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Integrating peripheral biomarker analyses from JAVELIN Renal 101: avelumab + axitinib (A + Ax) vs sunitinib (S) in advanced renal cell carcinoma (aRCC)

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JAVELIN Renal 101

SCOPE

- This analysis reports the correlation of clinical outcomes with baseline and on-treatment blood-based biomarkers in patients with aRCC treated with A + Ax or S

CONCLUSIONS

- Response to treatment with first-line A + Ax or S was associated with immune fitness and treatment-specific immunomodulation
- Multiple biomarkers were differentially associated with progression-free survival (PFS) in A + Ax vs S, including monocyte counts and levels of multiple T-cell–related metrics
- A novel proteomic classifier was prognostic for PFS in both treatment arms
- A subset of "double-mutant" patients harboring ≥2 interchangeable mutations in a set of 10 genes detected in baseline tissue displayed a unique baseline phenotype and a differential cytokine/angiokine response to treatment with A + Ax vs S
- Taken together, these data demonstrate the potential utility of novel peripheral biomarkers as predictive or prognostic tools for response to A + Ax vs S

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BACKGROUND

- The combination of avelumab, an anti–PD-L1 monoclonal antibody, and axitinib, a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor, is approved as a first-line treatment for patients with aRCC[1,2]
- In the phase 3 JAVELIN Renal 101 trial (NCT02684006), treatment-naive patients with aRCC receiving A + Ax showed improved PFS and objective response rate compared with patients receiving S[3,4]
- Previous work demonstrated that outcomes of patients with interchangeable multiple mutations (termed "double mutants") in a set of 10 identified genes were associated with prolonged PFS in the A + Ax arm[5]
- We report the association of blood-based biomarkers with differential responses to treatment with either A + Ax or S, and with specific genomic variants in tumor tissue

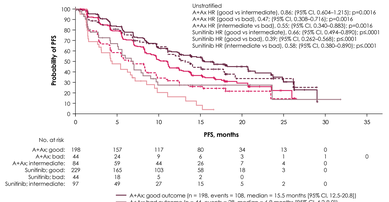
METHODS

- Biomarkers in baseline and on-treatment blood samples from 886 enrolled patients were correlated with clinical outcomes and molecular profiling data from corresponding tumor samples; the previously published definition of baseline tumor tissue "double-mutant" patients[5] was further refined
- Levels of mature T cells were examined by T-cell receptor sequencing (TCRseq), and peripheral blood cell populations were assessed via complete blood count with differential
- Circulating proteins were analyzed via multiplex Luminex cytokine analyses and proteomic matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry
- PFS analyses were conducted with and without age and sex adjustment with no observable differences; nonadjusted data are presented.

RESULTS

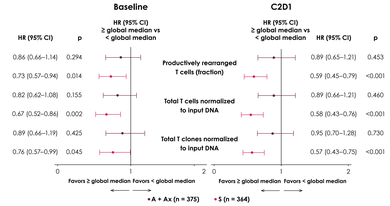
- A novel proprietary proteomic signature was shown to be prognostic for both both A + Ax and S (**Figure 1**)
- In the S arm only, both baseline and on-treatment T-cell levels were associated with PFS benefit (**Figure 2**); T cells showed much greater expansion at cycle 2 day 1 (C2D1) following S treatment (**Table 1**)
- Peripheral blood cell subset levels were differentially associated with PFS at baseline and C2D1, both within and between treatment arms (**Figure 3**)
- Treatment-emergent effects on peripheral cell counts were more moderate with A + Ax vs S, and changes in these populations mirrored S dosing schedule (**Figure 4**)
- Baseline and on-treatment levels of ICAM-1, VEGF, CRP, and several interleukins showed differential associations with PFS in the treatment arms (**Figure 5**)
- Double-mutant patients treated with A + Ax had prolonged PFS, while those treated with S fared worse (**Figure 6**)
- Double-mutant status in baseline tumor was associated with differences in baseline blood cell subsets, as well as baseline and on-treatment angiokine/cytokine levels (**Tables 2** and **3**)

Figure 1. Kaplan-Meier plot of PFS by treatment arm and proteomic classifier



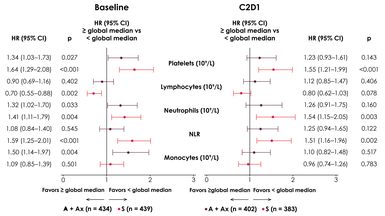
HR, hazard ratio; **MALDI-TOF**, matrix-assisted laser desorption ionization–time of flight.
MALDI-TOF proteomic signature was developed in second-line non-small cell lung cancer population treated with avelumab monotherapy. 2-sided p-value is from log-rank test.

