Circulating immune landscape and activity of immune checkpoint inhibitors in metastatic renal cell carcinoma

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BACKGROUND

Immune checkpoint inhibitors (IO) combinations are standard of care in metastatic renal cell carcinoma (mRCC) but biomarkers to help select patients to either anti-PD-1 + CTLA-4, or PD-1 plus tyrosine kinase inhibitors (TKI) are still lacking.

Circulating immune cells (CIC) may inform antitumor immune response. Our group showed that subtypes of memory B-cells could inform response to nivolumab in refractory mRCC (Carril et al. JITC 2021).

Though, these findings have been reported only in patients with IO monotherapy.

OBJECTIVE

We aimed at exploring the association between baseline CIC and outcomes in patients with mRCC treated with IO as single agent and combinations.

METHODS

Phenotyping of peripheral blood mononuclear cells by flow cytometry in baseline samples collected in PREMIS (NCT03984318) & NIVOREN (NCT03013335) trials.

Explored baseline CIC:

. T cells: CD8+ and senescent CD8+, CD4+ and senescent CD4+. Senescence was explored specifically on the PREMIS cohort using markers KLRG1 and CD57 in CD28- T cells (N=70).

. B cells: naive, naïve , memory, double negative, plasmablasts.

Associations between CIC and prospectively collected outcomes were assessed across treatment subgroups.

CIC and association with tissue immune infiltrate was conducted including tertiary lymphoid structures and lymphoid aggregates on HE slides.

RESULTS

Among 112 patients, median age was 61 y.o; 75% had clear cell histology, 64% intermediate or poor risk disease according to the international metastatic renal cell carcinoma database consortium (IMDC) classification (**Table 1**).

Treatment regimens included:

IO-TKI in 30%
dual IO in 15%
IO monotherapy in 54%

Table 1. Patient characteristics

Patients	PREMIS N=70 (%)	NIVOREN N=44 (%)	Overall N=114, %
Age, median (min:max)	60 (28:83)	62 (33:81)	61 (28:83)
Male	47 (67)	29 (66)	76 (67)
Histological subtype			
Clear-cell	43 (61)	44 (100)	87 (76)
Non-clear-cell	27 (39)	0	27 (24)
ISUP grade			
I-II	14 (27)	13 (29)	27 (28)
III-IV	38 (73)	30 (70)	68 (72)
Unknown	18	1	19
IMDC risk group			
Favorable	25 (36)	20 (46)	45 (39)
Intermediate	35 (50)	17 (39)	52 (46)
Poor	9 (13)	7 (16)	16 (14)
Unknown	1	0	1
Zubrod score			
0-1	64 (91)	39 (89)	103 (90)
≥2	6 (9)	5 (11)	11 (10)
Nephrectomy	55 (77)	42 (96)	97 (85)
Sarcomatoid features	9 (13)	5 (11)	14 (12)
Metastatic sites			
Liver	17 (24)	12 (27)	29 (25)
Bone	18 (26)	13 (30)	31 (27)
Brain	3 (4)	9 (21)	12 (11)
Line of IO therapy			
1	41 (59)	0	41 (36)
2	23 (33)	28 (64)	51 (45)
3+	6 (9)	14 (32)	20 (18)
Type of IO therapy			
PD(L)1 inhibitor only	17 (24)	44 (100)	61 (54)
Dual PD(L)1 – CTLA4 inhibition	17 (24)	0	17 ((15)
IO + TKI	34 (49)	0	34 (30)
Triplet	1 (1)	0	1 (1)
IO + PARPi	1 (1)	0	1 (1)
Tertiary lymphoid structures / lymphoid aggregates	16/44 (36%)	NA	16/44 (36%)

Immune contexture in the overall population

Levels of CD8+ T cells were highly correlated with senescent CD8+ T cells (r=0.51, p<0.001) that harbour a CD28- CD57+ KLRG1+ phenotype (**Fig. 1a**).

CD8+ T cell senescence was inversely associated with the presence of tertiary lymphoid structures or lymphocyte aggregates within the tumor (**Fig. 1b**).

