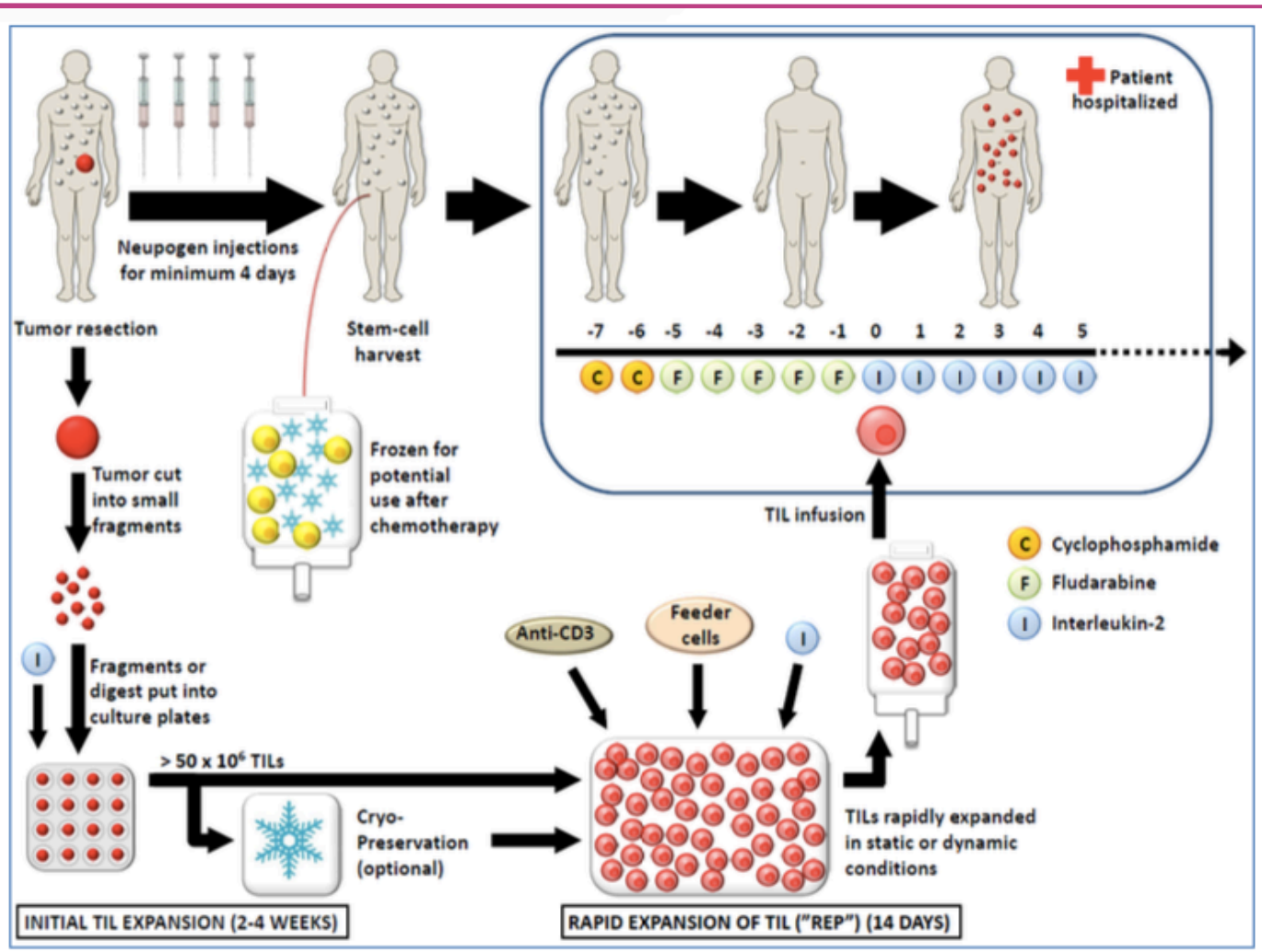
How can we improve these results?