Figure 2. Forest plots of PFS by TCRseq metrics at baseline and C2D1, by treatment arm



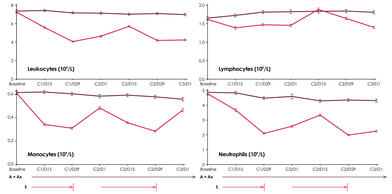
HR, hazard ratio; **TCRseq**, T-cell receptor sequencing.
HR (95% CI) from Cox proportional hazards model. Biomarker is dichotomized at global median with < global median as the reference group. An HR of <1 indicates better PFS for biomarker high (≥ global median) group. 2-sided p-value is from log-rank test.

Figure 3. Forest plots of PFS by peripheral cell populations at baseline and C2D1, by treatment arm



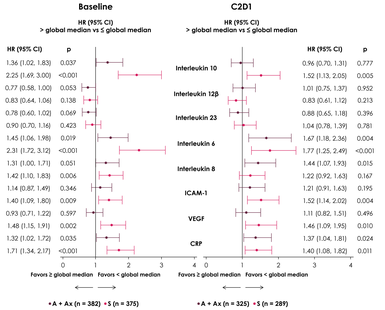
NLR, neutrophil-lymphocyte ratio.
HR (95% CI) from Cox proportional hazards model. Biomarker is dichotomized at global median with < global median as reference group. An HR of <1 indicates better PFS for biomarker high (≥ global median) group. 2-sided p-value is from log-rank test.

Figure 4. Line plot of peripheral cell population counts over time, by treatment arm



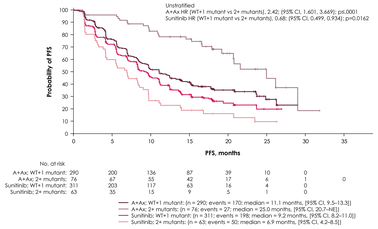
Error bars indicate the SEM.

Figure 5. Forest plots of PFS by most significant cytokine and angiokine levels at baseline and C2D1, by treatment arm



CRP, C-reactive protein; **HR**, hazard ratio; **ICAM-1**, intercellular adhesion molecule 1.
Cox proportional hazards model with ≤ global median as the reference group was used to calculate the HR and 95% CI. An HR of <1 indicates better survival in the > global median group. 2-sided p-value is from log-rank test.

Figure 6. Kaplan-Meier plot of PFS by treatment arm and mutant subgroup



2+, double mutant; **HR**, hazard ratio; **NE**, not estimable; **WT**, wildtype.
Double-mutant patients are classified as having ≥2 variants in baseline tumor tissue: somatic variants in any of 6 specific genes (*CD163L1*, *DNMT1*, *MC1R*, *ABCA1*, *MYH7B*, and *STAB2*) and/or germline single-nucleotide polymorphisms in any of 4 specific genes (*LOC728763*, *FOXO1*, *SPATA31C2*, *IL16* [P9L]). HR reference level is 2+ mutants, 2-sided p-value is from log-rank test.

Table 1. TCRseq metrics at C2D1 by treatment arm

TCR metric	A + Ax (n=328)* median (95% CI)	S (n=311)* median (95% CI)	P†
Productively rearranged T-cell fraction	0.199 (0.188-0.211)	0.261 (0.250-0.271)	<0.0001
Total T-cell counts‡	27.310 (25.832-28.790)	36.069 (34.860-38.031)	<0.0001
Total T clone counts‡	0.792 (0.708-0.851)	1.035 (0.955-1.073)	<0.0001
Log2FC productively rearranged T-cell fraction§	0.092 (0.044-0.133)	0.449 (0.369-0.504)	<0.0001
Log2FC in total T clone counts‡,§	0.046 (0.022-0.073)	0.364 (0.300-0.440)	<0.0001

Log2FC, log2 fold change; **TCRseq**, T-cell receptor sequencing.
*N varied depending on availability of baseline-C2D1 matched pairs. For Log2FC productively rearranged T-cell fraction A + Ax (n=326) and S (n=310), and for Log2FC T clones A + Ax (n=326) and S (n=308); †Wilcoxon rank-sum test (2 sided); ‡Normalized to input DNA; §C2D1 vs baseline.

