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Exposure-response relationship of nivolumab and ipilimumab in patients with metastatic renal cell carcinoma (mRCC) from the randomised phase 2 BIONIKK study.

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Background

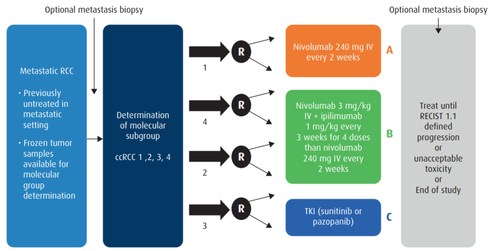
- Nivolumab-Ipilimumab is one of the first-line treatment in patients with mRCC.
- No data are available for the exposure-response (E/R) relationship of these immunotherapies in mRCC patients.
- BIONIKK study is a biomarker-driven, open-label, non-comparative, randomised, phase 2 trial

Objective

- To investigate the E/R relationship of nivolumab and ipilimumab in a subgroup of mRCC patients included in the BIONIKK trial (**study design below**).

Patients and Methods

BIONIKK study design (NCT02960906)



NB: ccRCC1: immune-low TME, ccRCC4: immune-high and immunosuppresive TME; ccRCC2: angio-high TME; ccRCC3: normal like TME

- This ancillary study included mRCC patients treated with either nivolumab alone (Nivo group, n=39) or nivolumab-ipilimumab (Ipi/Nivo group, n=71)
- Patients in the Nivo group received intravenous nivolumab 240 mg every 2 weeks. In the Nivo/Ipi group, patients were treated with intravenous nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses (3 or more doses were mandatory to continue study treatment) followed by intravenous nivolumab 240 mg every 2 weeks
- Trough concentrations (C_{min}) of Nivo and Ipi were measured using mABXmise Kit (Promise Proteomics, Grenoble, France) at week 6 after treatment initiation. The median nivolumab C_{min} (range) was 56.5 (6.6-96.7) µg/mL and 30.7 (1.0-56.7) µg/mL in the Nivo and Ipi/Nivo arms, respectively. The median ipilimumab C_{min} was 4.9 (1.0-22.5) µg/mL.
- Antidrug antibodies (ADA) were assayed using ELISA kit (Assay Genie, Dublin, Ireland).
- **The primary endpoint was progression-free survival (PFS).**
- Statistical analyses were performed using R software.

Contact and Fundings

- The BIONIKK study was sponsored by ARTIC and funded by a grant from BMS
- This research was supported by a grant from the Institut du Cancer Paris Carpem.
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Results

Variable	Nivo group (n=39)	Ipi/Nivo group (n=71)	p-value
Age (years)	61.5 [43.9.5-78.2]	64.3 [37.5-82.6]	0.44
Gender, n(%)			0.12
Female	11 (28)	10 (14)	
Male	28 (72)	61 (86)	
ECOG PS, n(%)			0.72
0	29 (74)	57 (80)	
1	8 (21)	12 (17)	
2	2 (5)	2 (3)	
IMDC risk group, n(%)			0.25
Favourable	9 (23)	26 (37)	
Intermediate	18 (46)	31 (44)	
Poor	12 (31)	14 (20)	
Number of metastasis, n(%)			0.47
≥ 2	27 (69)	55 (77)	
1	12 (31)	16 (23)	
Albumin (g/L)	42.0 [14.9-49.4]	42.0 [28.0-50.2]	0.37
CRP (mg/L)	9.3 [1.0-308.5]	5.1 [0.5-238.4]	0.20

Table 1. Baseline patients' characteristics (n = 110).

Nivo C_{min} was statistically lower in patients with Nivo-ADA compared to those without (p=0.002), while no statistical difference in Ipi C_{min} was observed between patients with IPI-ADA or without (**Figure1**). In Nivo and Ipi/Nivo groups, no statistical association was observed between presence of NIVO-ADA and PFS (HR 0.87 [0.30-2.56], p=0.80 and HR 0.53 [0.23-1.26], p=0.15, respectively).

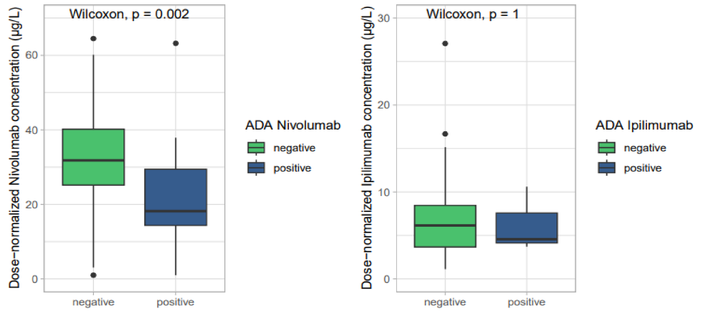

Figure 1. Association between ADA status and C_{min} of nivolumab and ipilimumab

No difference in Nivo Cmin was observed between patients with and without DLT in the Nivo group (36.3 [IQR 25.3-46.7] µg/mL vs 57.0 [IQR 41.4-62.5] µg/mL, respectively; p=0.10) and in the Ipi/Nivo group (25.0 [IQR 17.9-36.2] µg/mL vs 30.9 [IQR 21.3-37.7] µg/mL, respectively; p=0.36), nor did IPI Cmin (4.1 [IQR 2.8-6.4] µg/mL vs 5.1 [IQR 2.8-7.0] µg/mL, respectively; p=0.41).

