Baseline and dynamic changes in haemoglobin levels predict treatment response and disease progression in metastatic renal cell carcinoma

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Background

- Immune checkpoint inhibitors (ICI) and VEGF inhibitors (VEGFI) alone or in combination have become established treatments for metastatic renal cell carcinoma (mRCC)
- However, early clinical biomarkers of response are limited
- Recent studies have suggested that blood test parameters such as neutrophil to lymphocyte ratio[1,2,3] or CRP[4] may be of prognostic significance
- In this study, we explore whether dynamic changes in Haemoglobin (Hb) levels is associated with treatment response and progression

Methods

- We conducted a retrospective analysis in the context of an audit of 276 patients treated between January 2014 and July 2021 across three tertiary centres in the United Kingdom and Netherlands: (1) Barts Cancer Institute, London (2) Beatson West of Scotland Cancer Centre, Glasgow and (3) Netherlands Cancer Institute, Amsterdam
- Hb levels at baseline, 6 and 12 weeks after commencing treatment, and at disease progression or death were collected
- First radiological disease assessment occurred at 12 weeks. Patients were classified based on this as either Responders (partial or complete) or Non-responders (stable or progressive disease)
- 35 patients were excluded from analysis due to receiving a blood transfusion within 12 weeks of treatment (n = 16), insufficient or missing data (n = 16) and outlier values (n = 3)
- Patients were grouped according to first-line treatment with ICIs alone (n = 90), combination ICI/VEGFI (n = 97) or VEGFI alone (n = 54) (**Table 1**)
- A mixed ANOVA model was used to assess the combined effect of time and treatment response on the variance of Hb. Significant mixed or individual effects were followed up with one-way ANOVA and pairwise tests
- The Kaplan-Meier method, Log rank test and Cox proportional hazards model were used to analyse survival data

Figure 1. ICI only: serial Hb levels

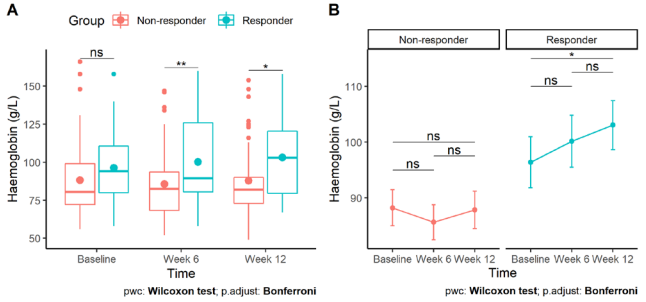


Figure 2. Combined ICI/VEGFI: serial Hb levels

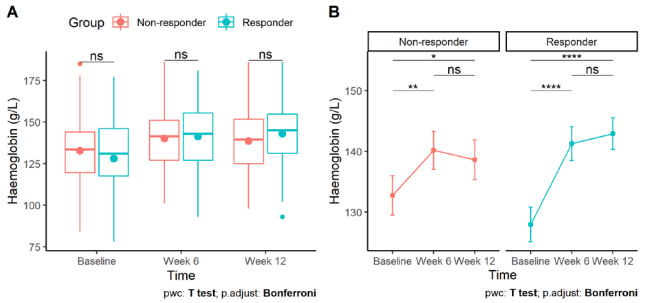


Figure 3. VEGFI only: serial Hb levels

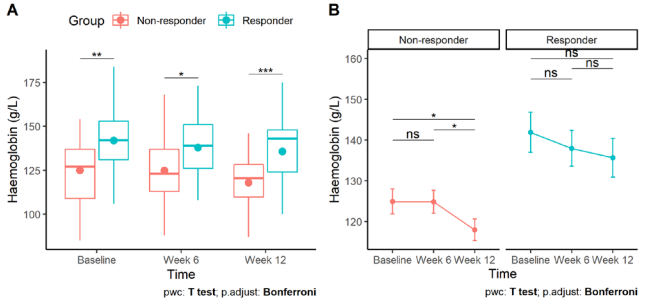
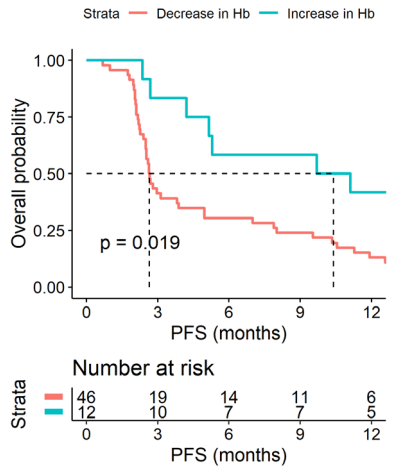


