

# Immune exclusion as a function of tumor genetics and heterogeneity

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# Ovarian Cancer: Overview

- Estimated 21,750 cases and 13,940 deaths in US in 2020
- High grade serous (HGSOC) is the most common histology
- Presents in metastatic stage in >80% of cases
- Initial therapy involves surgical debulking and platinum-based chemotherapy
- After initial therapy, >80% of patients relapse and eventually succumb to disease
- Cytotoxic therapy remains the mainstay of treatment

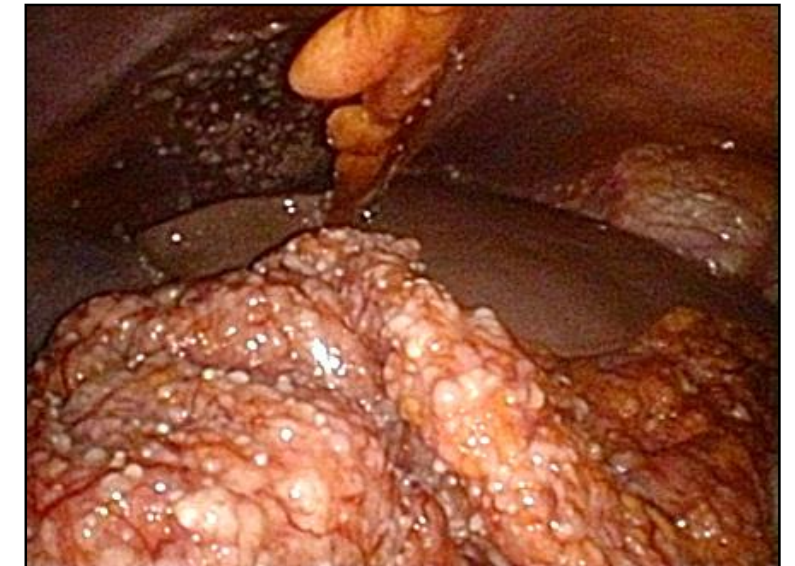
## Estimated cancer-related deaths in 2020

### Estimated Deaths

			Males	Females			
Lung & bronchus	72,500	23%			Lung & bronchus	63,220	22%
Prostate	33,330	10%			Breast	42,170	15%
Colon & rectum	28,630	9%			Colon & rectum	24,570	9%
Pancreas	24,640	8%			Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%			Ovary	13,940	5%
Leukemia	13,420	4%			Uterine corpus	12,590	4%
Esophagus	13,100	4%			Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%			Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%			Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%			Brain & other nervous system	7,830	3%
<b>All Sites</b>	<b>321,160</b>	<b>100%</b>			<b>All Sites</b>	<b>285,360</b>	<b>100%</b>

