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Genomic biomarkers in peripheral blood (PB) from patients (pts) enrolled in the JAVELIN Bladder 100 trial of avelumab first-line (1L) maintenance in advanced urothelial carcinoma (aUC)

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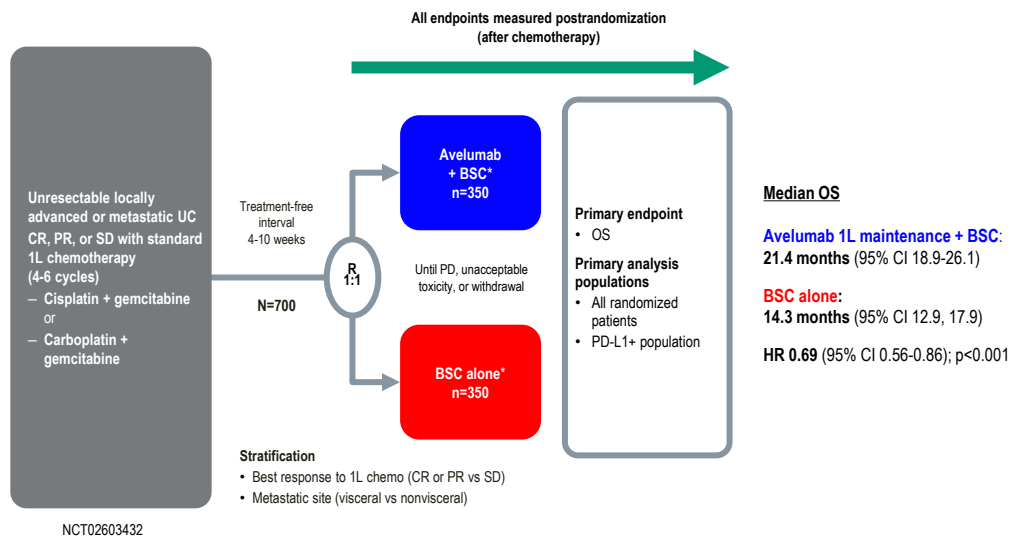
DECLARATION OF INTERESTS

Thomas Powles

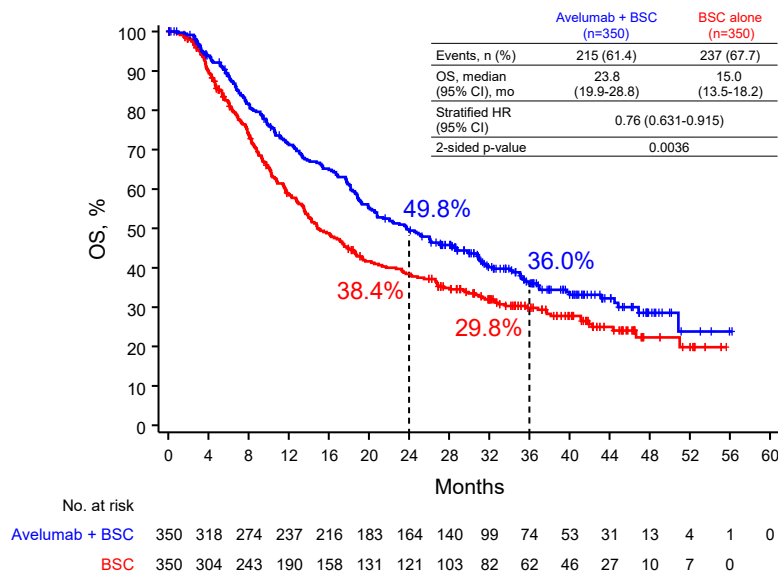
Consulting or advisory role: *Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Eisai, Exelixis, Incyte, Ipsen, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, Seattle Genetics, and Merck*; **research funding:** *Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Eisai, Exelixis, Ipsen, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, Seattle Genetics, and Merck*; **travel, accommodation, expenses:** *AstraZeneca, Ipsen, MSD, Pfizer, and Roche*

JAVELIN Bladder 100 demonstrated OS benefit from maintenance avelumab in patients with aUC that has not progressed with 1L chemotherapy

JAVELIN Bladder 100 study design and primary outcomes (data cutoff, October 21, 2019)¹