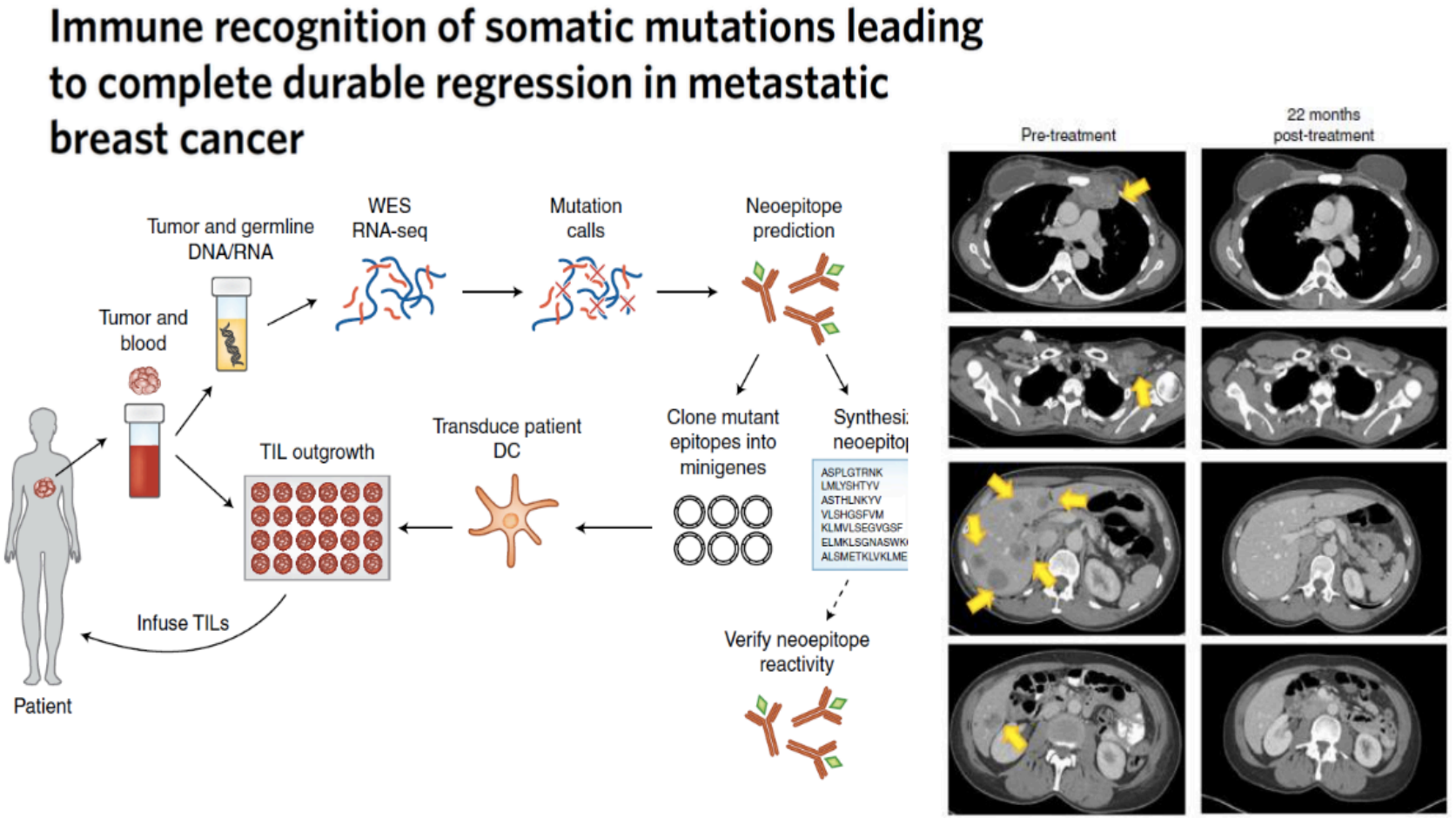
- **Check-point inhibitors combinations**
  - Anti-angiogenics
  - PARP inhibitors
- **A new option: T-cell therapy**
- **Better patients selection**
  - More efficient biomarkers
  - Immunophenotypes
  - Stroma and microbiome characterization

