

**Principles and Precepts of Cancer Immunotherapy:
Practical Considerations with the Use of Immune
Checkpoint Inhibitors**

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MEDICAL CENTER**

Herbert Irving Comprehensive Cancer Center

Complete Disclosure

- Consulting:
Agenus, Dendreon, NexImmune, ImmuneXcite, Janssen, Lilly, Merck, Pierre Fabre, Roche / Genentech
- Patents
Amplimmune, BMS, Janssen
- Stockholder
Compugen, NexImmune, Potenza, Tizona
- Sponsored Research Agreement
BMS, Janssen, Aduro Biotech

Several of the Agents Discussed are NOT FDA-approved for use in cancer treatment

Outline

- Basic Principles of Cancer Immunology
- Major approaches to GU Immunotherapy
- Blocking PD-1 vs blocking PD-L1
- PD-L1 staining as a predictive biomarker
- Other factors that may influence response

Sixty Years Ago:

“...the primary function of cellular immunity is in fact not to promote allograft rejection but rather to protect from neoplastic disease...”

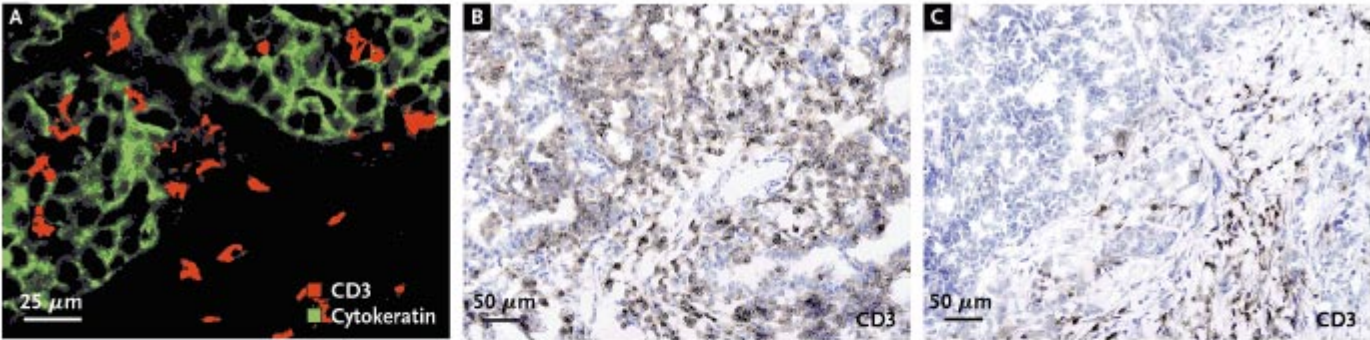
Lewis Thomas, 1957

“It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provoke an effective immunological reaction with regression of the tumour and no clinical hint of its existence.”

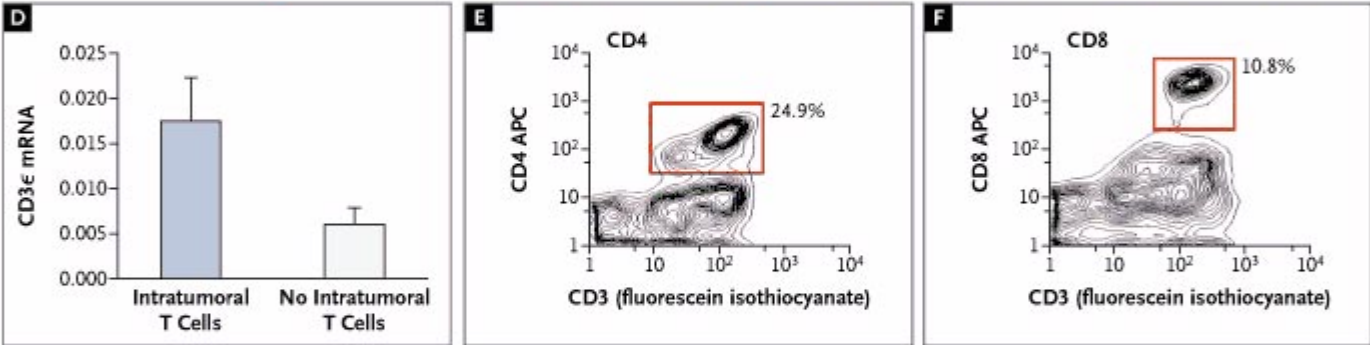
Sir Macfarlane Burnet, 1957

Lots of Tumors Have Infiltrating T Cells Are they SURVEYING?