Long-term OS in the overall population (data cutoff, June 4, 2021)²



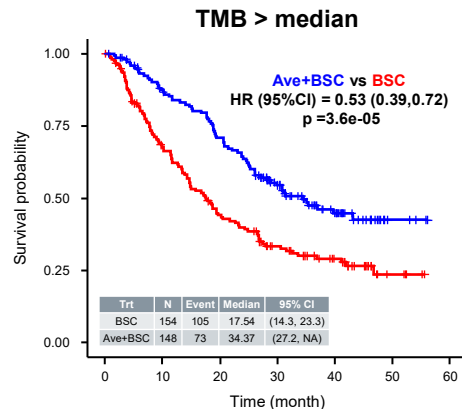
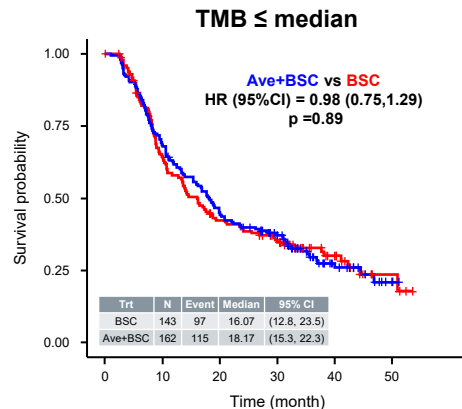
BSC, best supportive care; CR, complete response; HR, hazard ratio; OS, overall survival; PD, progressive disease; PR, partial response; R, randomized; SD, stable disease.

1. Powles T, et al. N Engl J Med. 2020;383(13):1218-30. 2. Powles T, et al. J Clin Oncol. 2022;40(Suppl 6). Abstract 487.

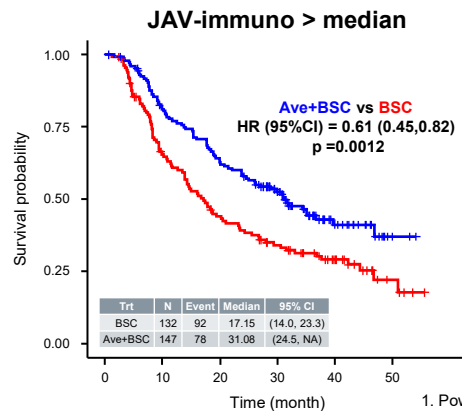
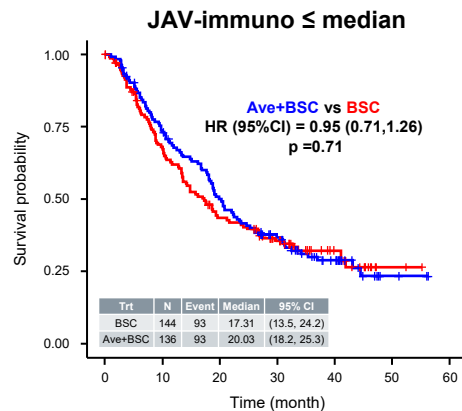
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Retrospective tumor biomarker analyses indicated that tumor mutation burden and tumor immune activity are associated with OS benefit from maintenance avelumab¹

Tumor mutation burden (TMB)

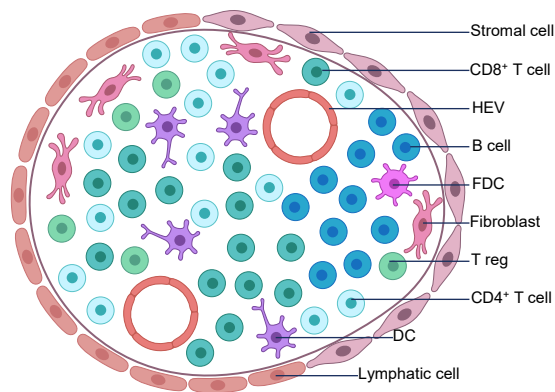


JAV-immuno²



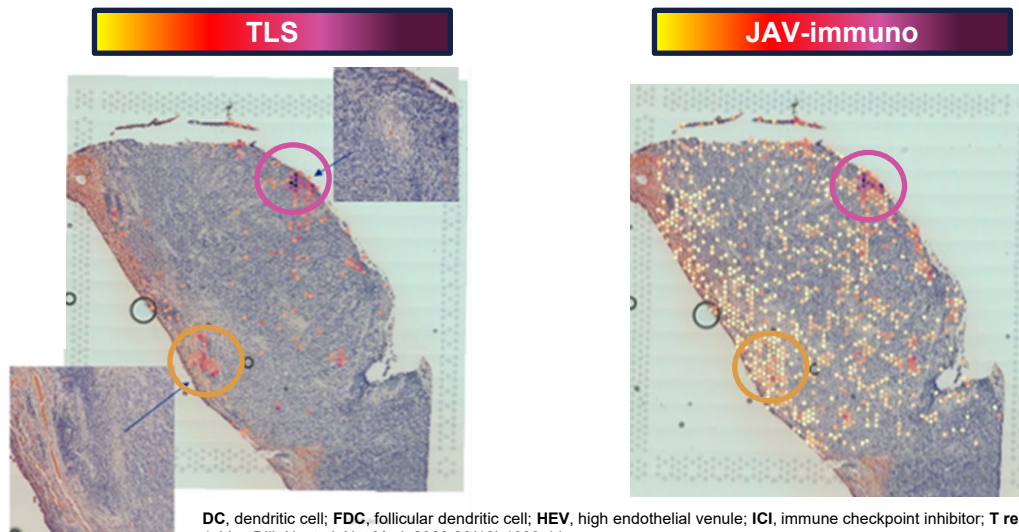
Tertiary lymphoid structures (TLS) in urothelial cancer