Tumor Infiltrating Lymphocytes



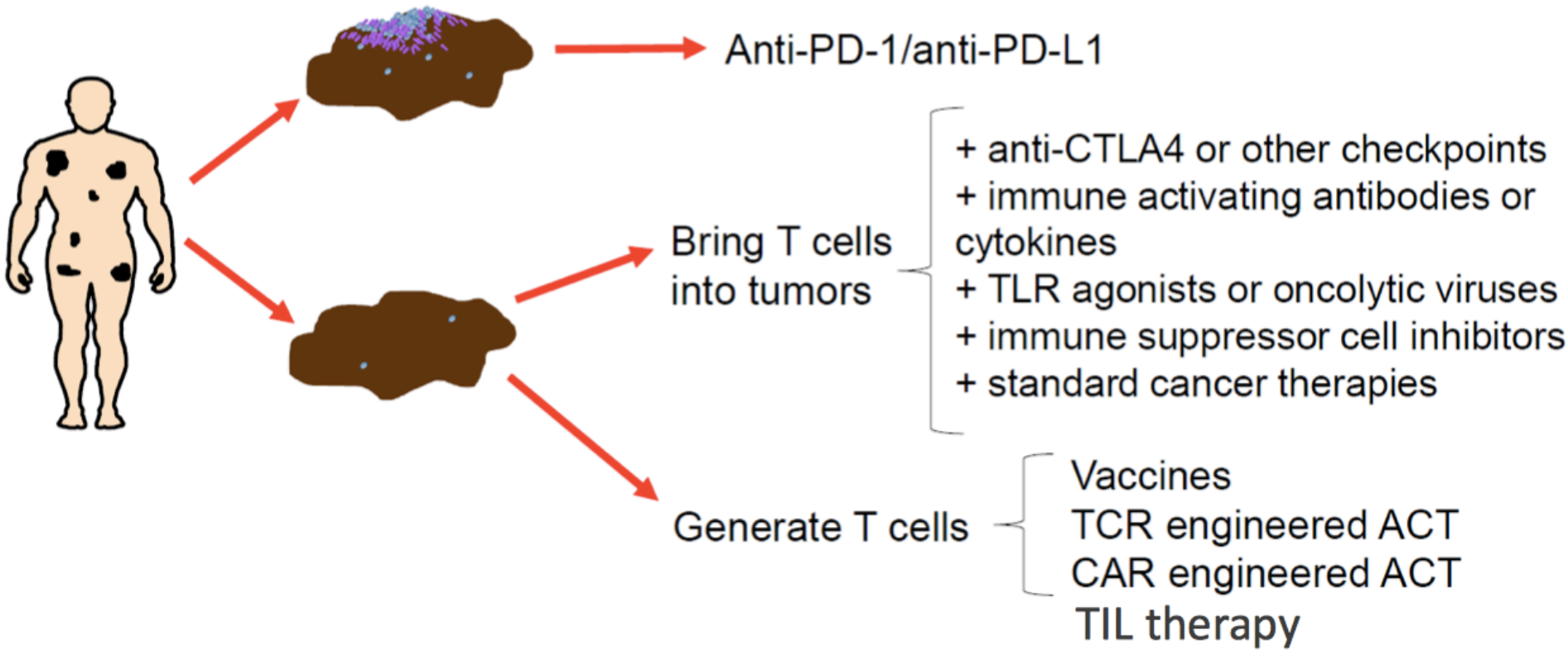
Pedersen M. et al. Adoptive cell therapy with tumor-infiltrating lymphocytes in patients with metastatic ovarian cancer: a pilot study. Oncoimmunology. 2018 Sep 26;7(12):e1502905. doi: 10.1080/2162402X.2018.1502905. eCollection 2018.

Patient specific neo-antigen targeting T-cell therapy



Zacharakis N. et al. Nature Medicine 2018, vol 24: 724-730

Moving forward to precision immunotherapy



Adapted from Ribas A et al, Cancer Discovery 2016

How can we improve these results?