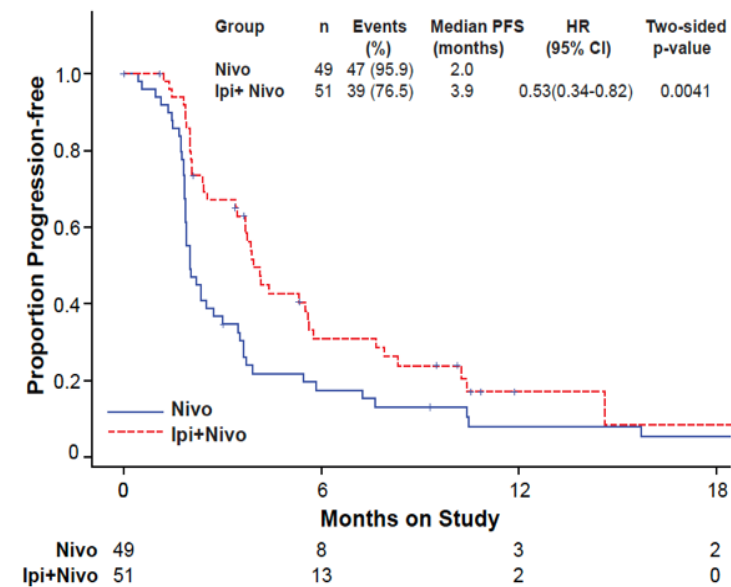
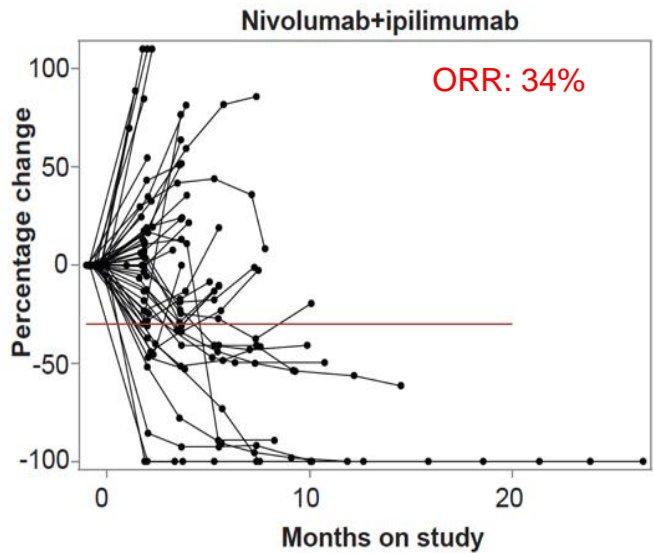
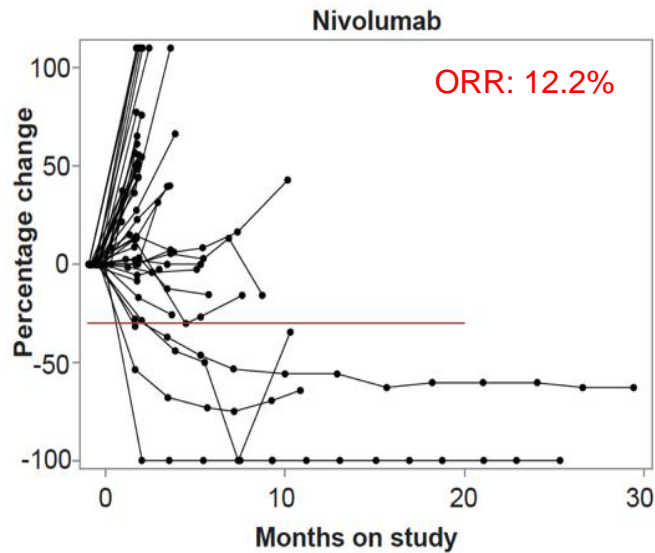


## Ascites and Carcinomatosis



# Immune checkpoint blockade has limited efficacy in ovarian cancer

**NRG-GY003: CTEP-sponsored randomized trial of nivolumab vs. nivolumab with ipilimumab in platinum- resistant ovarian cancer**