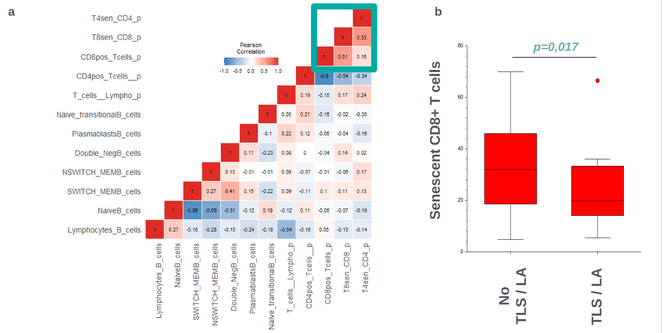

Figure 1. a) correlation between baseline CIC in patients with mRCC. Relationship between CD8+ T cells and proportion of senescent CD8+ T cells within the overall CD8+ T cell population are highlighted. b) Proportion of circulating senescent CD8+ T cells and presence of tertiaty lymphoid structures (TLS) or lymphoid aggregates (LA) within baseline tumor tissue

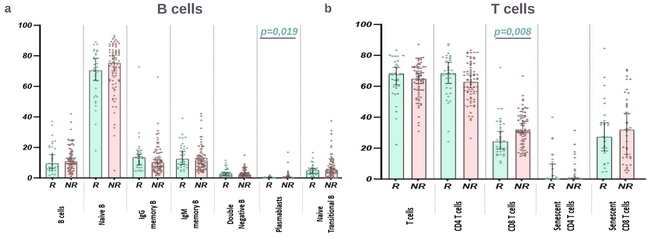

Figure 2. Baseline CIC proportions according to response in the overall population. R, responders; NR, non-responders

T cells and outcomes

CD8+ T cell levels were inversely associated with response in the overall population (p=0.008, **Fig. 2a**)

Across treatments, lower CD8+ T cells were associated with improved ORR and PFS in patients treated with IO monotherapy or dual IO, but not TKI-IO (**Fig. 3 & 4**).

Impact of CD8+ T cells on PFS was greater in patients with dual IO (HR 0.13) than IO monotherapy (HR 0.71).

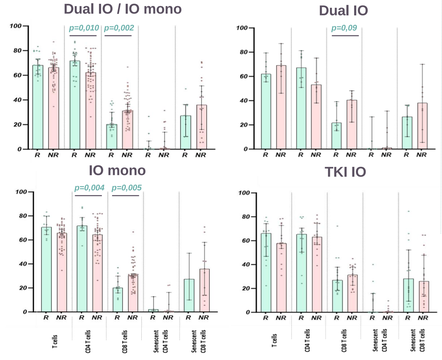

Figure 3. Baseline T cell proportions according to response and treatment type. R, responders; NR, non-responders

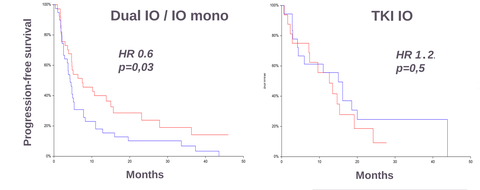

Figure 4. Progression-free survival according to CD8+ T cells and therapy

B cells and outcomes

Plasmablasts were inversely associated with response in the overall population (**Fig. 2b**), but not PFS.

Across treatments, IgG memory B cells were associated with response to IO monotherapy only, contrary to naïve B cells (**Fig. 5**), along with improved PFS trend in this population (HR 0.6, p=0.06, not shown).

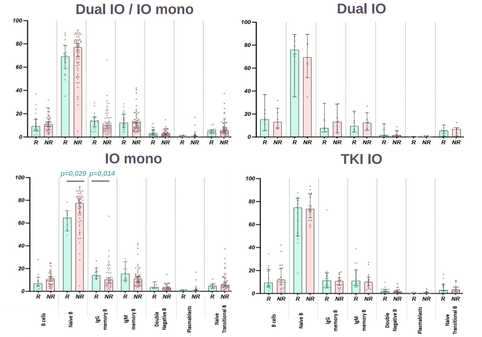

Figure 5. Baseline B cell proportions according to response and treatment type. R, responders; NR, non responders

CONCLUSION

High levels of circulating CD8+ T cells are associated with an expanded senescent CD8+ T cell pool, which may hinder establishment of efficient tissular antitumor immunity

Circulating CD8+ levels may inform resistance to IO-based therapies but not IO-TKI, which could be relevant for first-line therapy selection in patients with mRCC

The role of B cell subpopulations remain to be investigated in larger cohorts.

Analysis of TLS characteristics including structure and maturation is pending, as well as longitudinal analyses to explore evolution of CIC on therapy.