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Search for more efficient biomarkers Keynote-100

Neither HRD nor BRCA mutation were associated with response to pembrolizumab

Figure 3. Box Plot (A) and AUROC (B) of Association of HRD With Response (N = 71)[a]

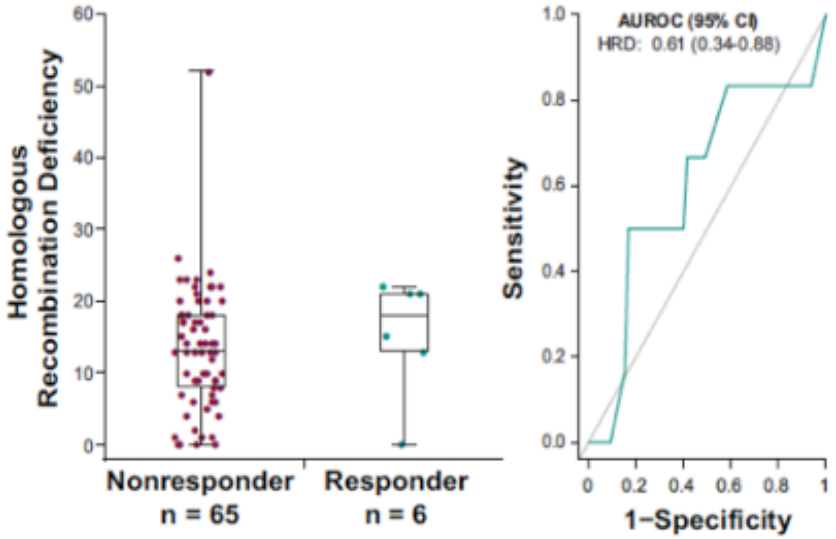


Table 3. Association of *BRCA* Mutation With Response[a]

BRCA Status	No Response n (%)	Response n (%)	*P*[b]
Wild type	55 (91.7)	5 (8.3)	0.65
Mutation	10 (90.9)	1 (9.1)	

[a]Samples analyzed from cohort A training set population.
[b]One-sided Fisher exact test.

All 319 pts were MS stable

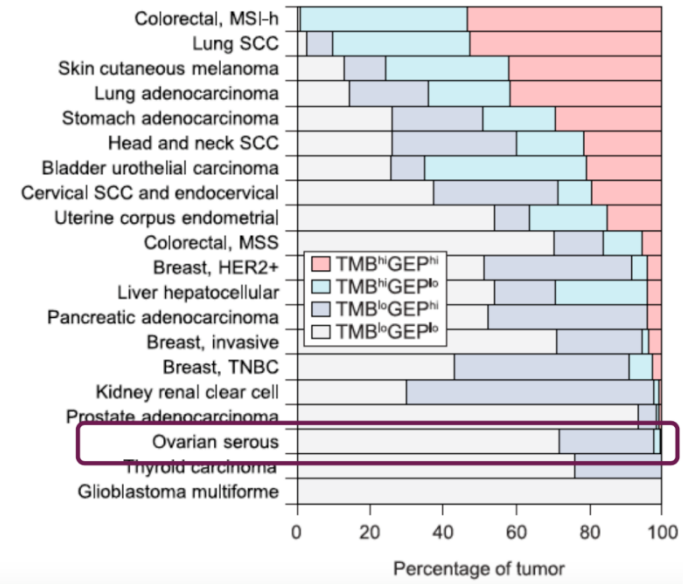
Lerderman J. et al. Association of PD-L1 expression and Gene Expression Profiling with clinical response to pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase 2 KEYNOTE-100 study. LBA 4294- Poster Presentation ESMO Congress 2018.

Search for more efficient biomarkers: Keynote-100

	Cohort A (285)	Cohort B (91)	Cohort A+B (376)
CPS < 1	107 3.7% (1.0-9.3)	34 8.8% (1.9-23.7)	141 5.0% (2.0-10.0)
CPS ≥ 1	147 10.2% (5.8-16.3)	50 10% (3.3-21.8)	197 10.2% (6.3-15.2)
CPS ≥ 10	60 16.7% (8.3-28.5)	22 18.2% (5.2-40.3)	82 17.1% (9.7-27.0)