Table 2. Differences in peripheral blood cell populations and selected cytokines/angiokines at baseline, by mutant subgroup

Cell population, ×10⁹/L	WT + single mutants median (95% CI)*	Double mutants median (95% CI)*	P†
Leukocytes	7.100 (6.900-7.300)	6.270 (6.000-6.700)	<0.0001
Basophils	0.040 (0.030-0.040)	0.030 (0.020-0.040)	0.3168
Eosinophils	0.160 (0.140-0.190)	0.150 (0.110-0.200)	0.9477
Lymphocytes	1.580 (1.500-1.610)	1.520 (1.410-1.630)	0.3224
Monocytes	0.600 (0.560-0.600)	0.500 (0.440-0.540)	0.0019
Neutrophils	4.480 (4.320-4.600)	4.100 (3.740-4.400)	0.0013
Platelets	259 (250-266)	250 (230-278)	0.6339
NLR	2.846 (2.676-3.000)	2.830 (2.478-3.129)	0.2379
Cytokine/angiokine			
Eotaxin 1	170.0 (153.0-182.0)	142.5 (118.0-157.0)	0.0095
Factor VII	451.0 (436.0-468.0)	471.5 (453.0-494.0)	0.1131
IL-17	2.6 (2.6-2.6)	2.6 (2.6-2.6)	0.0674
IL-7	51.0 (51.0-51.0)	51.0 (51.0-51.0)	0.0034
MCP-1	394.0 (372.0-421.0)	331.5 (306.0-386.0)	0.0060
MIP-1β	278.0 (268.0-302.0)	333.5 (307.0-368.0)	0.0035
VEGF	299.0 (281.0-317.0)	323.5 (284.0-357.0)	0.0755

IL, interleukin; **MCP-1**, monocyte chemotactic protein 1; **MIP-1β**, macrophage inflammatory protein 1β; **NLR**, neutrophil-lymphocyte ratio; **WT**, wildtype. No differences between arms were observed for any analyte either in WT or double-mutants.
*For cell population n=601 for WT + single mutants and n=139 for double mutants.
For cytokine/angiokine n=513 for WT + single mutants and n=132 for for double mutants.
†Wilcoxon rank-sum test (2 sided).

Table 3. Greatest differences in circulating cytokine/angiokine levels at C2D1, by mutant subgroup and treatment arm

	A + Ax			S		
Cytokine/angiokine median (95% CI)	WT + single mutants (n=209)	Double mutants (n=66)	p*	WT + single mutants (n=201)	Double mutants (n=46)	p*
BDNF	13.0 (12.0-15.0)	13.0 (11.0-14.0)	0.275	9.0 (7.9-9.7)	11.0 (8.4-13.0)	0.0259
Eotaxin-1	214.0 (189.0-235.0)	173.0 (148.0-204.0)	0.0143	179.0 (164.0-193.0)	174.0 (142.0-210.0)	0.7269
MCP-1	435.0 (393.0-474.0)	380.0 (316.0-420.0)	0.0545	458.0 (423.0-489.0)	432.0 (343.0-490.0)	0.1641
MIP-1β	312.0 (271.0-359.0)	404.0 (364.0-466.0)	0.0332	218.0 (194.0-240.0)	289.5 (233.0-354.0)	0.0008
MMP3	8.5 (8.1-9.4)	10.0 (8.9-12.0)	0.0536	9.9 (8.9-11.0)	11.0 (7.8-13.0)	0.6958
VEGF	362.0 (341.0-401.0)	385.5 (332.0-432.0)	0.7129	244.0 (219.0-263.0)	303.0 (248.0-377.0)	0.0131

BDNF, brain-derived neurotrophic factor; **MCP-1**, monocyte chemotactic protein 1; **MIP-1β**, macrophage inflammatory protein 1β; **MMP3**, matrix metalloproteinase 3; **VEGF**, vascular endothelial growth factor; **WT**, wild type.
* Wilcoxon rank-sum test (2 sided).

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