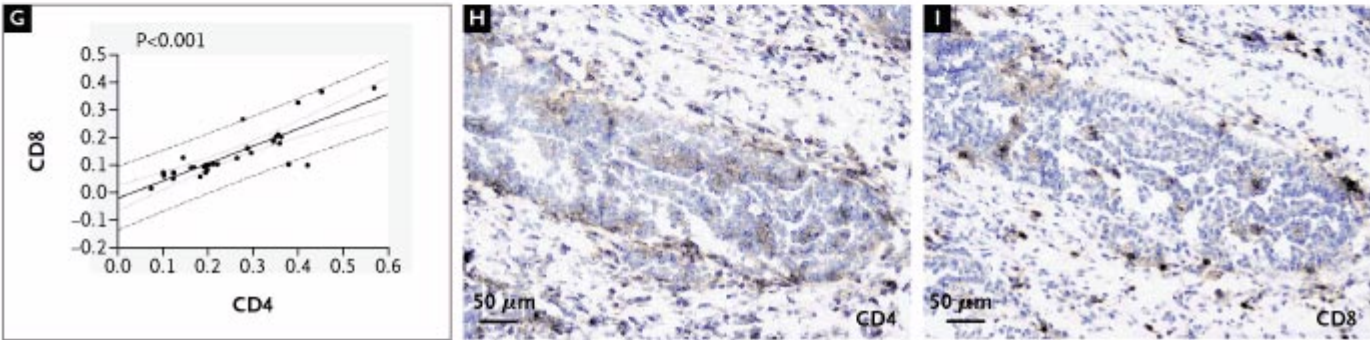
CD3 (All T Cells)



CD4 or CD8
(By Flow)