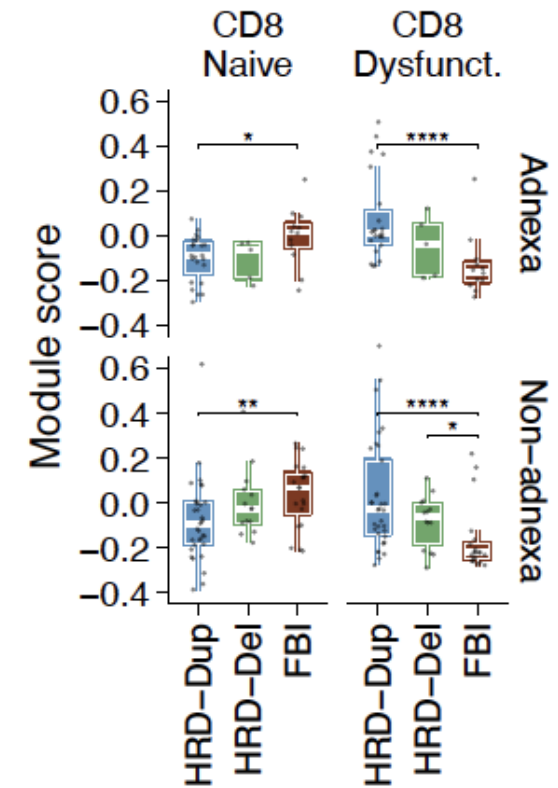
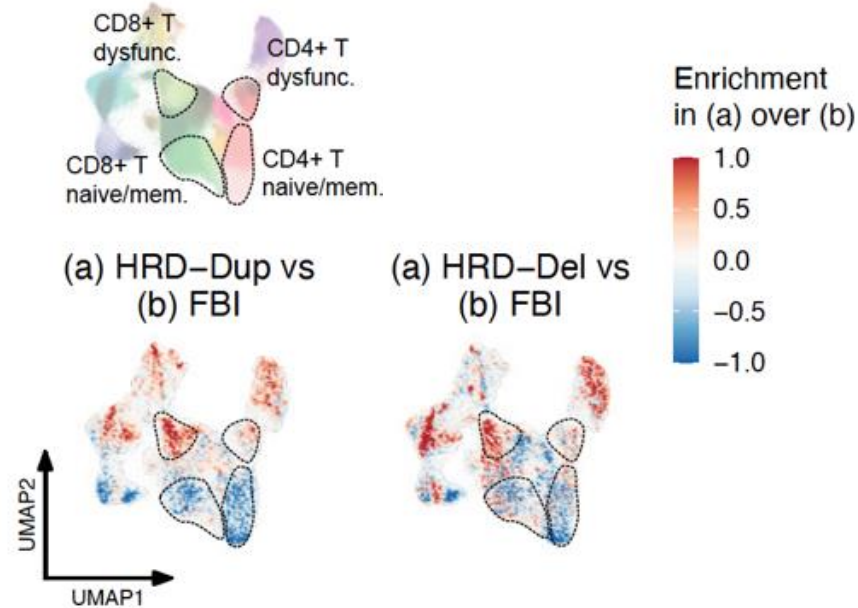
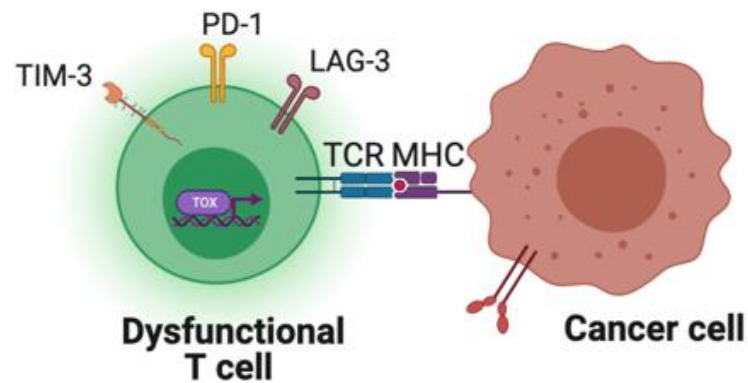
# Immune recognition in ovarian cancer is patterned by the underlying tumor genetics: tumors with underlying homologous recombination deficiency (HRD) exhibit heightened immune recognition and T cell infiltration