- TLS are ectopic lymphoid tissues that arise in inflamed tissue, including cancer.
- TLS are characterized by variably organized lymphoid regions with presence of **B cell zones** and **adjacent T cells**.
- Previous exploratory work from single arm trials has suggested that TLS may correlate with outcome to ICI therapy¹



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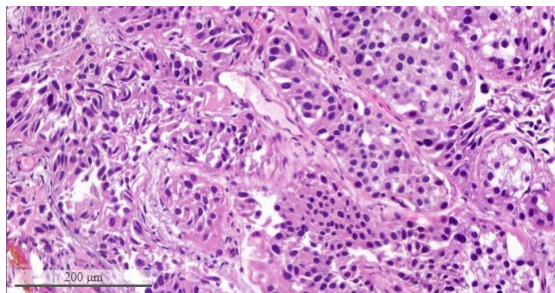
Spatial transcriptomic analysis indicates that tumor regions with elevated JAV-immuno scores colocalize with TLS



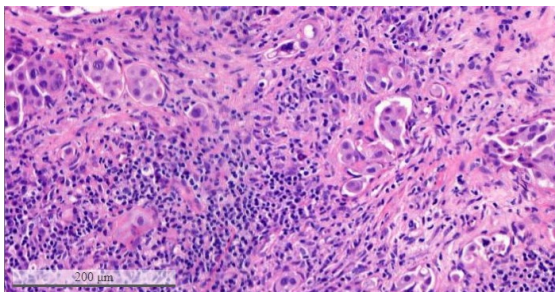
DC, dendritic cell; FDC, follicular dendritic cell; HEV, high endothelial venule; ICI, immune checkpoint inhibitor; T reg, regulatory T cell.
1. Van Dijk N, et al. Nat Med. 2020;26(12):1839-44.

TLS gene expression scores are positively associated with lymphoid aggregates and maintenance avelumab survival benefit in JAVELIN Bladder 100¹

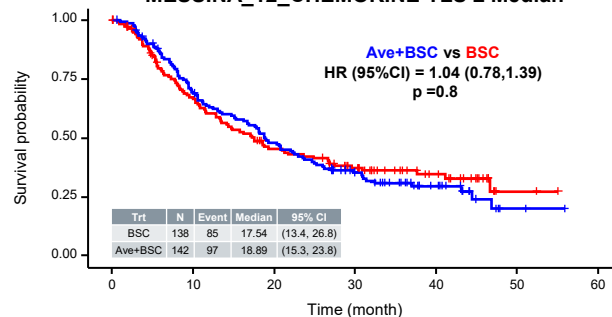
Low Messina_TLS (-2.018)



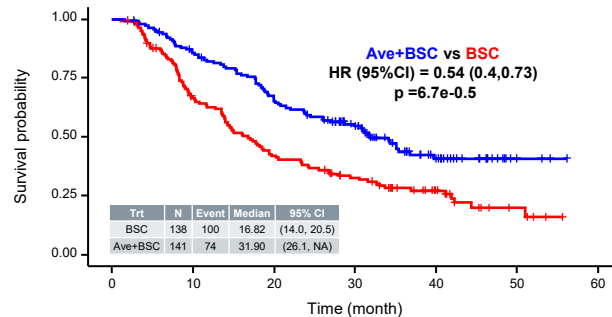
High Messina_TLS (2.070)



