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Disclosure Information

Maria Libera Ascierto is a full employee of AstraZeneca.

Tumoral and peripheral immunophenotype of refractory vs. relapse to PD-(L)1 blockade in patients with advanced NSCLC

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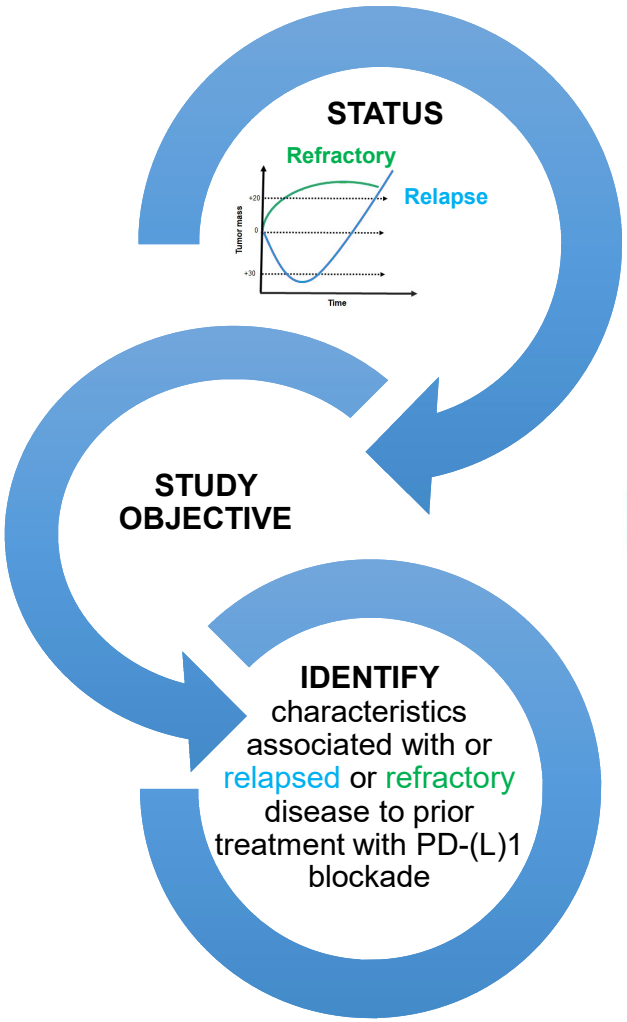
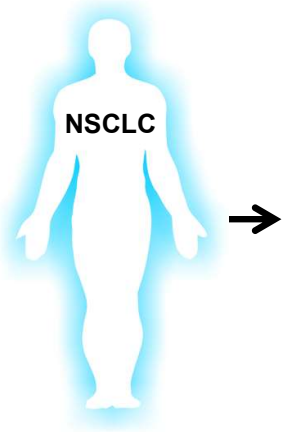
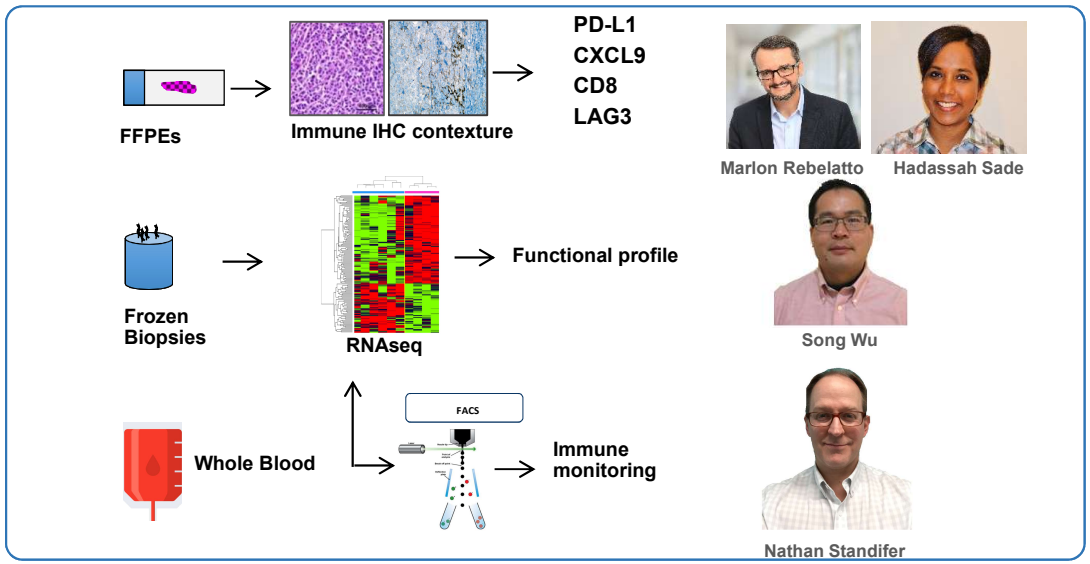
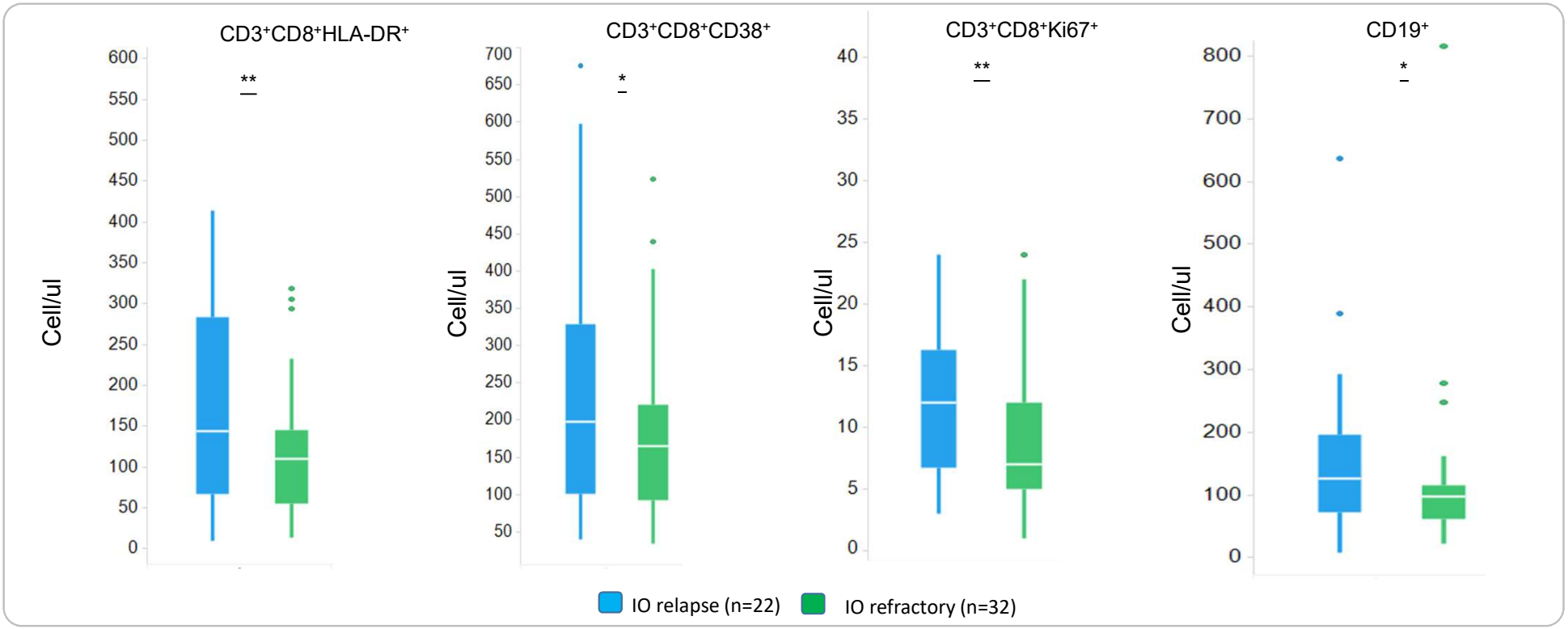