HRD-Dup: *BRCA1* mut-like

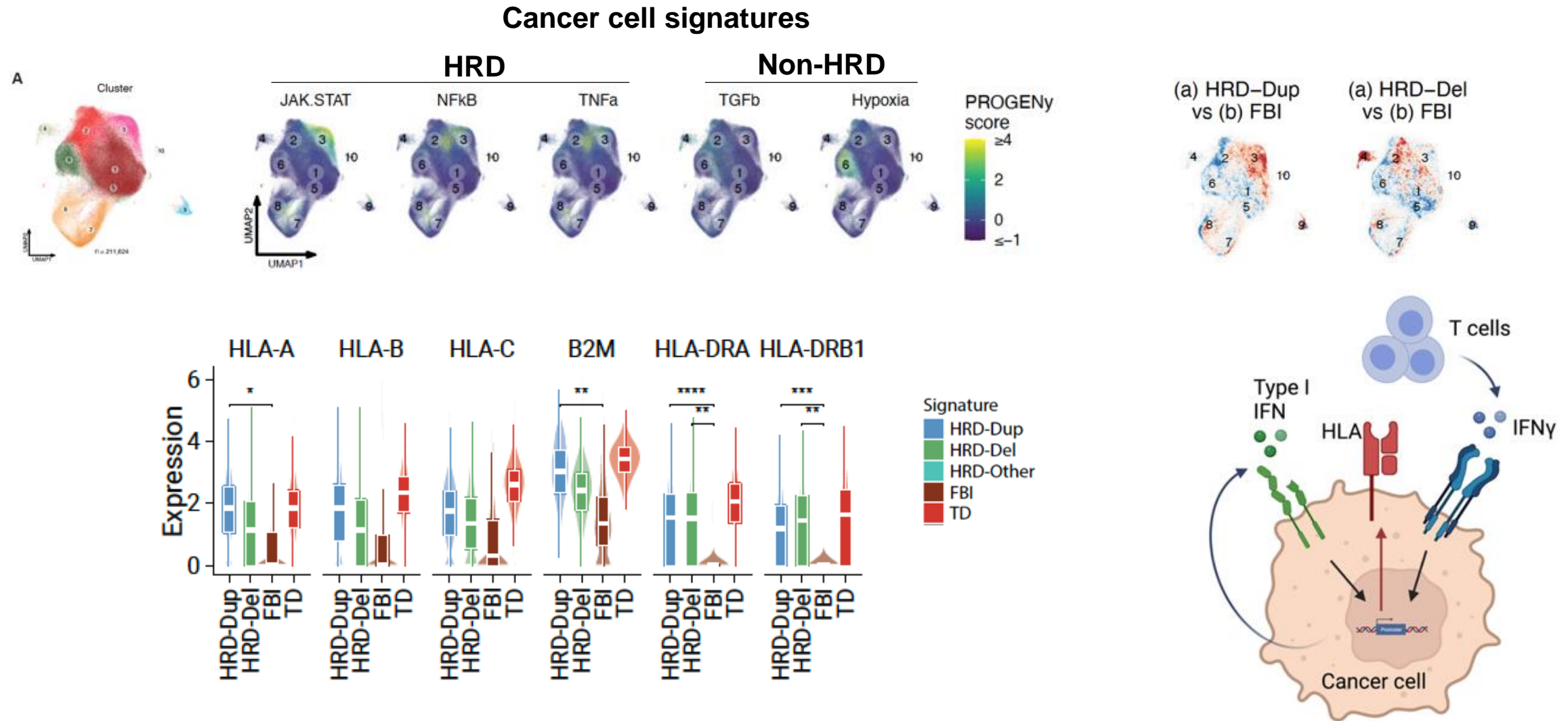
HRD-Del: *BRCA2* mut-like

FBI: Foldback inversions (*CCNE* amplification-associated)

TD: Tandem duplicators (*CDK12* deletion-associated)