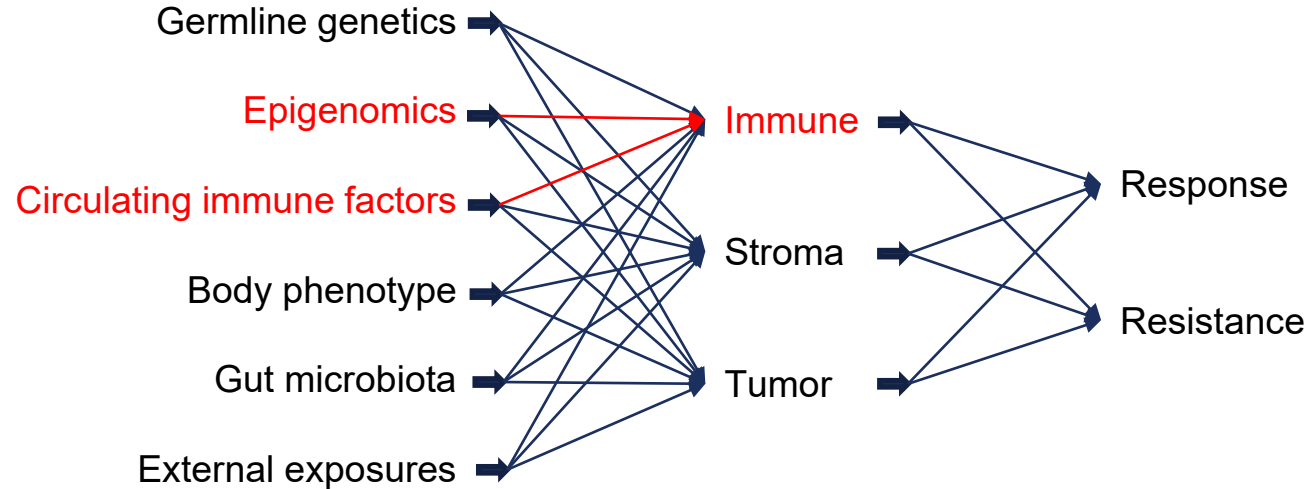
MESSINA_12_CHEMOKINE TLS ≤ Median



MESSINA_12_CHEMOKINE TLS > Median

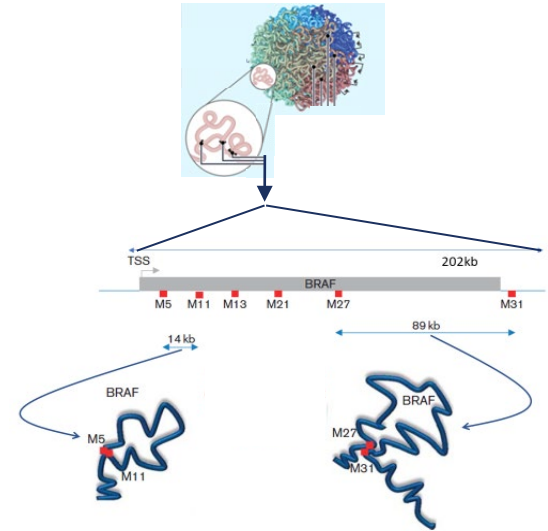


Host factors have been reported to influence the efficacy of ICIs through interactions in the tumor microenvironment^{1,2}



Analysis of chromatin conformation has the potential to identify host immune factors in circulating WBCs that are associated with anti-tumor immune activity

- DNA packaging into chromatin plays a crucial role in regulating gene expression in response to developmental and environmental cues
- Gene loci can assume distinct chromatin structures (loops) associated with differential gene activity¹⁻²
- The EpiSwitch platform is based on an annotated 3D genome architecture consisting of >900 annotated chromatin loops
- Chromatin conformation signatures (CCSs) consist of panels of chromatin loops measurable by nested PCR³⁻⁷
- CCSs may be useful for assessing disease diagnosis,⁴⁻⁶ prognosis,⁶⁻⁷ potential response to ICI therapy⁷ and risk of severe COVID-19 disease⁸