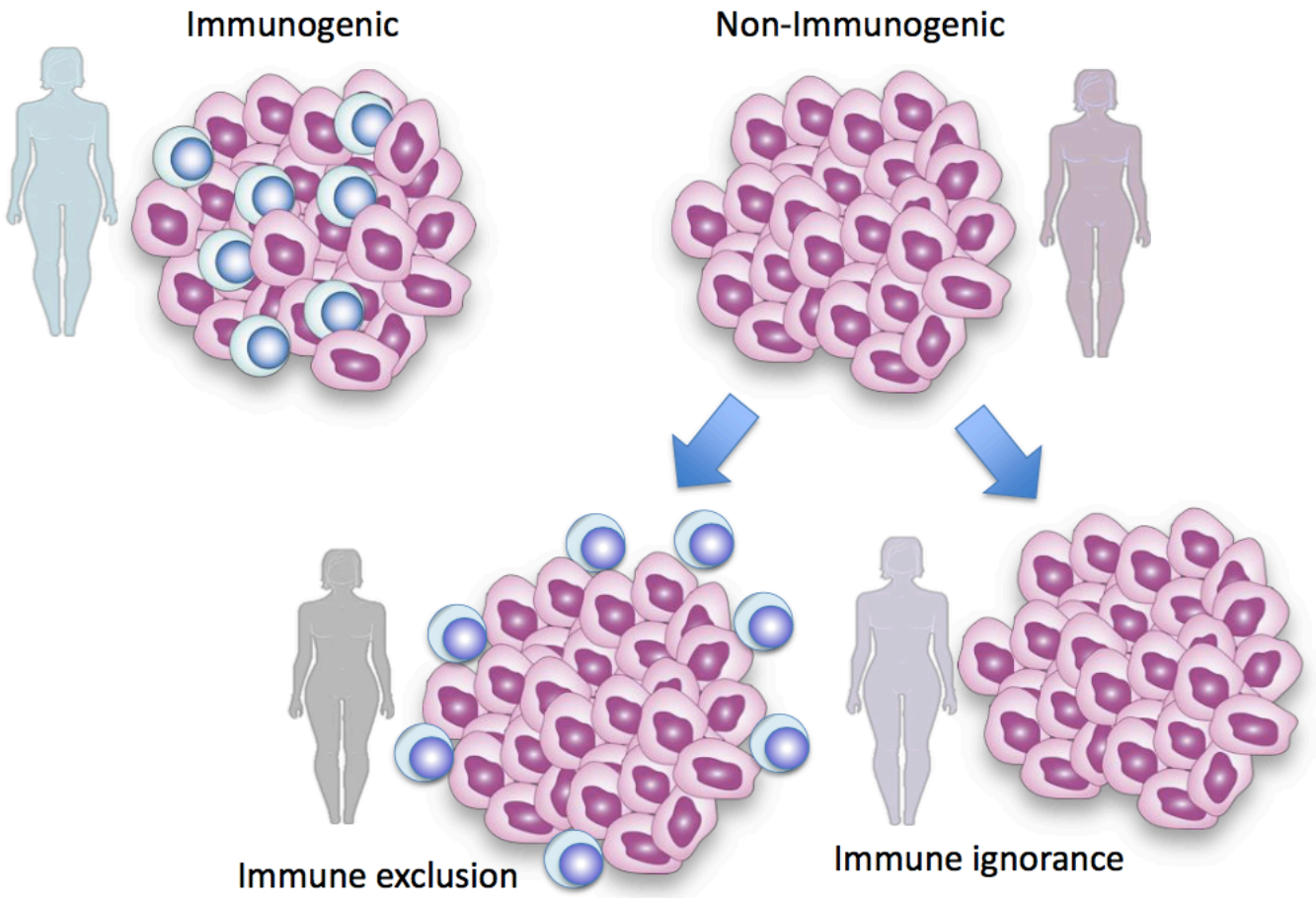
Ovarian cancer is mainly TMB^{low} and GEP^{low}

- **CPS = [Total number of PD-L1+ cells (Tumor, lymphocytes, Macrophages) / total numer of cells]** $^{x\ 100}$
- **GEP (T-cell–inflamed gene expression profile)** score was derived from an18-gene signature measured using extracted tumor RNA (81pts)