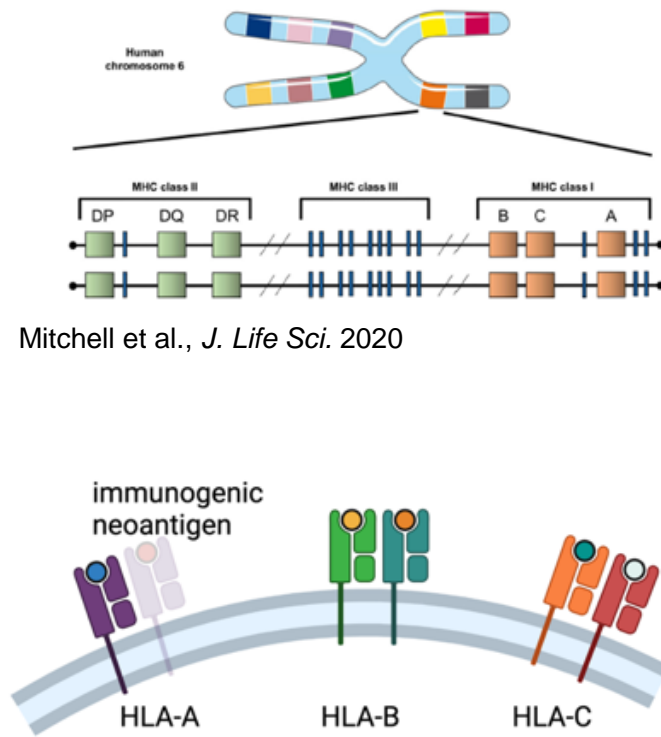


# HRD+ ovarian cancer cells are intrinsically “more immunogenic”

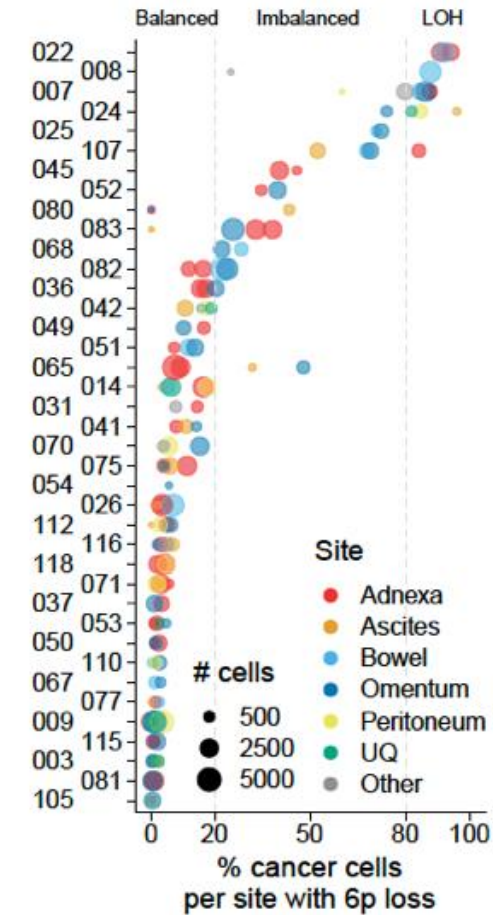
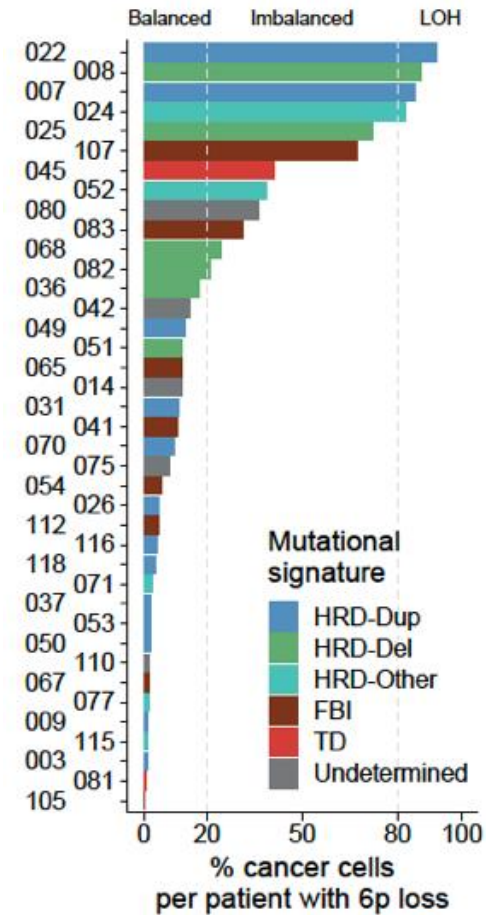