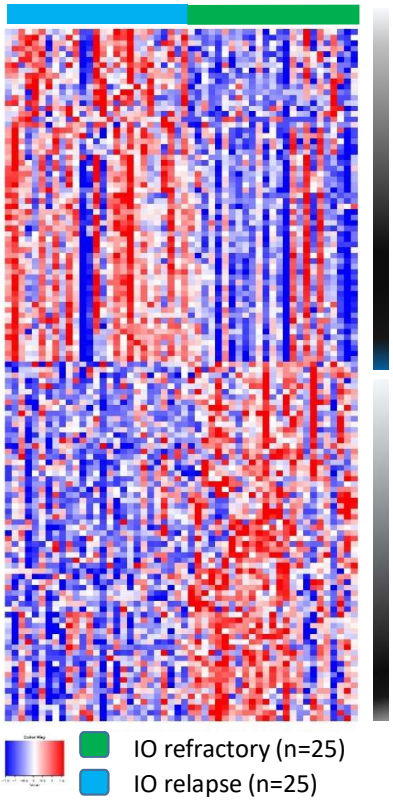
- Samples collected during screening for clinical trial of second line immunotherapy with Durvalumab (anti PD-L1) + Tremelimumab (anti-CTLA4) [Study 006; NCT02000947] were analyzed according to Relapse vs. Refractory response to first line of therapy with anti-PD-(L)1 blocking Abs.
- Patient response to PD(L1) blocking Abs were prospectively defined:
  - "refractory": progression within 16 weeks of initiating PD-(L)1
  - "relapse": initial clinical benefit (CR, PR, SD) followed by progression.
- No stratification according to PD-L1 status occurred.

In the periphery, higher B cells and activated or proliferating CD8+ cells counts are observed in patients with relapse status following PD-(L)1 blockade

