# Immune tumor microenvironnement (iTME) post neoadjuvant chemotherapy, beyond PD-L1: novel immune targets in ovarian cancer, data from the CHIVA trial, a GINECO/GINEGEPS study

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## BACKGROUND

- Anti PD1/PDL1 have been disappointing so far in the treatment of ovarian cancer (OC).
- A greater understanding of the complex iTME could uncover promising immune targets.
- We previously reported the impact of neoadjuvant chemotherapy (NACT) on immune cells (IC)

CD4+ CD8+ ↗ FOXP3+ ↘

- Here we aimed to describe the expression of **PDL1** as well as **other co-regulatory molecules** in OC and their changes under NACT.

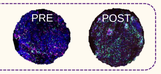
## METHODS

### Immune microenvironment characterization

- Immune cells (IC) were stained for **CD4**, **CD8**, **FOXP3** and **GRZB** and scored as number of IC+/mm2. A mean score was calculated from three TMA cores from each sample.
- **PDL1**, **LAG3**, **TIM3** and **IDO** expression were reported as the average percentage of tumor and immune cells with moderate to strong membranous staining in three TMA cores

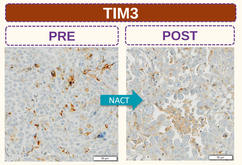
TILs: CD4, CD8, FOXP3, GRZB

Nb of IC/mm2
CD4 CD8 Foxp3

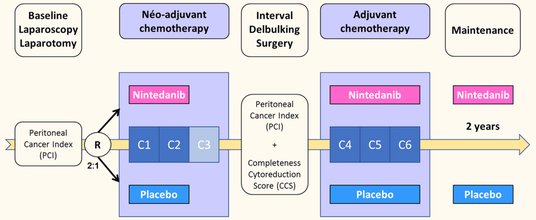



Coregulators: PDL1, LAG3, TIM3, IDO

PDL1+ / LAG3+ TIM3+ / IDO+ = ≥ 1% IC or TC expression

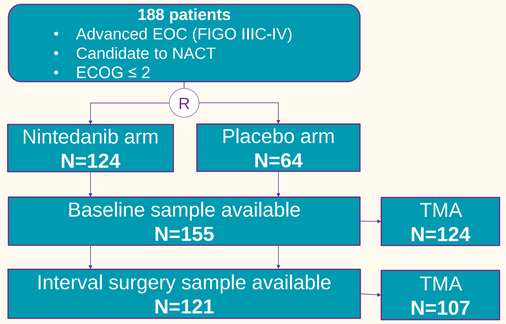



### CHIVA Study design

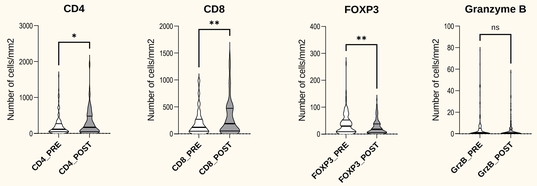



Paclitaxel: 175mg/m2, I.V Carboplatin: AUC 5 or AUC 6 (6 to 8 cycles)
Nintedanib: (oral TKI inhibiting VEGFR/PDGFR/FGFR): 400 mg/day
IDMC run 3 planned safety interim analyses after 30, 60 and 90 patients had completed the neo-adjuvant and IDS phase

### Study flowchart

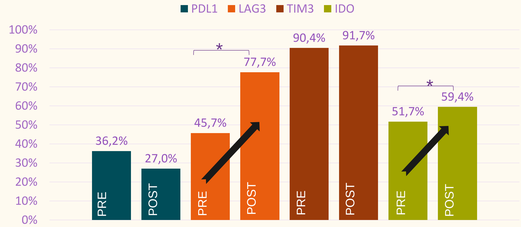



### Number of CD4+, CD8+, FOXP3+ and Granzyme B+ cells before and after NACT. * = p<0.05



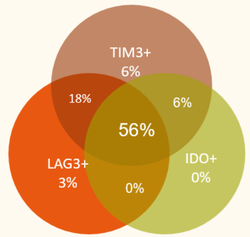

## RESULTS

**SIGNIFICANT INCREASE** OF **LAG3+** AND **IDO+** PATIENTS WITH NACT. * = p<0.05
**TIM3** IS ALMOST **UBIQUITOUS** (90% and 92%)




No significant impact of anti-VEGF TKI on immune coregulator expression

**56% with LAG3+ & TIM3+ & IDO+ post NACT**
Only **4%** with LAG3- & TIM3- & IDO-




PDL1 is the least represented immune coregulatory in EOC

**TIM3** expression, **CD4** and **CD8** infiltration **increased in highly sensitive patients**

| Outliers | RESISTANT (N=37) | SENSIBLE (N=26) | p value |
|---|---|---|---|
| PDL1_POST | | | 0.789 |
| - Mean (SD) | 3.5 (8.9) | 6.0 (10.3) | |
| LAG3_POST | | | 0.058 |
| - Mean (SD) | 5.1 (6.3) | 11.1 (11.7) | |
| TIM3_POST | | | **< 0.001** |
| - Mean (SD) | 3.6 (3.4) | 14.5 (8.6) | |
| IDO_POST | | | 0.322 |
| - Mean (SD) | 3.9 (8.3) | 5.9 (9.7) | |
| CD4_POST | | | **0.049** |
| - Mean (SD) | 228.5 (294.4) | 460.7 (313.9) | |
| CD8_POST | | | **0.037** |
| - Mean (SD) | 225.4 (283.6) | 505.1 (400.4) | |
| FOXP3_POST | | | 0.136 |
| - Mean (SD) | 22.7 (24.5) | 37.6 (36.0) | |
| GrzB_POST | | | 0.547 |
| - Mean (SD) | 5.8 (10.5) | 1.5 (1.8) | |

No PDL1+, LAG3+ IDO+ difference between RESISTANT and SENSIBLE pts

## CONCLUSIONS

- Other immune coregulators (beyond PDL1) are **highly expressed in OC** and most pts co-express multiple coregulators.
- NACT appears to **prime the iTME** by increasing effector T cell infiltration and expression of relevant co-regulatory molecules (LAG3, TIM3 and IDO)
- **TIM3** appears to be a **major player** in OC iTME and represents an attractive target for future clinical trials
- Future frontline immune checkpoint strategies should be based on target expression in **samples obtained after NACT**

## ACKNOWLEDGEMENTS

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