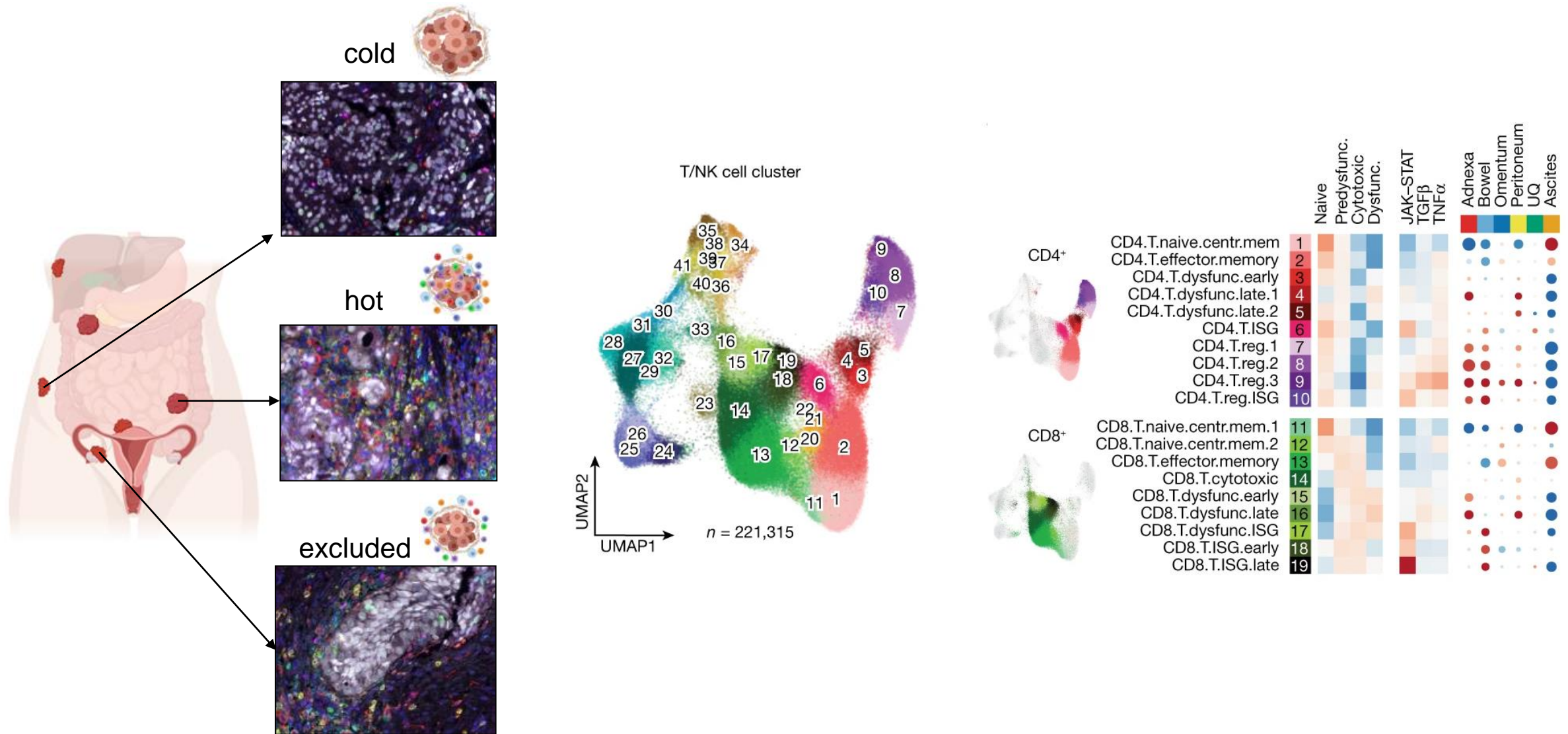
# Evolution through immunoediting drives immune resistance in HRD+ ovarian cancers