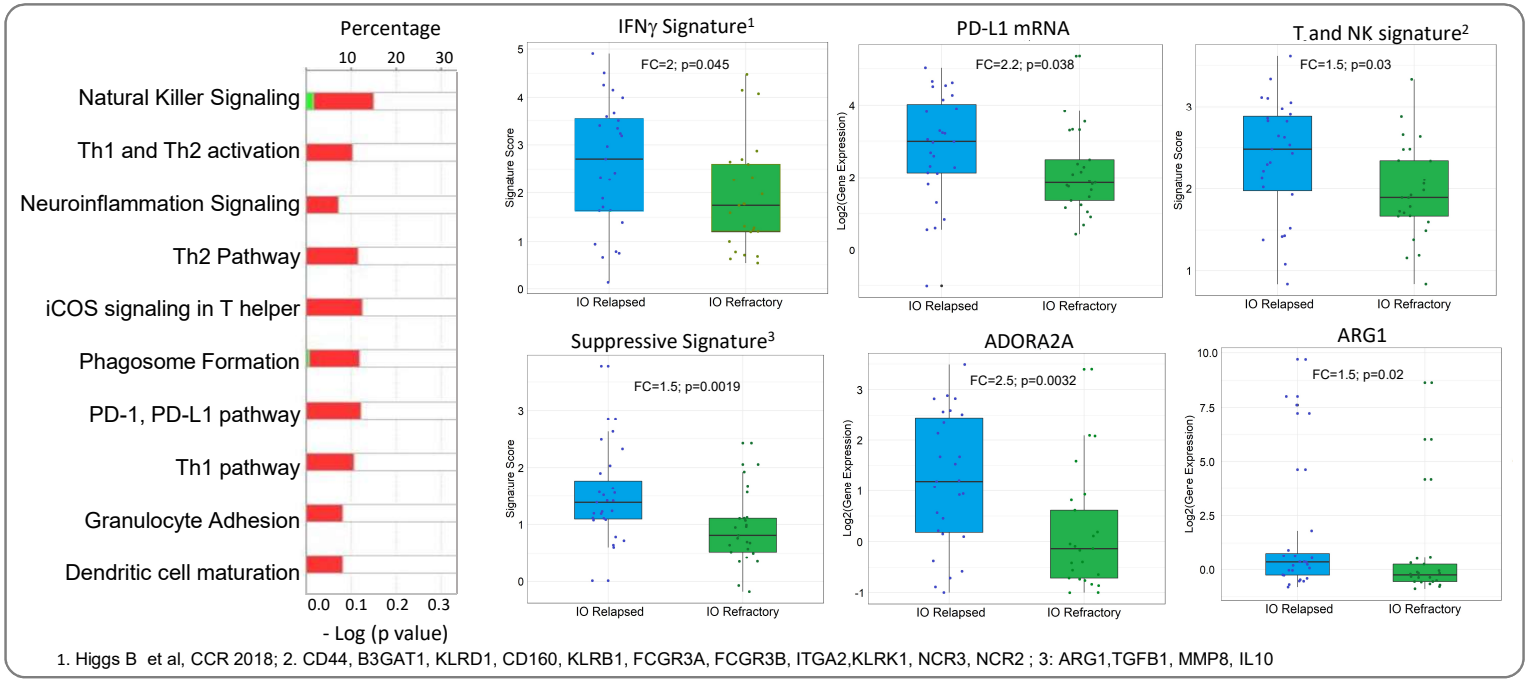


A distinctive gene expression portrait is observed in the TME of patients with relapse status following PD-(L)1 blockade

Differential gene expression (n=504) defined as unadjusted p<0.05 and fold-difference >1.5.



IO refractory (n=25)
IO relapse (n=25)



1. Higgs B et al, CCR 2018; 2. CD44, B3GAT1, KLRD1, CD160, KLRB1, FCGR3A, FCGR3B, ITGA2,KLRK1, NCR3, NCR2 ; 3: ARG1,TGFB1, MMP8, IL10

Genes associated with MDSCs (S100A14, CEACAM6), B cell negative regulation (FOXJ1) and metabolism, found upregulated in IO refractory)

Increased PD-L1 and CXCL9 expression is observed by IHC in the TME of patients with relapse status following PD-(L)1 blockade

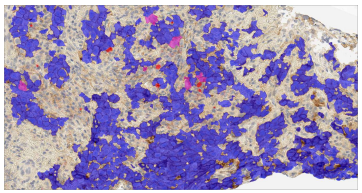
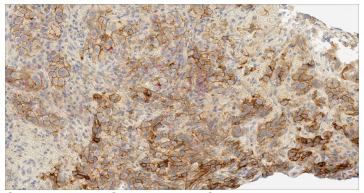


Image segmentation results. PD-L1+ Tumor (blue), Lag3+ TILs (red), PD-L1+Lag3+ Cells (magenta).



Original IHC image of PD-L1 (SP263, brown) and Lag3 (red) duplex assay on an NSCLC biopsy

