27P - Peripheral biomarker analysis in patients with advanced urothelial carcinoma (UC) after platinum chemotherapy treated with Cabozantinib (CABO) plus Durvalumab (DURVA): preliminary analysis from the Phase 2 ARCADIA trial.

Francesco Sgambelluri[1], P. Giannatempo[2], M. Stellato[2], V. Guadalupi[2], D. Raggi[5], A. Bottiglieri[2], M. Claps[2], W. Ferrari Bravo[2], S. Oldani[2], M. Zimatore[2], G. Calareso[3], A. Alessi[3], L. Cattaneo[4], E. Verzoni[2], F.G.M. De Braud[2], G. Procopio[2], A. Necchi[5], A. Anichini[1], R. Mortarini[1]

[1]Dept. of Experimental Oncology, [2]Dept. of Medical Oncology, [3]Dept. of Radiology , [4]Dept. of Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]IRCCS Ospedale San Raffaele, Milan, Italy.

Background

Preliminary results of the interim analysis of the ARCADIA trial have shown that combining multitargeted receptor tyrosine kinase inhibitor CABOZANTINIB with the PD-L1 checkpoint inhibitor DURVALUMAB has promising activity and a manageable safety profile in patients (pts) affected by urothelial carcinoma (UC) or non-urothelial carcinoma histology (VHs) recurred or progressed after failure of at least one line of platinum-based chemotherapy for metastatic disease in a phase II study (NCT03824691)[1]. To identify peripheral blood biomarkers potentially associated with clinical response, we carried out a quantitative profiling of innate and adaptive immune subsets from a subset of treated pts.

Methods

ARCADIA is an open-label, single-arm, phase 2 study, whose pts were treated with daily oral doses of 40 mg CABOZANTINIB and DURVALUMAB 1500 mg, intravenously, every 4 weeks. The immune profile was analyzed in 27 pts; 12 pts were classified as Responders (Resp) and 15 pts were classified as Non Responders (Non Resp). Freshly isolated blood samples from these pts, collected at baseline and at first radiological re-evaluation (after two cycles) were characterized by a quantitative multiparametric flow cytometry assay enabling determination of absolute cell counts/mL for 29 innate and adaptive immunity subsets. Evaluated immune subsets included the total of Leukocytes, T- and HLA-DR+ T cells, B cells, Monocytes, Neutrophils, Eosinophils, Dendritic cells, monocyte-derived-MDSCs (mo-MDSCs), polymorphonuclear-derived-MDSCs (pmn-MDSCs), NK and NKT-like cells. Statistical analysis was done by Mann-Whitney test comparing Resp vs Non Resp groups of pts, while Pre vs Post-therapy samples comparison was done by Wilcoxon matched pair test.

Conclusions

These preliminary findings suggest that:

- High baseline counts for granulocytes, monocytes and MDSCs may impact negatively on response in pts treated with CABO+DURVA.
- In Pre- vs Post-therapy analysis for responder pts we found that an increase in Eosinophils subset is positively associated with therapy response, as already reported in literature[2].
- In non responder pts analysis of Pre- vs Post-therapy indicated a significant decrease of MDSCs. This may be a potential effect of CABO+DURVA combination that disrupts the tumor's ability to suppress the immune response (by recruiting MDSCs). Such effect however was not sufficient to prevent a significant reduction of other immune subsets associated with response.

Future Perspective

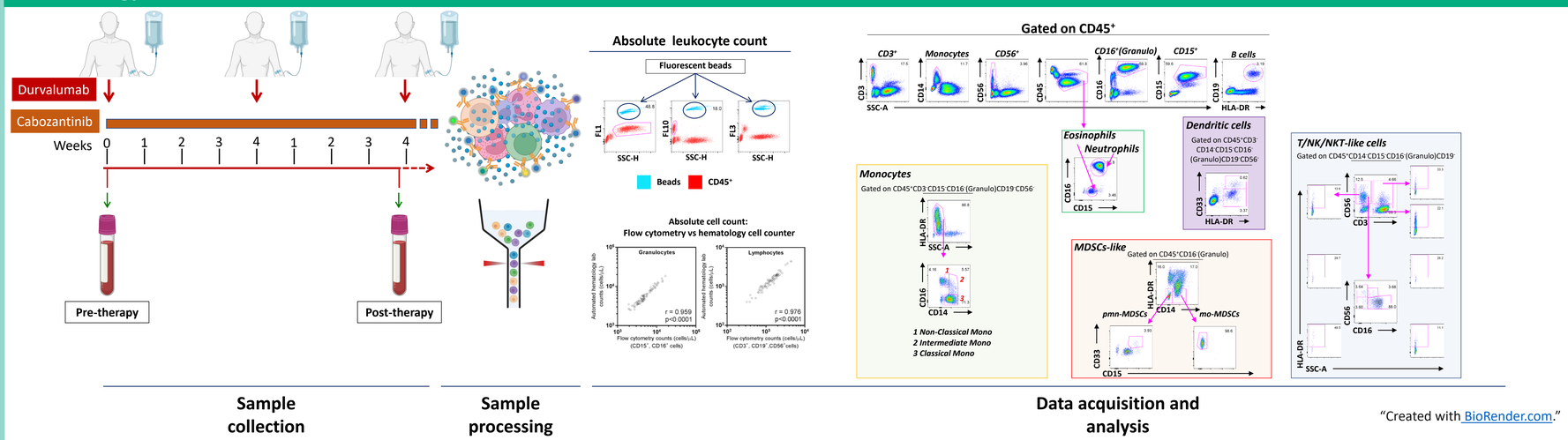
For improving the comprehension of both the mechanisms of therapy efficacy in responder pts and of immuno-escape in Non-Responder pts, we plan to increase both the number of pts enrolled in the study and to test additional post-therapy samples at later stages of treatment, beyond the second cycle .