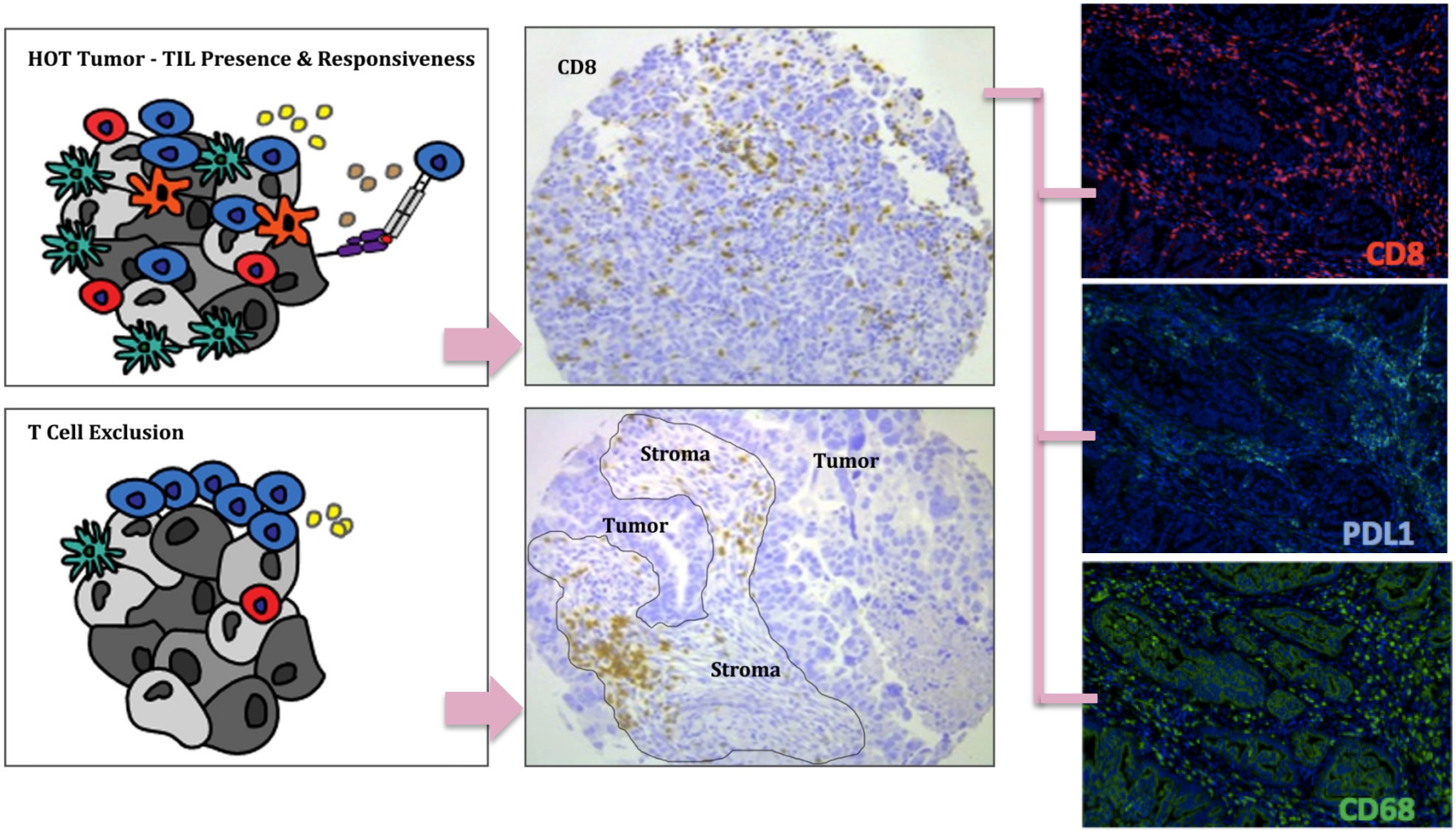
Cristescu R. et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. Science. 2018 Oct 12;362(6411).