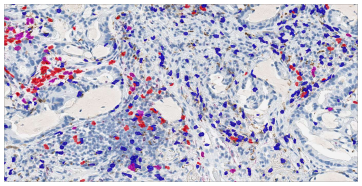
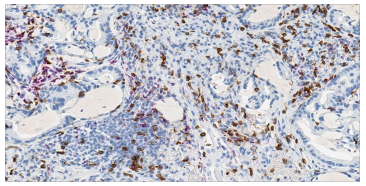
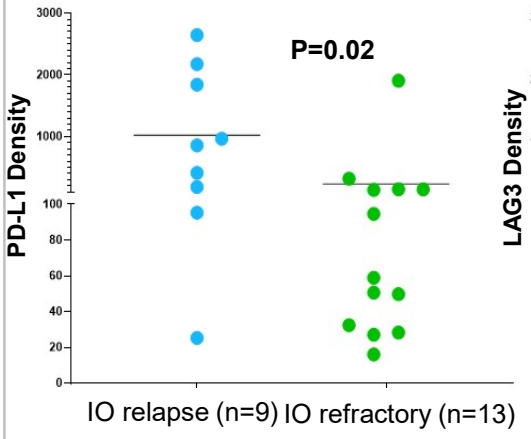
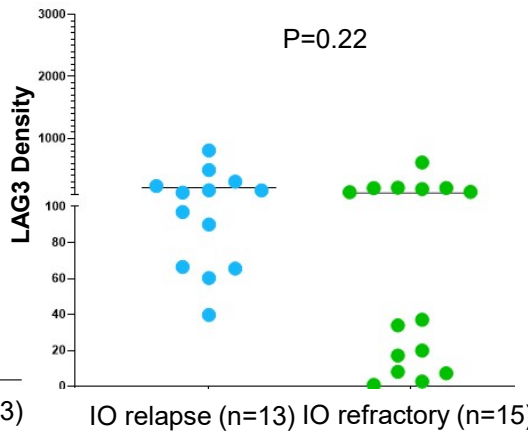


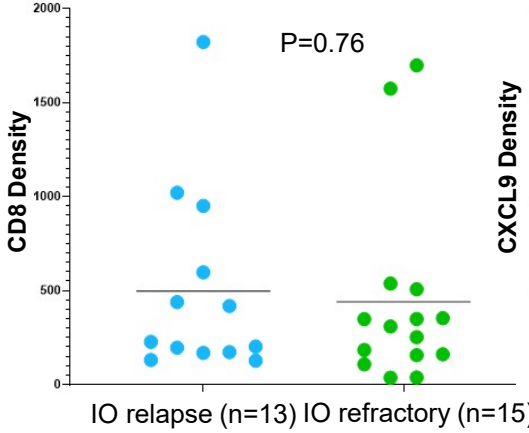
Image segmentation results. CD8+ TILs (blue), CXCL9+ TILs (red), CD8+CXCL9+ TILs (magenta)

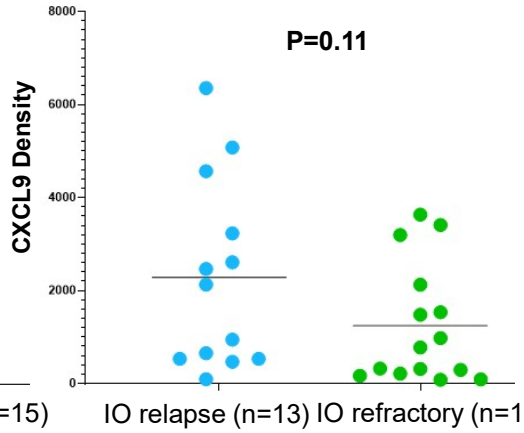


Original IHC image of CD8 (brown) and CXCL9 (red) duplex assay on an NSCLC biopsy









CONCLUSIONS

- The tumor and peripheral compartments of patients with NSCLC previously treated with PD-(L)1 blockade differ based on prior response.
- Relapsed patients tend to have signals of sturdy immune activation and chronic inflammation led by dysfunctional IFNγ signaling thus ultimately leading to immune exhaustion and upregulation of immune checkpoints
- These results may help inform rational therapeutic strategies to overcome resistance to PD-(L)1 blockade in NSCLC.

Too Much of a Good Thing? Chronic IFN Fuels Resistance to Cancer Immunotherapy

Reading JL and Quezada SA, Immunity, 2016

Acknowledgments

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