Table 1. Baseline demographics

	ICI (N=90)	ICI + VEGFI (N=97)	VEGFI (N=54)	Overall (N=241)
Sex				
Male	75 (83%)	68 (70%)	41 (76%)	184 (76%)
Female	15 (17%)	29 (30%)	13 (24%)	57 (24%)
Age				
Median [IQR]	64 [16]	61 [14]	62 [15]	62 [15]
Histology				
Clear cell	85 (94%)	83 (86%)	47 (87%)	215 (89%)
Papillary	1 (1%)	2 (2%)	2 (4%)	5 (2%)
Sarcomatoid	3 (3%)	1 (1%)	1 (2%)	5 (2%)
Chromophobe	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Unknown	1 (1%)	10 (10%)	4 (7%)	15 (6%)
Performance status (ECOG)				
0	36 (40%)	60 (62%)	28 (52%)	124 (51%)
1	44 (49%)	35 (36%)	24 (44%)	103 (43%)
2	9 (10%)	2 (2%)	2 (4%)	13 (5%)
3	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Treatment received				
Ipilimumab + Nivolumab	90 (100%)	0 (0%)	0 (0%)	90 (37%)
Pembrolizumab + Axitinib	0 (0%)	75 (77%)	0 (0%)	75 (31%)
Atezolizumab + Bevacizumab	0 (0%)	14 (14%)	0 (0%)	14 (6%)
Avelumab + Axitinib	0 (0%)	8 (8%)	0 (0%)	8 (3%)
Sunitinib	0 (0%)	0 (0%)	42 (78%)	42 (17%)
Pazopanib	0 (0%)	0 (0%)	12 (22%)	12 (5%)
Follow up time (months)				
Median [IQR]	6.7 [9.2]	12 [12]	11 [18]	9.7 [12]

Figure 4. PFS for ICI-only non-responders



Results

- ICI-only responders (n = 58) had a higher baseline Hb than non-responders (n = 32), p = 0.08. This intergroup difference increased significantly at week 6 (p = 0.01) and 12 (p = 0.01) (**Fig. 1A**), due to responders experiencing an increase in Hb at 12 weeks (n = 58, 6.58±12.7, p = 0.02) (**Fig. 1B**)
- Combination ICI/VEGFI responders (n = 55) also demonstrated a significant increase in Hb at 12 weeks (14.6±17.8, p = $5x10^{-7}$), a trend which was less marked in non-responders (n = 42, 5.86±14.5, p = 0.04) (**Fig. 2B**)
- VEGFI-only responders (n = 17) had a higher Hb at all three timepoints (p = 0.01, 0.04 and 0.003 respectively) (**Fig. 3A**). Non-responders (n = 37) showed a significant reduction in Hb at week 12 (-6.75±14.4, p = 0.03), a trend which was non-significant amongst responders (-6.24±11.4, p = 0.1) (**Fig. 3B**)
- Amongst patients receiving ICIs alone, an increase in Hb at time of disease progression or death (n = 12) was positively prognostic compared to a decrease in Hb (n = 46) (Median PFS 10.4 vs 2.6 months, p = 0.02). This survival advantage remained significant on cox regression analysis for age, sex and performance status (p = 0.02) (**Fig. 4**)

Conclusions

- A significant increase in Hb at 12 weeks of receiving first-line ICIs alone or combined with VEGFI predicts response to treatment
- Higher baseline Hb levels associate with treatment response to ICI and VEGFI
- Increasing Hb in patients receiving ICIs alone may be positively prognostic for longer PFS

References

1. Zahoor *et al.*, J Immunother Cancer 2018
2. Lalani *et al.*, J Immunother Cancer 2018
3. Bilen *et al.*, J Clin Oncol 2020
4. Ishihara *et al.*, Target Oncol 2019

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DECLARATION OF INTERESTS

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Please state your disclosures here

The author has no disclosures to state.