

## Immunomodulatory effects of tyrosine kinase inhibitors (TKIs) in renal cell carcinoma (RCC) patients.

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[View Less](#)[Abstract Disclosures](#)**Background:**

RCC is considered a highly immunogenic tumor responding to anti-angiogenetic TKI and immunotherapy. A better understanding of the functions of immune cells in RCC, the immune-modulatory effects of TKIs treatment as well as defining patients most likely to benefit to the different therapies will be crucial to optimize combined or sequential immunotherapeutic approaches in RCC patients.

**Methods:**

Monocyte derived Dendritic Cells (DCs) from 10 healthy donors were differentiated in presence of Pazopanib and Sunitinib used at plasmatic equivalent concentration (Sigma-Aldrich). At the end of the culture, DCs were characterized for marker expression, endocytosis, signal transduction and microvesicle release. Similarly, DCs derived from RCC patients were analyzed together with circulating T cells before and during TKI treatments.

**Results:**

Pazopanib and Sunitinib differently affect DC differentiation. Pazopanib, but not Sunitinib, strongly improves DC performance as antigen-presenting cells, promoting the upregulation of the maturation markers HLA-DR (+1,5 fold increase compared to Sunitinib-treated DCs), CD40 (+3 fold increase) and CCR7 (+2 fold increase) a decrease in phagocytosis and the inhibition of pERK1/2 signaling. 99% of Sunitinib-DCs expressed PD-L1 vs 80% Pazopanib-DCs, with a higher expression of the receptor as indicated by mean fluoresce intensity (MFI fold increase of +2,1). Similar results were obtained analyzing shedded microvesicles. Results were confirmed in DCs differentiated from RCC patients during Pazopanib treatment (before and at 30 and 60 days) and suggest a reverse of the tumor induced immunosuppression. Moreover, only Pazopanib treatment appears to induce in these patients a defined circulating CD4<sup>+</sup> T cell population highly expressing CD137 molecule (%CD4<sup>+</sup>CD137<sup>+</sup>: T<sub>0</sub>:0,3; T<sub>30</sub>: 4,7; T<sub>60</sub>:29,4).

**Conclusions:**

TKIs can affect immunity in RCC patients. In particular, Pazopanib appears to function as a potent activator of DCs in vitro and in vivo associated with the neo-activation of a CD137<sup>+</sup> T cell population. These results can guide for designing novel protocols to combine TKIs with immunoregulatory receptors targeting in RCC.