Better patients selection: three different immunophenotypes of OC



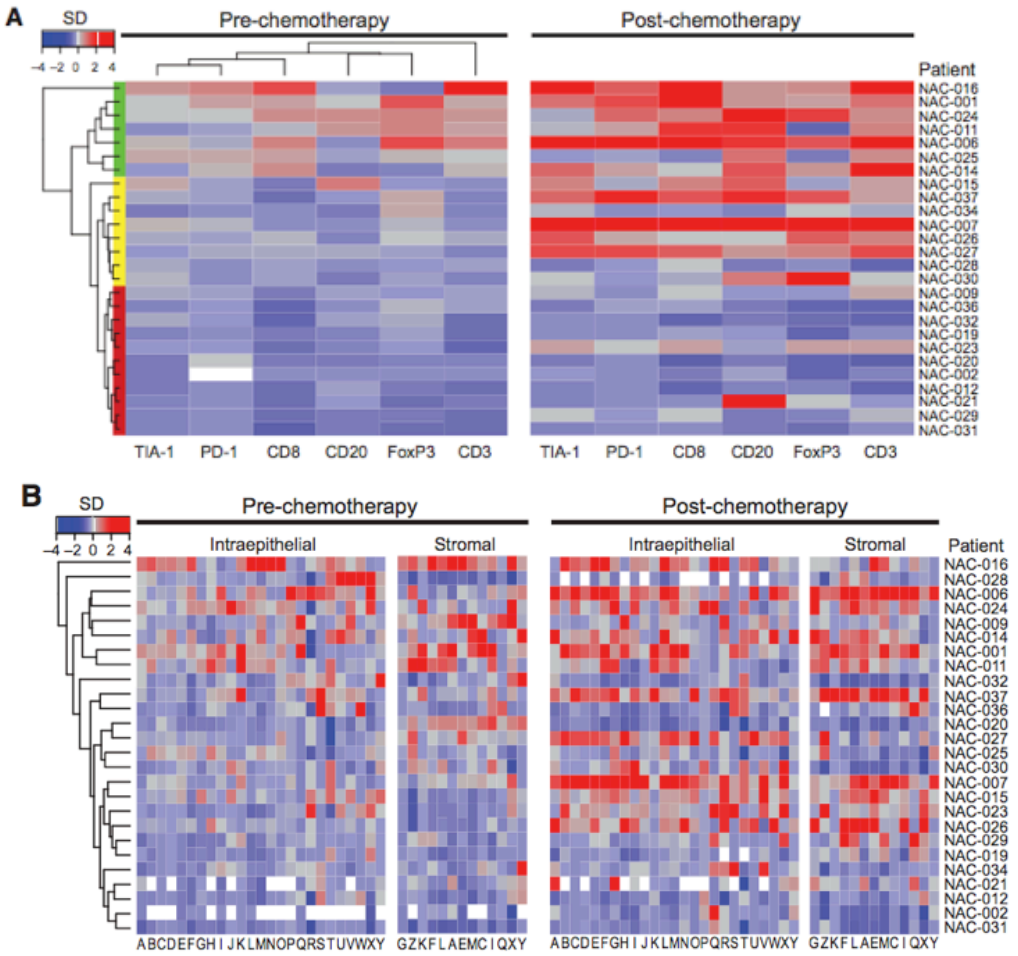
Adapted from Kandalaft L., ESMO Immuno-Oncology Nov 2017