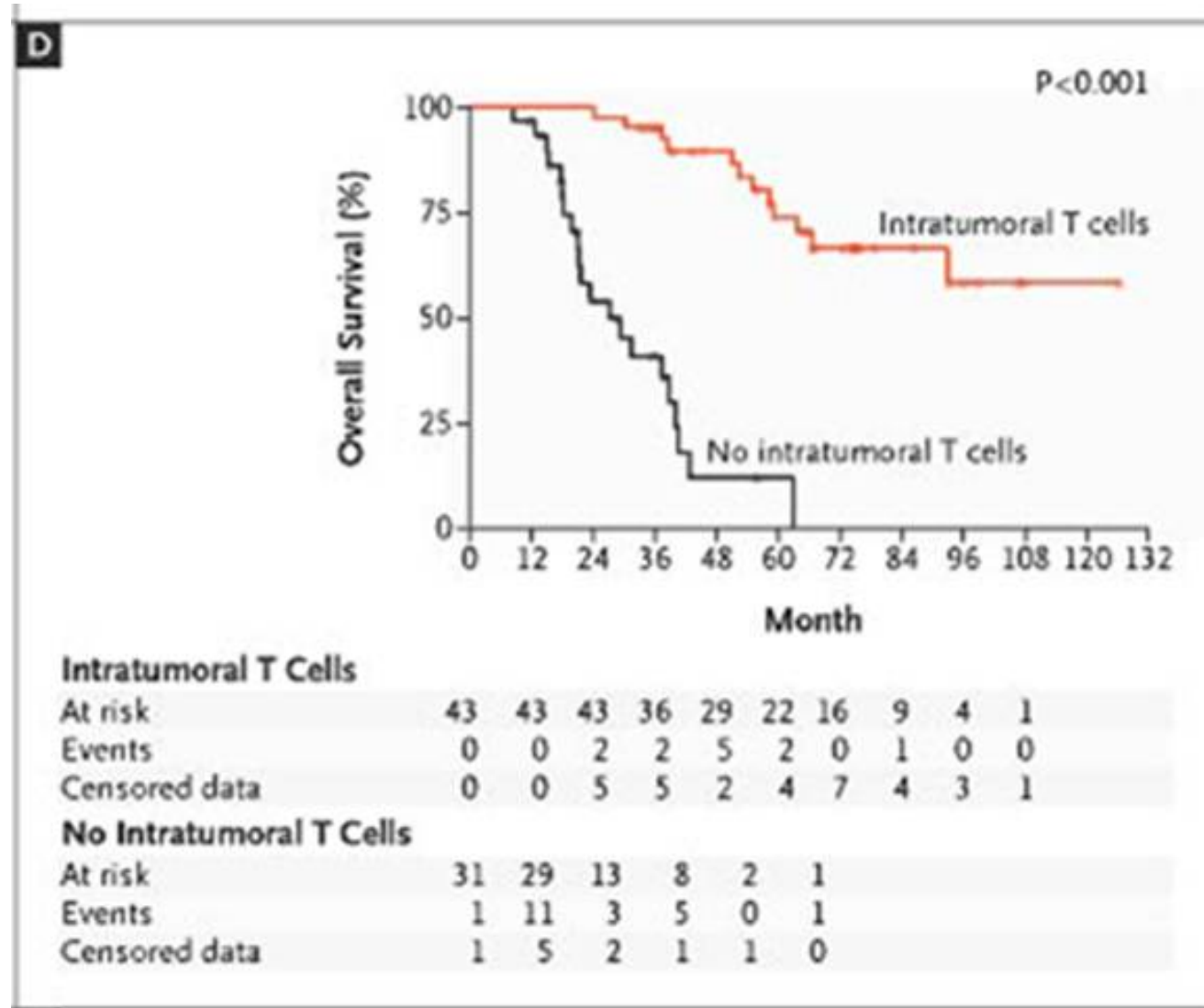


CD4 or CD8
(By IHC)