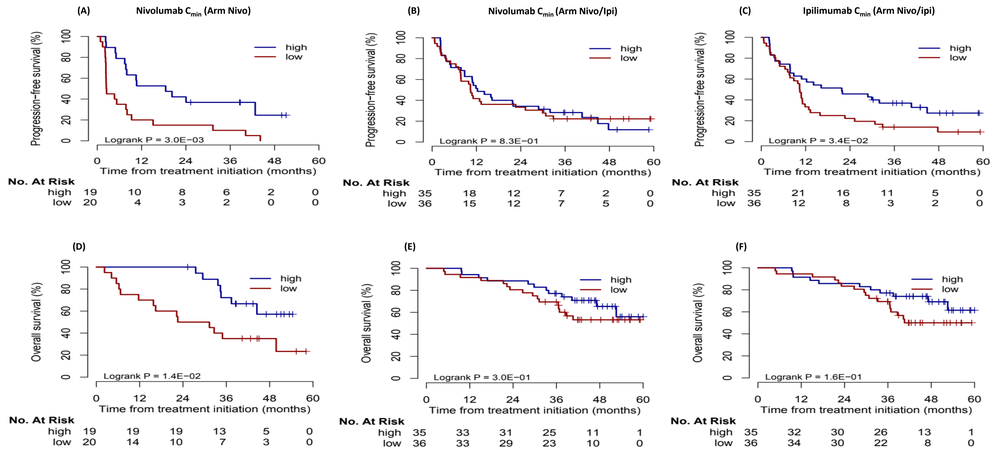

Figure 2. Kaplan-Meier curves for PFS (A-C) and OS (D-F) according to nivolumab C_{min} and ipilimumab C_{min} in each treatment group

- In the Nivo group, median PFS was statistically shorter in patients with a low Nivo C_{min} (<median) than in those with a high Nivo C_{min} (2.5 [95% CI, 2.3–9.3] vs 18.5 [95% CI, 8.0–NA months, respectively; log rank-test p=0.003) (**Figure 2A**), while no difference was observed in the Ipi/Nivo group (log rank-test p=0.83) (**Figure 2B**).
- Patients with a low IPI C_{min} (<median) had a shorter PFS than those with a high IPI C_{min} (10.4 [95% CI, 7.7–12.6] vs 21.8 [95% CI, 8.8–NR months], respectively; log rank-test p=0.034)(**Figure 2C**).
- Finally, patients with a low Nivo C_{min} (<median) had a shorter median OS than those with a high Nivo C_{min} (26.9 [95% CI, 15.8–NA] vs NA [95% CI, 37.4–NA] months, respectively; log rank-test p=0.014) in the Nivo group but not in the Ipi/Nivo group (**Figure 2D and E**).
- IPI C_{min} had no statistically significant impact on OS (log rank test p=0.16) (**Figure 2F**).

	Nivo group (n=39)		Ipi/Nivo group (n=71)	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
IMDC				
Intermediate/poor vs favourable	0.54 (0.21–1.44)	0.22	0.88 (0.49–1.57)	0.66
Albumin				
≥ 35 vs < 35 g/L	0.74 (0.23–2.39)	0.61	0.83 (0.35–1.98)	0.68
CRP (per mg/L increase)				
≥ 10 vs < 10 mg/L	1.75 (0.61–5.00)	0.30	0.59 (0.31–1.10)	0.10
Nivolumab C_{min} (median)				
Low vs high	2.78 (1.25–6.15)	**0.012**	1.07 (0.55–2.05)	0.85
Ipilimumab C_{min} (median)				
Low vs high			1.90 (1.04–3.49)	**0.038**

Table 2. Multivariate Cox proportional hazard models for PFS in both treatment groups.

- Low Nivo C_{min} (<median) was identified as an independent risk factor for disease progression in the Nivo group (HR, 2.78; p=0.012) but not in the Ipi/Nivo group (p=0.85) (**Table 2**)
- Interestingly, low IPI C_{min} (<median) was independently associated with shorter PFS in the Ipi/Nivo group (HR, 1.90; p=0.038).

Conclusion

- In the Nivo group, the association between low Nivo C_{min} and shorter PFS probably reflects the deleterious impact of disease state (cachexia) on drug elimination and survival.
- However, Nivo C_{min} at week 6 is not a predictor of PFS in Ipi/Nivo group, suggesting a different pattern of E/R relationship in these patients putatively due to ipilimumab.