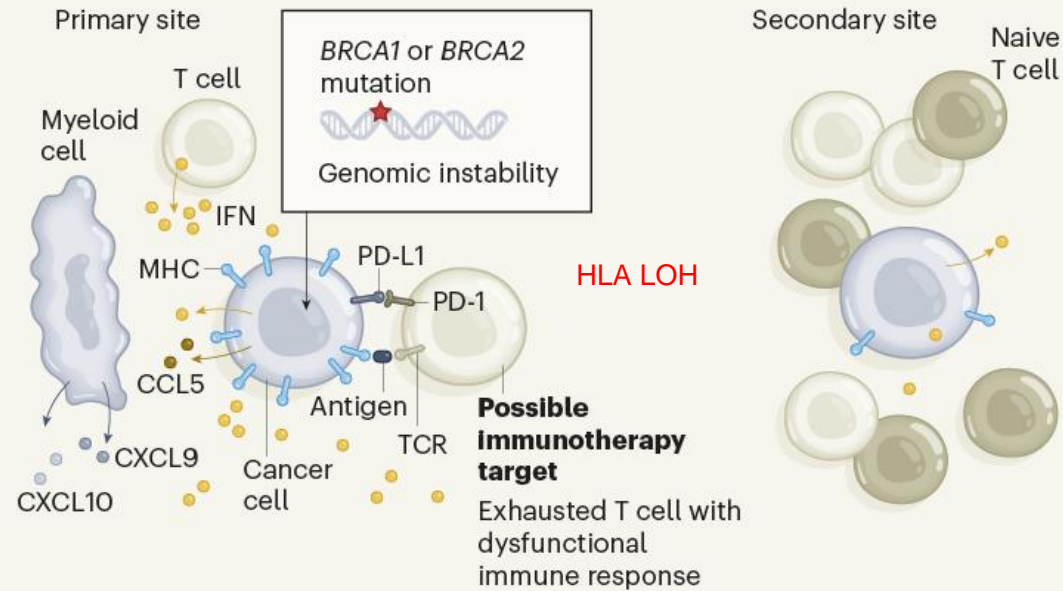
Mitchell et al., *J. Life Sci.* 2020



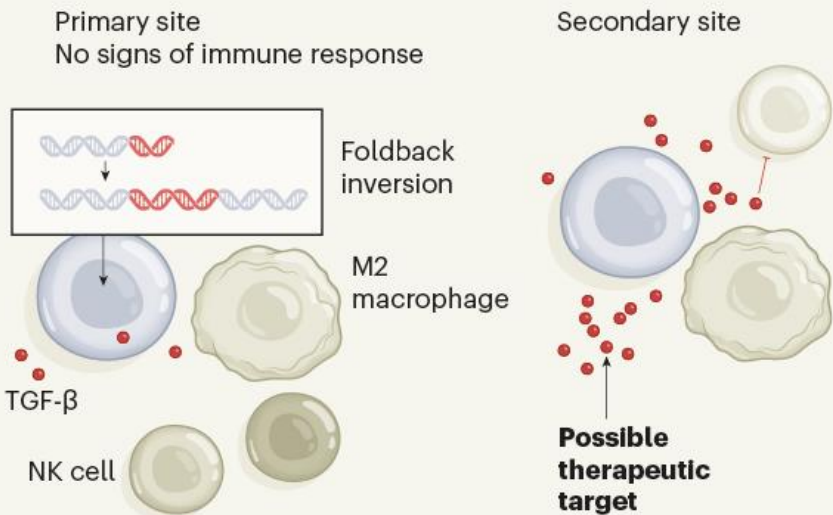
# Ovarian cancer is a disease of substantial inter-site immune heterogeneity, often within the same patient



**a HRD type of ovarian cancer**



**b FBI type**



Therapeutic approaches aiming to overcome the tumor microenvironment heterogeneity and the underlying causes of immune resistance will be key to immunotherapy success in ovarian cancer