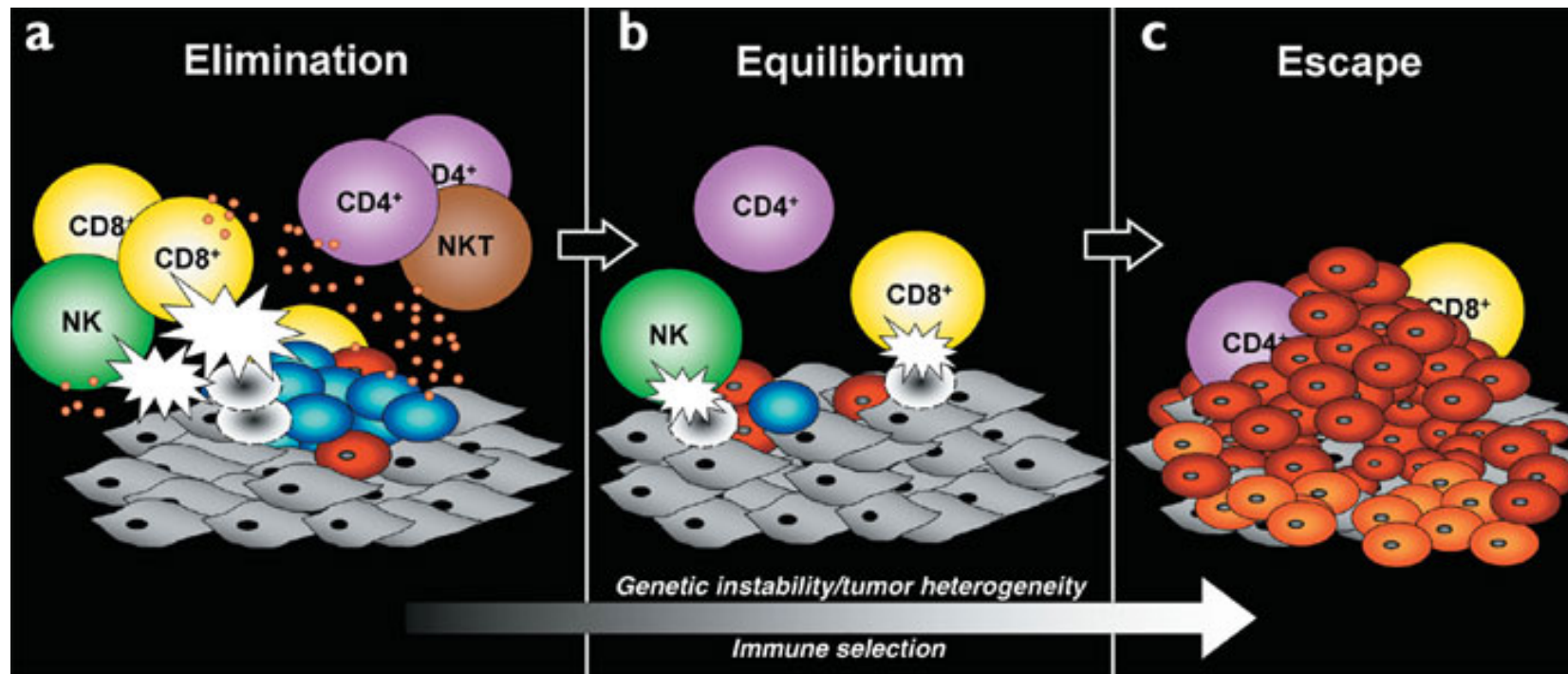


T Cells in Ovarian Cancer: A Life or Death Matter

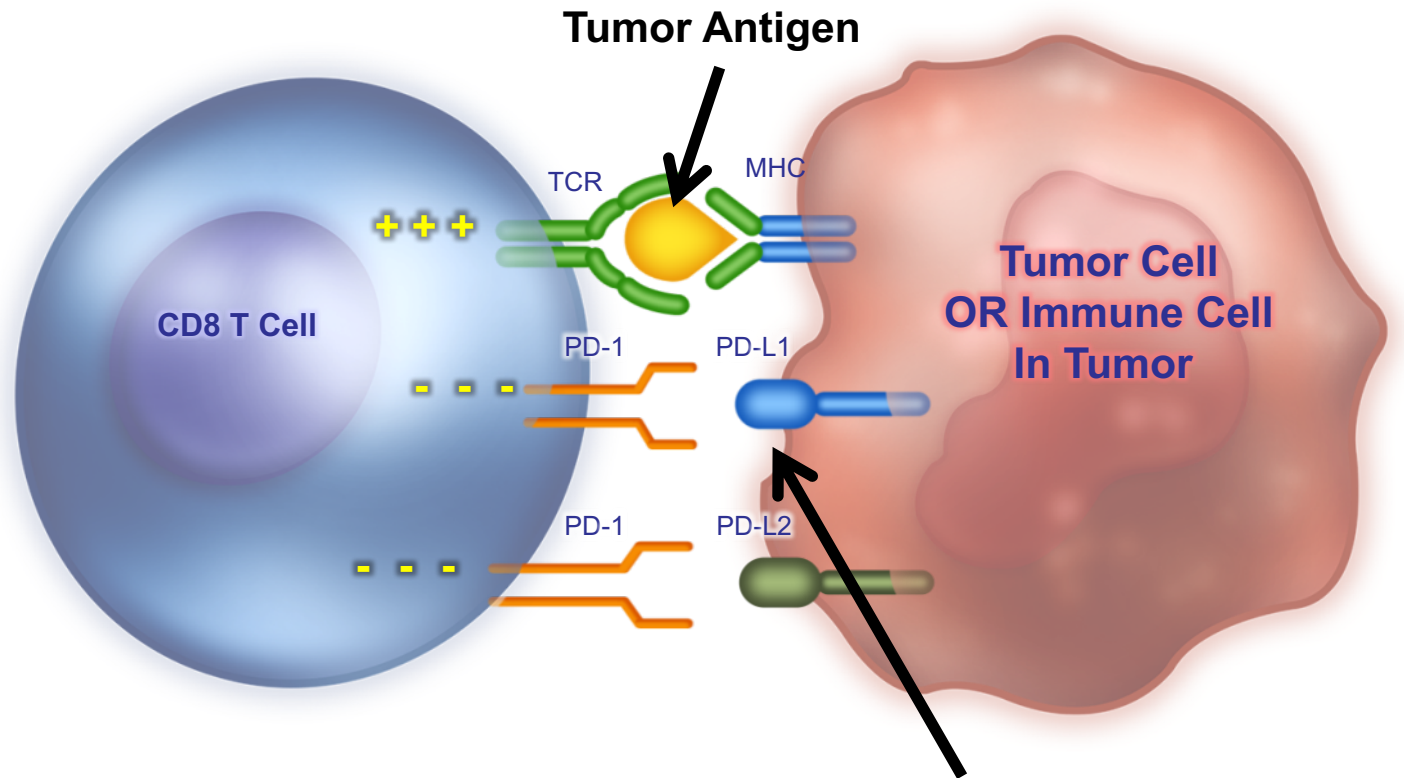
Stage IV Ovarian
CA
Complete response
to treatment



