to the number of AEs that occurred during the corresponding time period since the first dose of assigned treatment.

Figure 1. Average treatment-related AE costs of NIVO+IPI and SUN per patient with intermediate/poor-risk aRCC in CheckMate 214[a–c]



[a]Analyses were conducted among all patients with intermediate/poor-risk aRCC who received at least 1 dose of the study drug in CheckMate 214. The AE cost calculation was based on the number of AEs that occurred in the clinical trial during the designated analysis period.
[b]Grade 3–4 AE costs over 1, 2, and 3 years included grade 3–4 AEs reported between first dose and the last day in the designated analysis period.
[c]The cost difference Δ is calculated as follows: Δ = the per-patient AE cost of NIVO+IPI – the per-patient AE cost of SUN; the percentage of cost difference = Δ / per-patient cost of SUN.

- Compared with patients treated with SUN, patients treated with NIVO+IPI had fewer treatment-related grade 3–4 AEs over 1 year (399 vs 602 events), 2 years (458 vs 708 events), and 3 years (473 vs 753 events)
- The 3 most frequent treatment-related non-laboratory grade 3–4 AEs were fatigue (4.0%), diarrhea (3.5%), and hypophysitis (2.8%) in the NIVO+IPI arm and hypertension (14.7%), fatigue (8.4%), and palmar-plantar erythrodysesthesia syndrome (7.7%) in the SUN arm
- Compared with patients treated with SUN, patients who received NIVO+IPI therapy had lower per-patient treatment-related grade 3–4 AE costs during all assessment periods (year 1, 5662 CHF vs 9052 CHF; year 2, 6530 CHF vs 10,751 CHF; year 3, 6760 CHF vs 11,469 CHF)

Sensitivity analysis

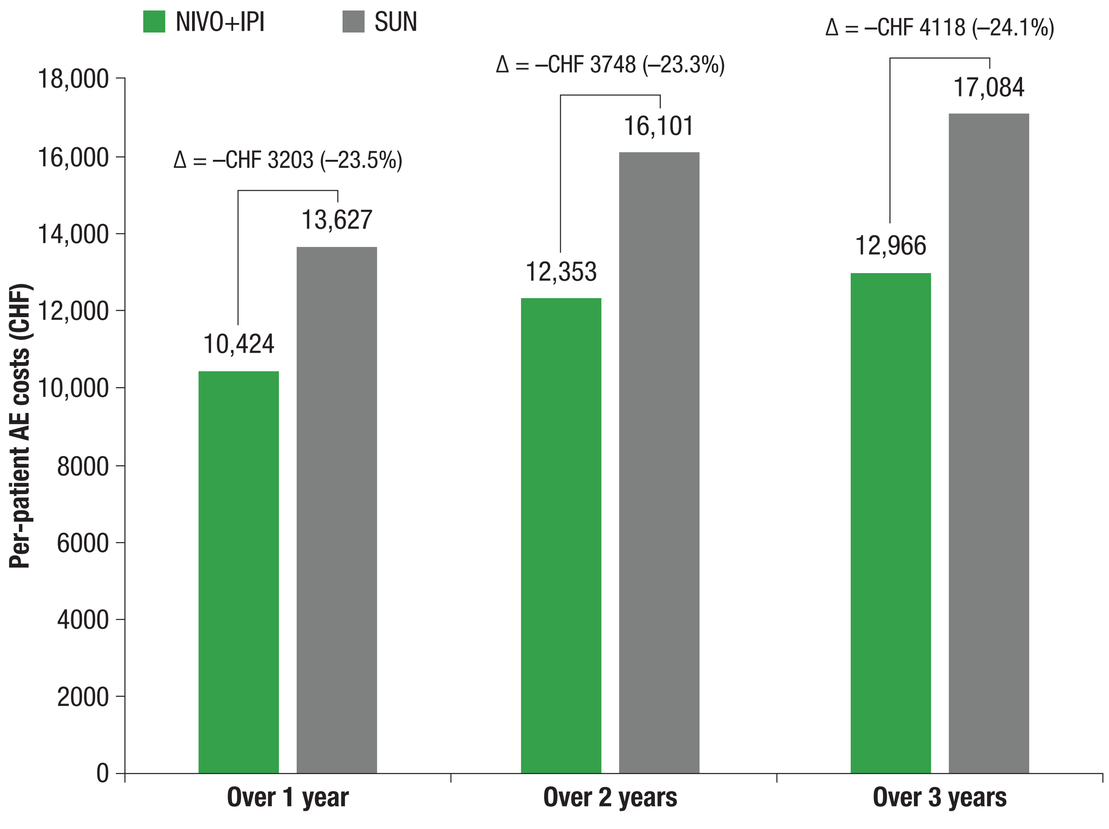
- The frequencies of all-cause grade 3–4 AEs for NIVO+IPI combination therapy and SUN monotherapy among intermediate/poor-risk aRCC patients in CheckMate 214 are presented in **Table 2.** The per-patient all-cause AE costs of NIVO+IPI combination therapy and SUN monotherapy among intermediate/poor-risk aRCC patients are provided in **Figure 2**