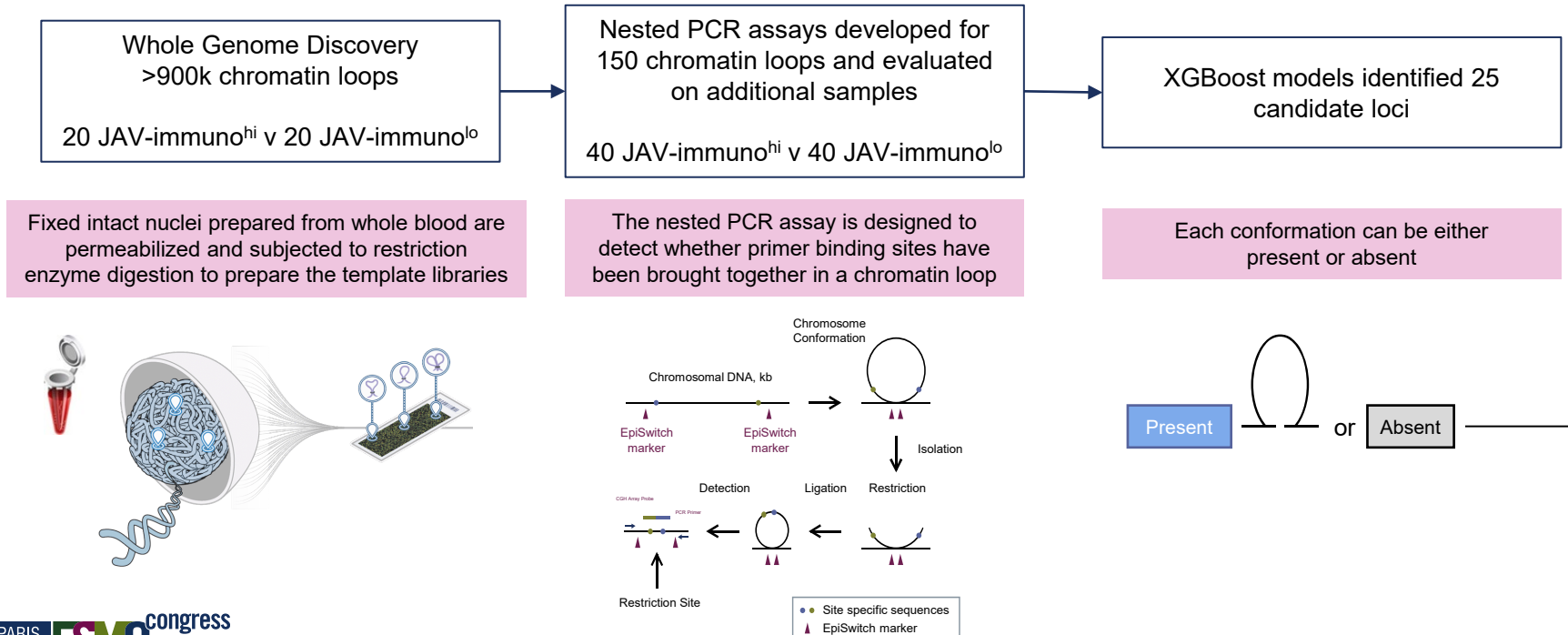


PCR, polymerase chain reaction; TSS, transcriptional start site; WBC, white blood cell.

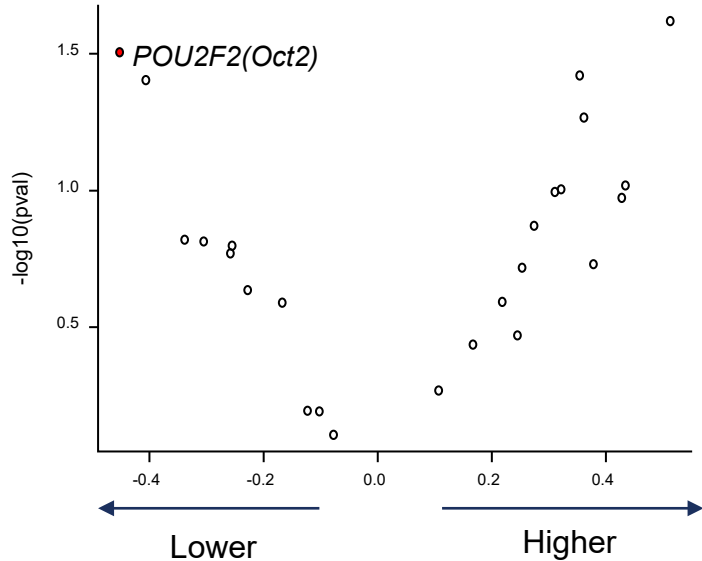
1. Crutchley JL, et al. Biomark Med. 2010;4(4):611-29.
2. Tordini F, et al. Front Genet. 2016;7:194.
3. Mukhopadhyay S, et al. Int Immunopharmacol. 2014;18(1):7-11.
4. Jakub JW, et al. Melanoma Res. 2015;25(5):406-11.
5. Salter M, et al. EBioMedicine. 2018;33:169-84.
6. Hunter E, et al. Transl Med Commun. 2020;5.
7. Alshaker H, et al. J Transl Med. 2021;19(1):46.
8. Hunter E, et al. medRxiv. Preprint posted online December 27, 2021.

The EpiSwitch platform was employed for exploratory analysis of WBC chromatin loops associated with tumor immune activity as measured by JAV-immuno scores

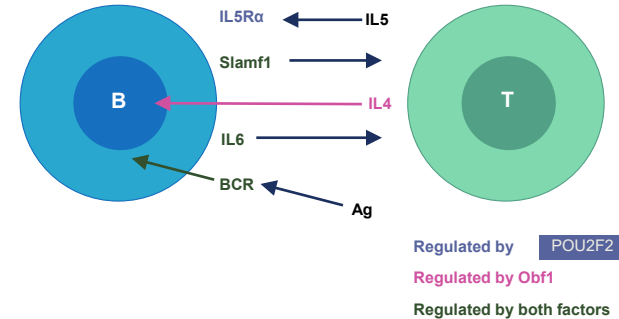
EpiSwitch analysis was performed on peripheral blood specimens collected from 496 JAVELIN Bladder 100 patients after non-progression with 1L chemotherapy and before randomization to avelumab/BSC or BSC



A chromatin loop associated with lower JAV-immuno scores encompasses POU2F2 (Oct2), a transcription factor with known roles in B cell maturation and participation in T-cell dependent humoral immunity