The Immune Editing Hypothesis (3 E's)

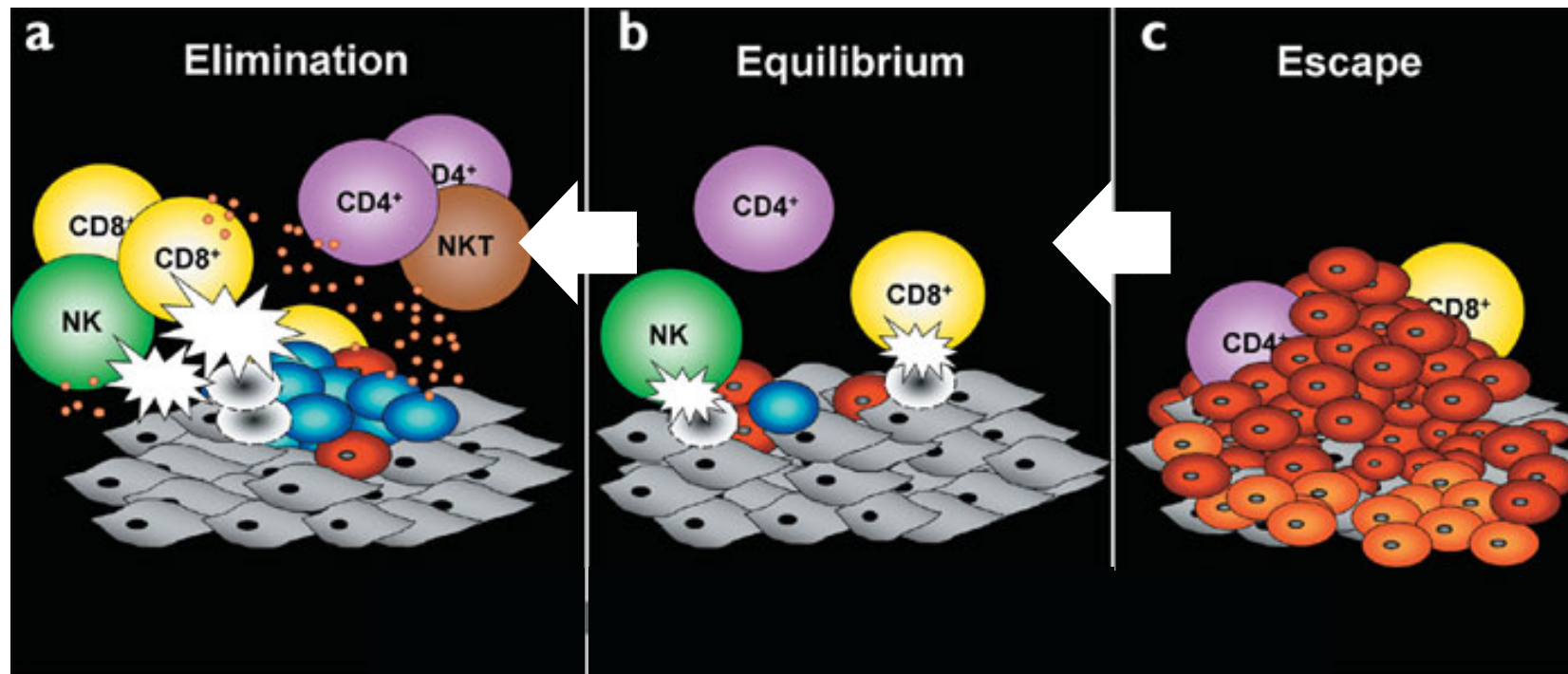


The PD-1 / PD-L1 Axis Is One Major Component of **Escape**