References

(1) Marandino L, Raggi D, Calareso G, et al. Cabozantinib Plus Durvalumab in Patients With Advanced Urothelial Carcinoma After Platinum Chemotherapy: Safety and Preliminary Activity of the Open-Label, Single-Arm, Phase 2 ARCADIA Trial. Clin Genitourin Cancer. 2021;19(5):457-465. doi:10.1016/j.clgc.2021.04.001

(2) Mota JM, Teo MY, Whiting K, et al. Pretreatment Eosinophil Counts in Patients With Advanced or Metastatic Urothelial Carcinoma Treated With Anti-PD-1/PD-L1 Checkpoint Inhibitors. J Immunother. 2021;44(7):248-253. doi:10.1097/CJI.0000000000000372

Methodology



Main results. Figure 1. At baseline, Non resp patients show higher counts for leukocytes, neutrophils, classical and intermediate monocytes and mo-MDSCs compared to Resp pts. In contrast, CD56^{dim} CD16^{+} NK cells have higher counts in Resp pts. **Figure 2.** Non resp pts. show significant reduction in absolute cell counts for several leukocyte subsets in the post-therapy samples compared to pre-therapy values .

Responders vs Non Responders: Pre-Therapy samples

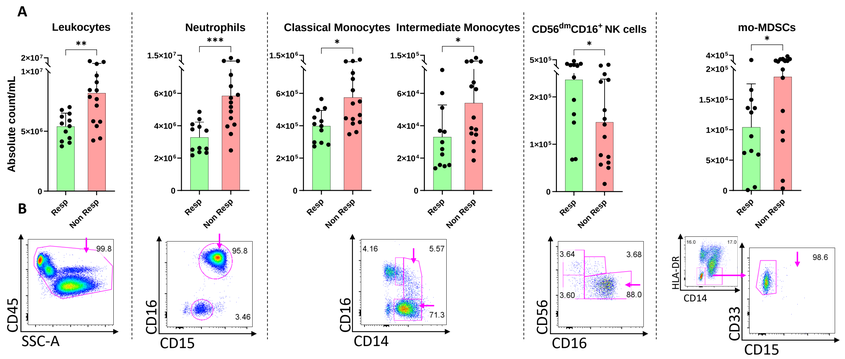
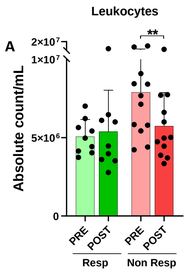


Fig 1. (A) Scatter plots of CD45^{+} Leukocytes, CD16^{+} Neutrophils, CD14^{+} CD16^{+} Classical Monocytes, CD14^{+} CD16^{+} Intermediate Monocytes, CD56^{DIM} CD16^{+} NK cells and Lin^{-} CD33^{+} HLA-DR$^{-/lo}$ CD14^{+} mo-MDSCs in Resp vs Non Resp pts at Pre-Therapy. Statistical analysis was done by Mann-Whitney test comparing Resp vs Non Resp pts for absolute immune cell counts. P values <0,05 were considered significant.
(B) Representative flow-cytometry pseudocolor plots showing the frequency of CD45^{+} leukocytes, CD16^{+} Neutrophils, CD14^{+} CD16^{+} Classical Monocytes, CD14^{+} CD16^{+} Intermediate Monocytes, CD56^{DIM} CD16^{+} NK cells and Lin^{-} CD33^{+} HLA-DR$^{-/lo}$ CD14^{+} mo-MDSCs from PT 30 (NR) at Pre-Therapy.

Pre- vs Post-Therapy sample analysis



B

		Responders	Non Responders
		Pre vs Post	Pre vs Post
Leukocytes	CD45^{+}		
B cells	CD45^{+}CD19^{+}		
T cells	CD45^{+}CD3^{+}		
NK cells	CD45^{+}CD3^{-}CD56^{dm}CD16^{-}HLA-DR^{+}		
Monocytes	CD45^{+}CD14^{+}		
Monocytes	CD45^{+}CD14^{+}HLA-DR^{+}		
Classical Monocytes	CD45^{+}CD14^{+}CD16^{-}		
mo-MDSCs	Lin^{-}CD33^{+}HLA-DR$^{-/lo}$CD14^{+}CD15^{-}		
pmn-MDSCs	Lin^{-}CD33^{+}HLA-DR$^{-/lo}$CD14^{-}CD15^{+}		
Neutrophils	CD45^{+}CD15^{+}CD16^{+}		
Eosinophils	CD45^{+}CD15^{+}CD16^{lo}		
pDCs	Lin^{-}HLA-DR^{+}CD33^{-}		
mDCs	Lin^{-}HLA-DR^{+}CD33^{+}		

Increase: *** ** *
Decrease: * ** ***

Fig 2. (A) Scatter plots of CD45^{+} Leukocytes in Resp vs Non Resp pts in Pre- vs Post-Therapy samples.
(B) Heatmap showing differences in absolute cell counts of several Leukocyte subsets in Resp vs Non Resp pts at Pre-Therapy and Post-Therapy. The colors in the heatmap represent a significant increase (in Red) or decrease (in Blue) of subpopulations at Pre- vs Post-therapy.
Statistical analysis was done by Wilcoxon matched-pairs signed rank test comparing Resp vs Non Resp pts for absolute immune cell counts in Pre- and Post-therapy samples. P values <0,05 were considered significant.

Disclosures: F. Sgambelluri has no conflict of interests to disclose.
E mail: francesco.sgambelluri@istitutotumori.mi.it; patrizia.giannatempo@istitutotumori.mi.it
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