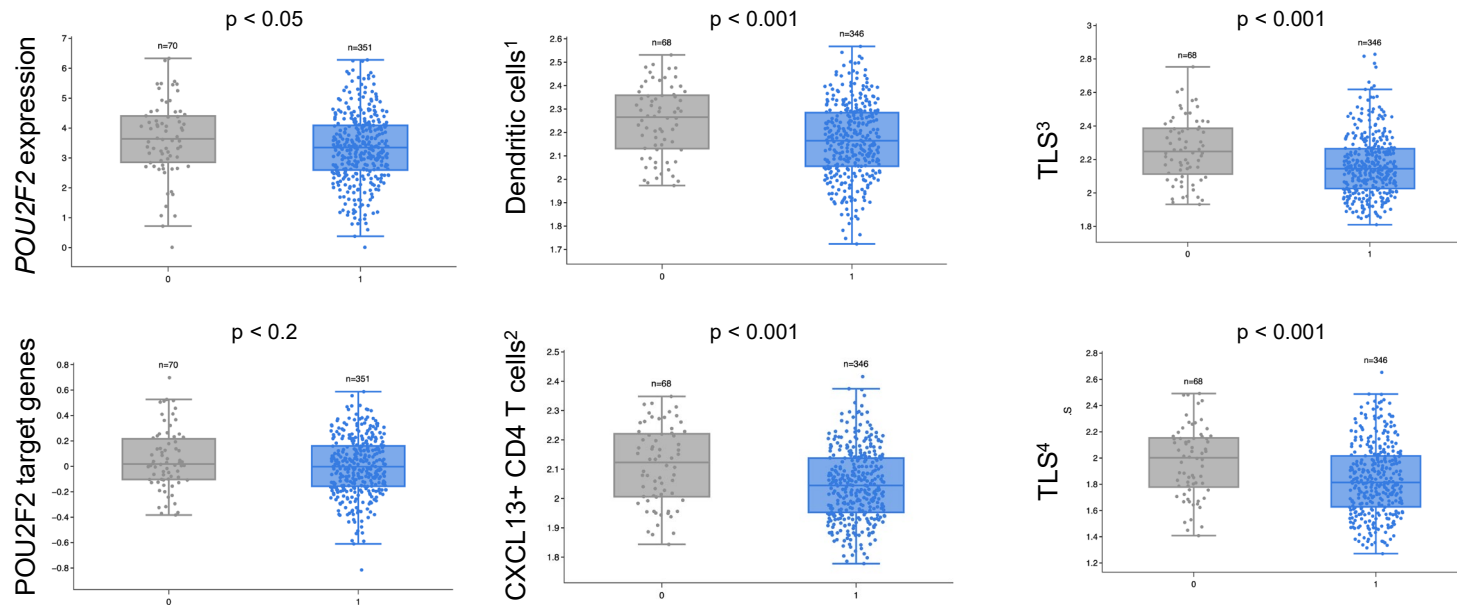
JAV-Immuno score in POU2F2 **Present** patients



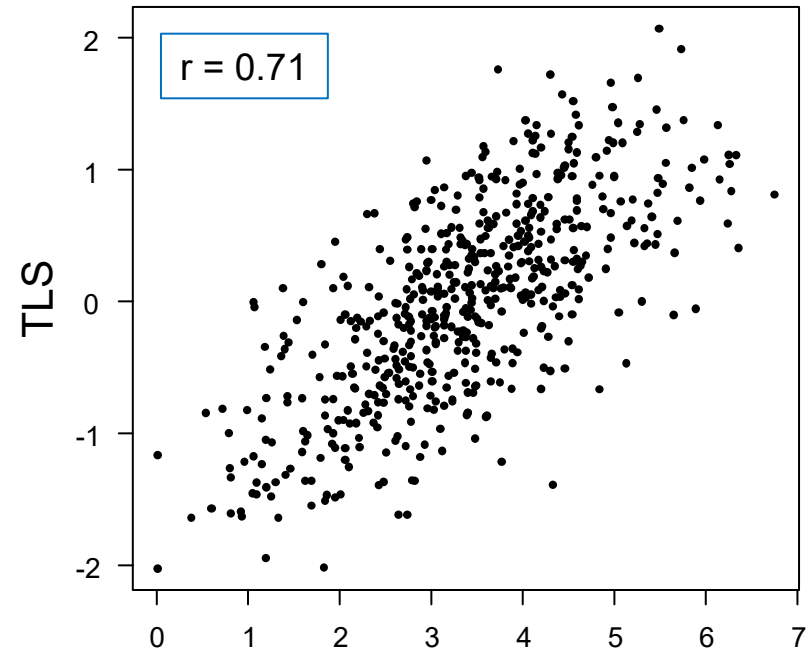
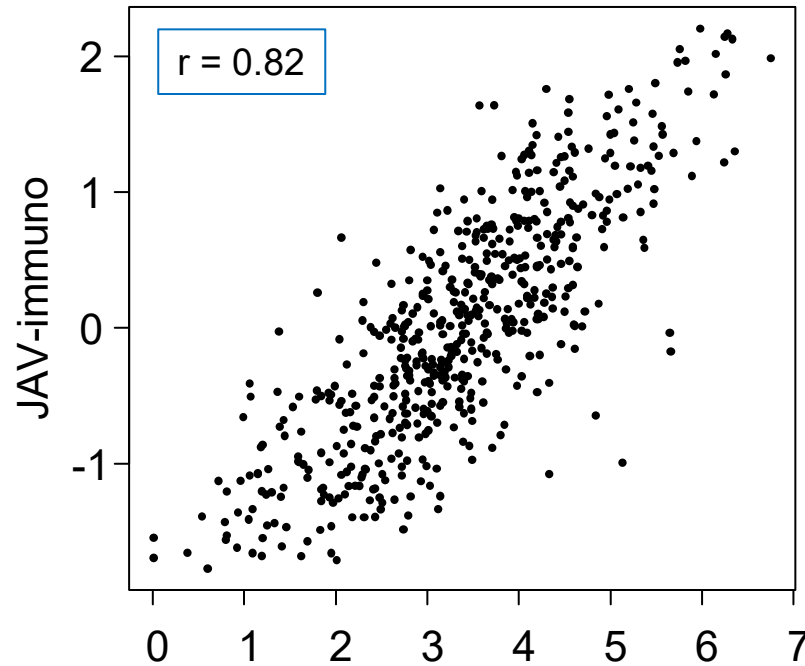
- Identified as a cell-type transcription factor binding to an octamer motif in immunoglobulin genes¹
- Key regulator of B cell responses to antigen receptor signaling and T-cell cytokines²
- Required for B cell proliferation and generation of plasma cells after immunization with T-dependent antigens³

