Spatial distribution of infiltrating T lymphocytes with Immunocore® CR T Cells Exhaustion test helps stratification of NSCLC patients treated with PD1 / PDL1 inhibitors in the PIONeER project

Vanina Leca1, Alboukadel Kassambra1, Lamia Ghezali1, Marcellin Landri1, Pernelle Outters1, Thomas Sbrarto1, Florence Monville1, Maryannick Le Ray2, Marie Roumieux3, Stéphane Garcia3, Richard Malkoun4, Noémie Resseguié4, Arnaud Boyer4, Louisiane Lebas5, Hervé Pegliascio5, Patricia Barre5, Clarisse Audigier-Valette5, Sarah Zahi6, Luc Odier7, Stéphane Hominal1, Maurice Pérol8, Julien Mazières1, Laurent Grelletier1, Fabrice Barlier3,1, Jacques Fieschi3

1Vercyta, Marseille, France; 2 Assistance Publique-Hôpitaux de Marseille (APHAM), Marseille, France; 3 Centre de Recherche en Cancérologie de Marseille, INSERM U1068, CNRS UMR7258, Aix Marseille University, Institut Paoli-Calmettes, Marseille, France; 4 Hôpital St Joseph, Centre médical Clichy, Marseille, France; 5 UMS Pneumologie CHU, FRA, France; 6 Canceropole, France; 7 Centre Hospitalier A. J. Carrel, Cahors, France; 8 Centre hospitalier St Charles, Montauban, France; 9 Hôpital Nord-Ouest, Villefranche-sur-Saône, France; 10 Centre Hospitaller Aix-en-Provence, Prilly, France; 11 Centre Léon Bérard, Lyon, France; 12 Toulouse University Hospital, Toulouse, France; 13 Institut Gustave Roussy, Villejuif, France.

This work is supported by French National Research Agency (17-BHSU-0007); a partnership of AML, CIBM, INSERM, Centre Léon Bérard, Institut Paoli-Calmettes, Astrazeneca, Vercyta formerly HalioOnc; Immune Pharma & ImmCyt Therapeutics; sponsored by 4P IMI and initiated by Marseille ImmunoCure Drug supply in funded by Astrazeneca.

Introduction

Immune checkpoint inhibitors (ICI), and particularly anti-PD1 / PDL1, improved long-term outcome in ~20% of NSCLC patients, meaning that 80% present primary or secondary resistance and need to be identified at diagnostic to avoid inefficient therapy [1]. To date, neither PD1-L tumor cell status nor TMB, both approved as companion diagnostics, can efficiently predict resistance. Tumor-infiltrating lymphocytes (TILs) play a major role in the immune response against malignant cells by infiltrating and interacting with tumor cells to achieve their cytocidal role. TILs’ immune Checkpoints’ (ICP) expression such as PD1, LAG3 or TIM3 may reflect their anti-tumor activity and be directly involved in responses to ICIs through regulation of T cell activity. Assessing their status within the tumor at diagnostic could help stratifying patients and refine population eligible to ICI therapy. The PIONeER project aims to predict the response to anti-PD1 / PDL1 ICIs in advanced NSCLC patients through a comprehensive agnostic multiparametric biomarkers assessment. Here, we aim to define tissue- and tissue-based immunotherapeutic implications of activated and exhausted TILs in a cohort of 79 patients from the multiplex immunohistochemistry (IHC) Brightplex™ CR T Cell Exhaustion assay. Among these patients, 24 were re-biopsied 6 weeks after anti-PD1/L1 treatment initiation, allowing comprehensive analysis of treatment action.

2. Spatial distribution of TILs stratifies NSCLC patients into 4 subtypes

A. Proportion of activated TILs in NSCLC patients based on CR T Cell assay

B. Stratification of IHC Hot map into 4 subtypes

C. Correlation of IHC and CR T Cell Hot maps

3. Spatial TILs stratification enriches anti-PD1/L1 immunotherapy responders’ group

A. Expression of PD1/L1 on Hot subtypes

B. Association between Spatial TILs subtypes and PD1/L1 tumor status shows significant enrichment of PD1/L1 tumor status in both Hot and Cold subtypes (Hot TILs and Cold TILs are defined in PD1/L1 positive patients) (pd1+/n; however, each subtype displays a sample of PD1/L1+ cases). Overall response rate (ORR) according to IHC Hot 1 subtype is displayed for each tumor profile.

4. Checkpoints expression across progression status and Spatial TILs Subtypes

A. PD1/LAG3/TIM3 expression in spatial TILs subtypes

B. Progression in Hot subtype is associated to lower checkpoints expression

C. Progression in Hot subtype is associated to lower checkpoints expression

5. Progression in Hot subtype is associated to lower checkpoints expression

A. Progression in Hot subtype is associated to lower checkpoints expression

B. Progression in Hot subtype is associated to lower checkpoints expression

6. Post-treatment induction of stromal infiltration can predict PFS

A. Pre-treatment and post-treatment analysis

B. Progression in Hot subtype is associated to lower checkpoints expression

C. Progression in Hot subtype is associated to lower checkpoints expression

Conclusion

Brightplex™ T-Cell Exhaustion assay could enrich NSCLC patients’ population eligible to anti-PD1/L1 therapy through the stratification into four Spatial TIL subtypes:

- Cold, 100% of patients progress within 10 months despite anti-PD1/L1 treatment
- Stromal infiltrated, enriched in ORR but with short time to progression
- Parenchyma Hot subtype, with intermediate time to progression
- Hot subtype, enriched in ORR, with long time to progression for more than 40% of patients (> 10 months), whatever the PDL1 status

In the hot subtype, activated T-cell clusters are high in tumors of patients with longer time to progression, suggesting stratification could be even more accurate integrating checkpoints expression such as PD1, LAG3 and TIM3.

Finally, whatever the subtype, anti-PD1/L1 therapy seems to recruit T-cells in the parenchyma, but not as systematically in the Stroma. Tumors with such a Stromal T-cell recruitment present longer time to progression. These preliminary results based on a first set of patients are under validation on the next 100 patients.

Reference
1. Nabet et al., 2020, Cell, 183, 363–77