Immunophenotypes' characterization



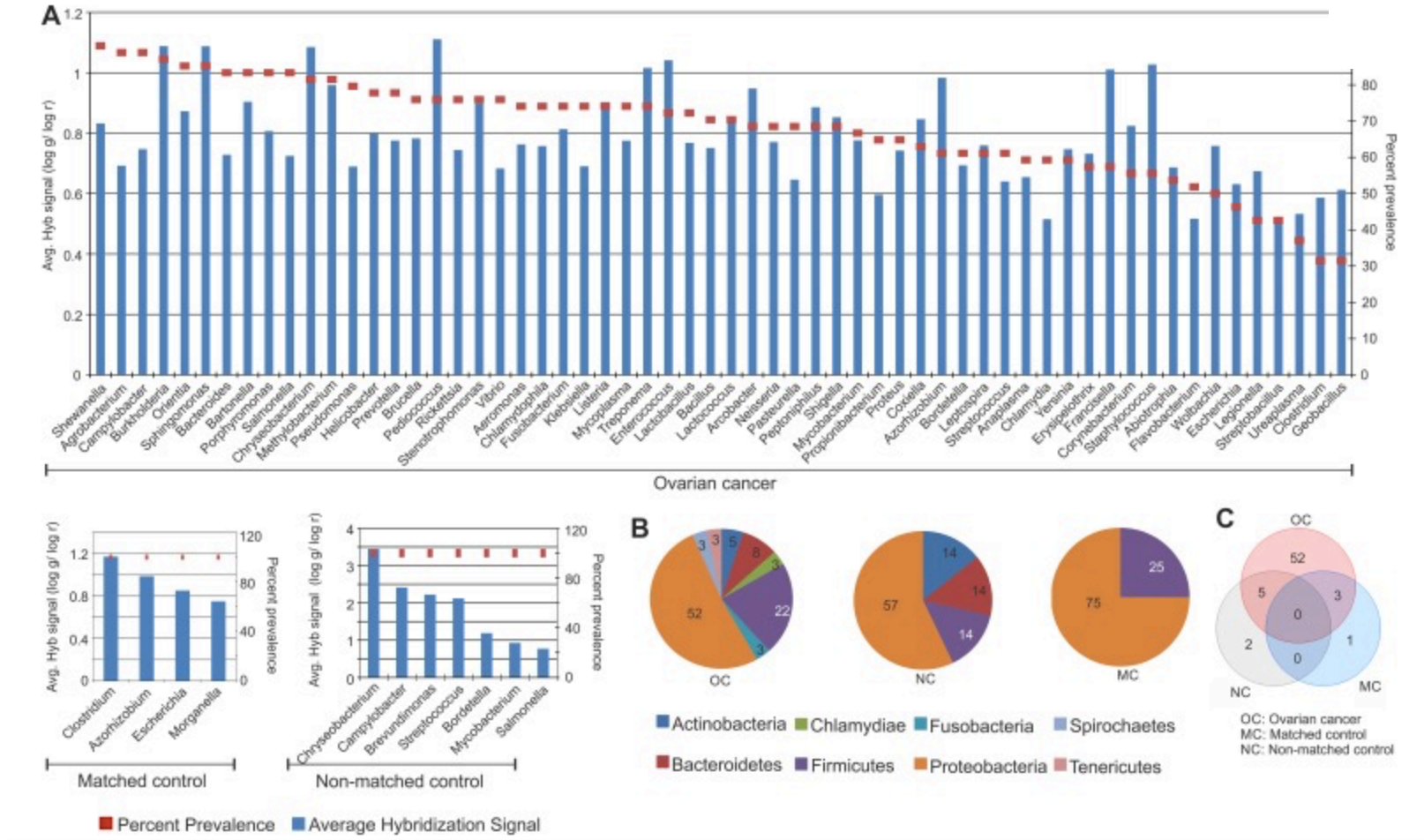
Cartoon images adapted from *Mechanisms regulating T cell infiltration and activity in solid tumors, Lanitis E. et al. Annals of Oncology 28 (Supplement 12): xii18–xii32, 2017*.

Issues: Neoadjuvant CT modifies both tumor and stromal TILs infiltration patterns



Charlotte S. Lo. et al. Neoadjuvant Chemotherapy of Ovarian Cancer Results in Three Patterns of Tumor-Infiltrating Lymphocyte Response with Distinct Implications for Immunotherapy. Clinical Cancer Research. Published Online First September 6, 2016; DOI: 10.1158/1078-0432.CCR-16-1433.

The role of microbiome



Matson et al., The commensal microbiome is associated with anti-PD1 efficacy in melanoma patients. Science 2018, Vol % (6371):104-108.
Banerjee S et al., The ovarian cancer microbiome. Oncotarget. 2017 May 30;8(22):36225-36245

Conclusions

- ✓ Strong rational for immunotherapy in OC **but** limited results with single CPIs → waiting for IPI+Nivo results
- ✓ Combinations with Bev and PARPis improve ORR **but** we almost have to define **Which** association, **How** (doublet or triplet?) and **When** (frontline or recurrence setting?)
- ✓ T-cell therapy is a promising option → poor application into daily clinical practice due to costs and high-level of facilities required
- ✓ Improve number and selection of patients partecipating to clinical trials
- ✓ Improve cooperative work group and translational research