Table 2. Frequency of all-cause grade 3–4 AEs for NIVO+IPI and SUN among intermediate/poor-risk aRCC patients in CheckMate 214[a,b]

Time period	Frequency of all-cause grade 3–4 AEs per treatment arm	
	NIVO+IPI (N = 423)	SUN (N = 416)
Over 1 year	715	912
Over 2 years	843	1070
Over 3 years	883	1133

[a]AE severity was graded according to the National Cancer Institute Common Technology Criteria for AEs, v.4.0.
[b]AE frequency refers to the number of AEs that occurred during the corresponding time period since the first dose of assigned treatment.

Figure 2. Average all-cause AE costs of NIVO+IPI and SUN per patient with intermediate/poor-risk aRCC in CheckMate 214[a–c]



[a]Analyses were conducted among all patients with intermediate/poor-risk aRCC who received at least 1 dose of the study drug in CheckMate 214. The AE cost calculation was based on the number of AE events that occurred in the clinical trial during the designated analysis period.
[b]Grade 3–4 AE costs over 1, 2, and 3 years included grade 3–4 AEs reported between first dose and the last day in the designated analysis period.
[c]The cost difference Δ is calculated as follows: Δ = the per-patient AE cost of NIVO+IPI – the per-patient AE cost of SUN; the percentage of cost difference = Δ / per-patient cost of SUN.

- In total, compared with patients treated with SUN, patients treated with NIVO+IPI had fewer all-cause grade 3–4 AEs over 1 year (715 vs 912 events), 2 years (843 vs 1070 events), and 3 years (883 vs 1133 events)
- Compared with patients treated with SUN, patients who received NIVO+IPI therapy had lower per-patient all-cause grade 3–4 AE costs during all assessment periods (year 1, 10,424 CHF vs 13,627 CHF; year 2, 12,353 CHF vs 16,101 CHF; year 3, 12,966 CHF vs 17,084 CHF)

Limitations

- The current analysis focused on costs associated with treatment-related and all-cause grade 3–4 AEs
  - Costs associated with grade 1–2 or grade 5 AEs were not included in this analysis. As a result, this study may underestimate the total AE costs associated with both treatments
  - Unit costs for AEs were mostly obtained from the Swiss pricing system for inpatient treatment (SwissDRG Online Grouper 2019); therefore, they may not reflect the true costs incurred during the trial and were subject to measurement errors, which may result in underestimation or overestimation of costs of individual AEs
- The current analysis relied on AE frequencies that occurred in a clinical trial setting. Further real-world studies are warranted to assess AE costs in the real-world setting

Conclusions

- NIVO+IPI offered patients greater efficacy and fewer grade 3–4 AEs (both treatment-related and all-cause) than SUN
- In Switzerland, NIVO+IPI was associated with 37.5%–41.1% lower treatment-related grade 3–4 AE costs and 23.3%–24.1% lower all-cause grade 3–4 AE costs compared with SUN in patients with intermediate/poor-risk aRCC receiving first-line therapy
- This comparative analysis of AE costs associated with NIVO+IPI combination therapy and SUN monotherapy among previously untreated aRCC patients provides valuable evidence to payers, clinicians, and other healthcare decision makers

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