Associations between presence of the WBC POU2F2 loop and expression of POU2F2, POU2F2 targets, and TLS signatures in tumor

Presence of the loop may be associated with negative regulation of POU2F2 function relative to absence



POU2F2 expression is positively associated with JAV-immuno and signatures of TLS



POU2F2 gene expression

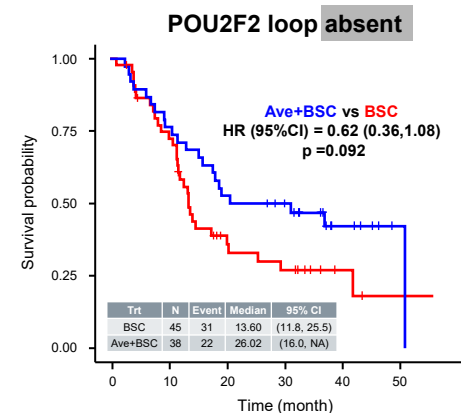
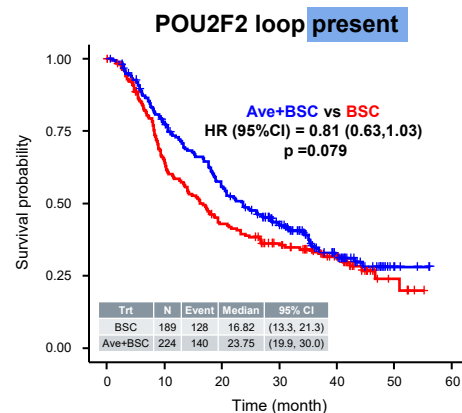
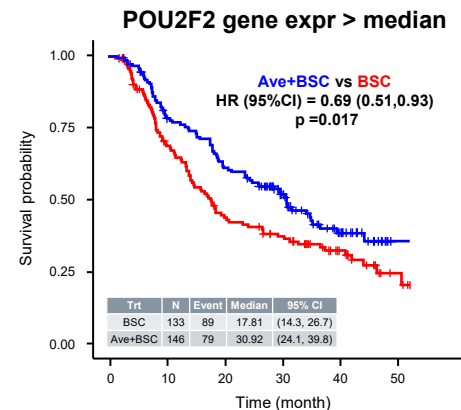
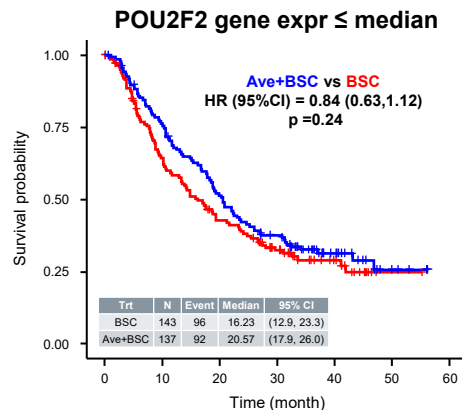
POU2F2 expression in tumor is associated with maintenance avelumab survival benefit

Presence or absence of the *POU2F2* loop in blood displays lower association

POU2F2 gene expression score (tumor)

POU2F2 loop (blood)

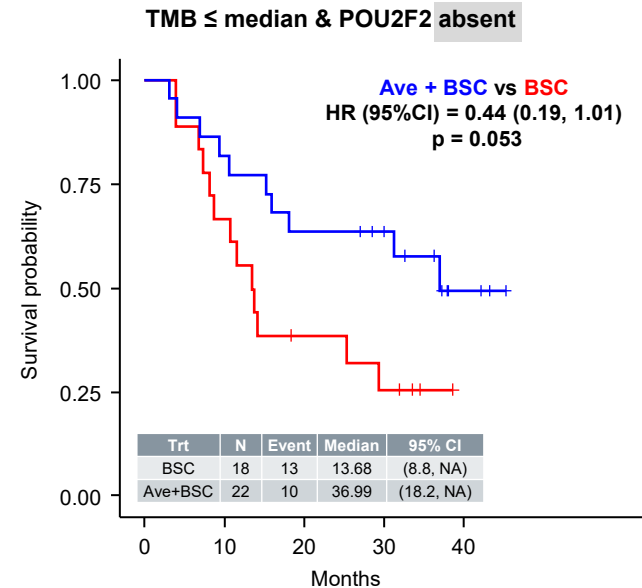
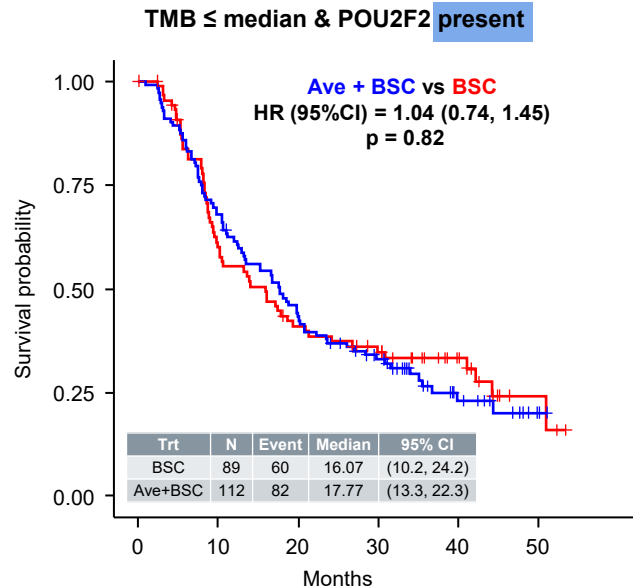
Combined *POU2F2* loop training and test set



Absence of the POU2F2 loop in blood may identify a group of TMB-low patients with improved maintenance avelumab survival benefit

Efficiency of TLS formation may partially compensate for reduced immunogenicity of TMB-low tumors

POU2F2 loop
(blood)

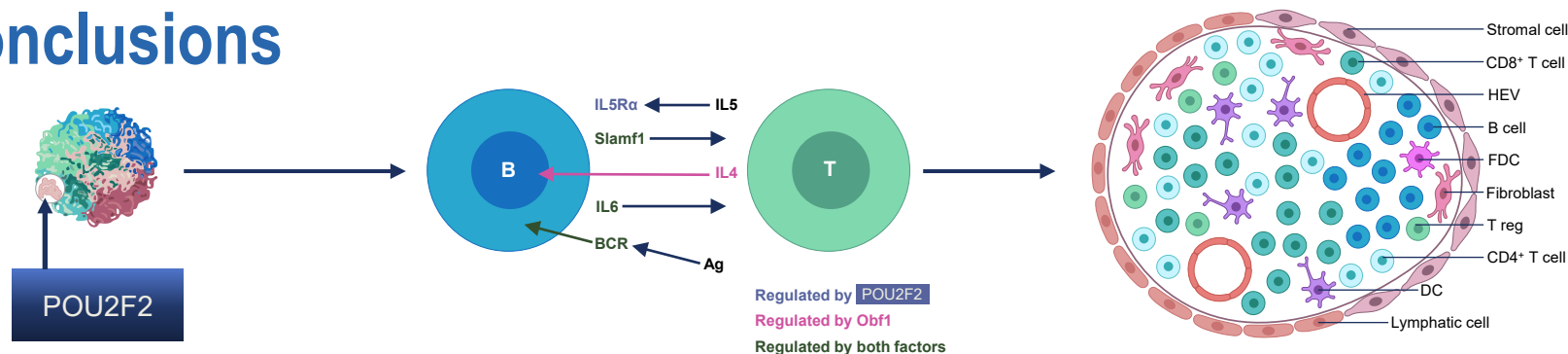


Combined POU2F2 loop training and test set

Limitations

- The JAVELIN Bladder 100 peripheral blood specimen set represents a single time point in the treatment cycle, and applicability to other time points should be investigated
- These analyses were exploratory in nature and not corrected for multiple testing; therefore, further statistical validation is required
- Bioanalytical validation of the *POU2F2* loop is also needed to confirm fitness for clinical applications

Conclusions



- TLS appear relevant for predicting outcome with maintenance avelumab
- Chromatin conformation loops measured in WBC nuclei were associated with JAV-immuno signature
 - The strongest association was with **POU2F2**, a transcription factor regulating B cell responses to T cells
 - The presence of the *POU2F2* loop was associated with reduced *POU2F2* expression and function, as well as TLS biomarkers, suggesting a negative regulatory role
- Ongoing research is assessing the potential use of chromatin loops identified by the EpiSwitch platform to form chromatin conformation signatures that may enrich patients that benefit from maintenance avelumab
- **The predisposition to form TLS in response to inflammatory stimuli may be a host factor influencing response to immune checkpoint inhibitors**
- **Measurement of circulating chromatin loops may be a useful method for evaluating systemic vs tumor-specific biomarkers**

ACKNOWLEDGMENTS

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