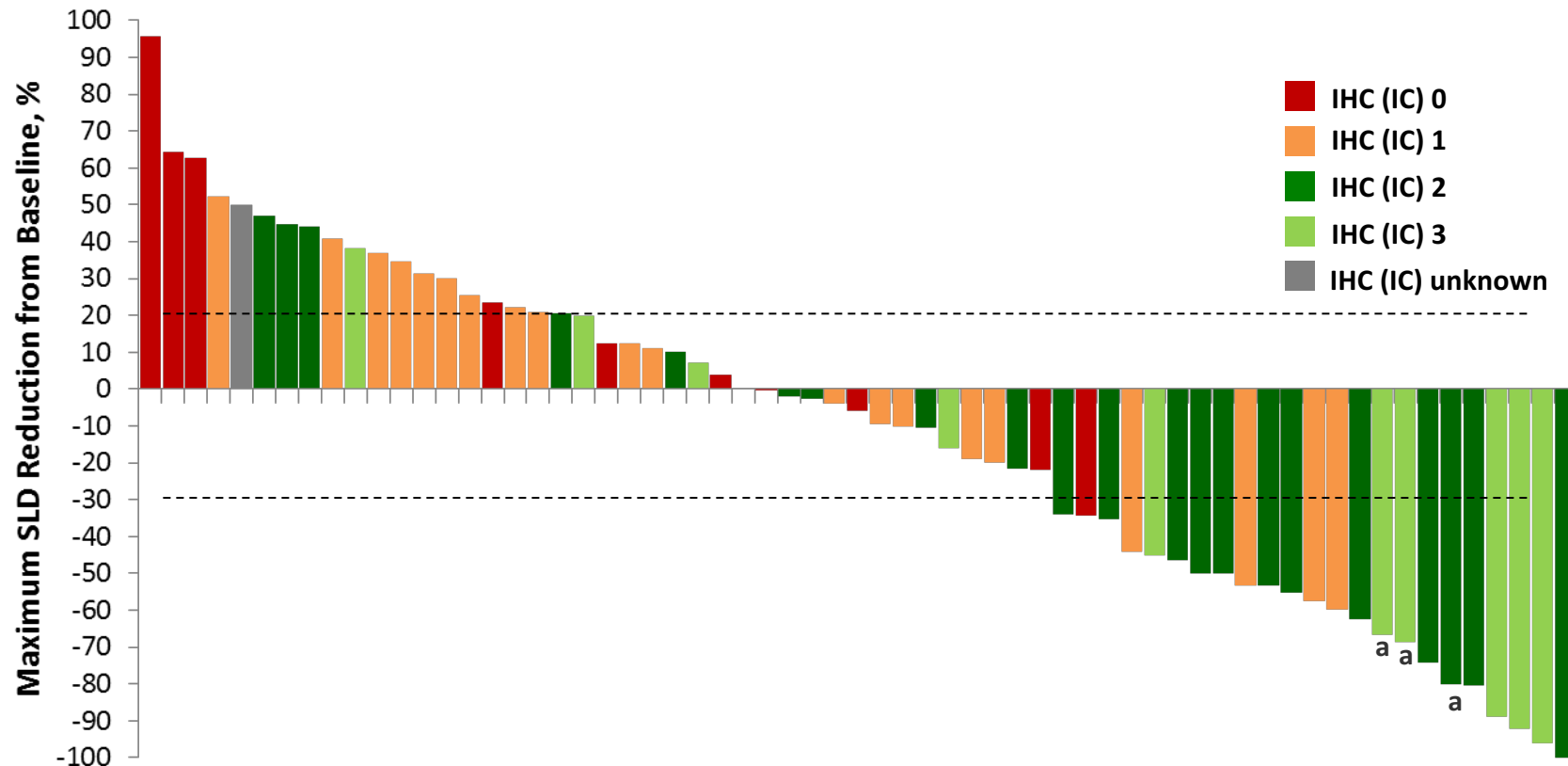


PD-L1 Expression on Tumor Cells OR Myeloid Cells SENDS that Negative Signal

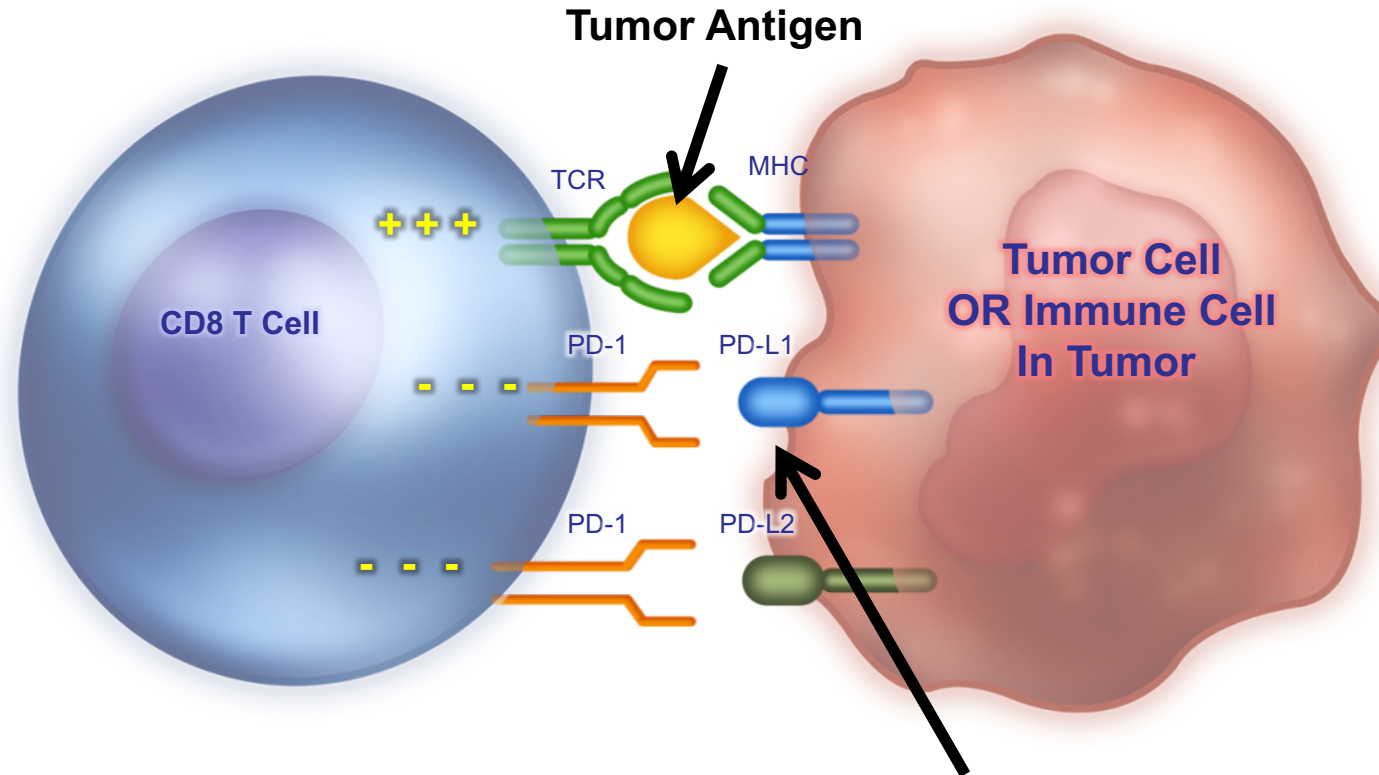
Reversing **Escape**?



Blocking PD-1 / PD-L1 Tilts the Balance Back To Elimination: Objective Responses to Anti-PD-L1 (Atezolizumab) in Urothelial Bladder Cancer

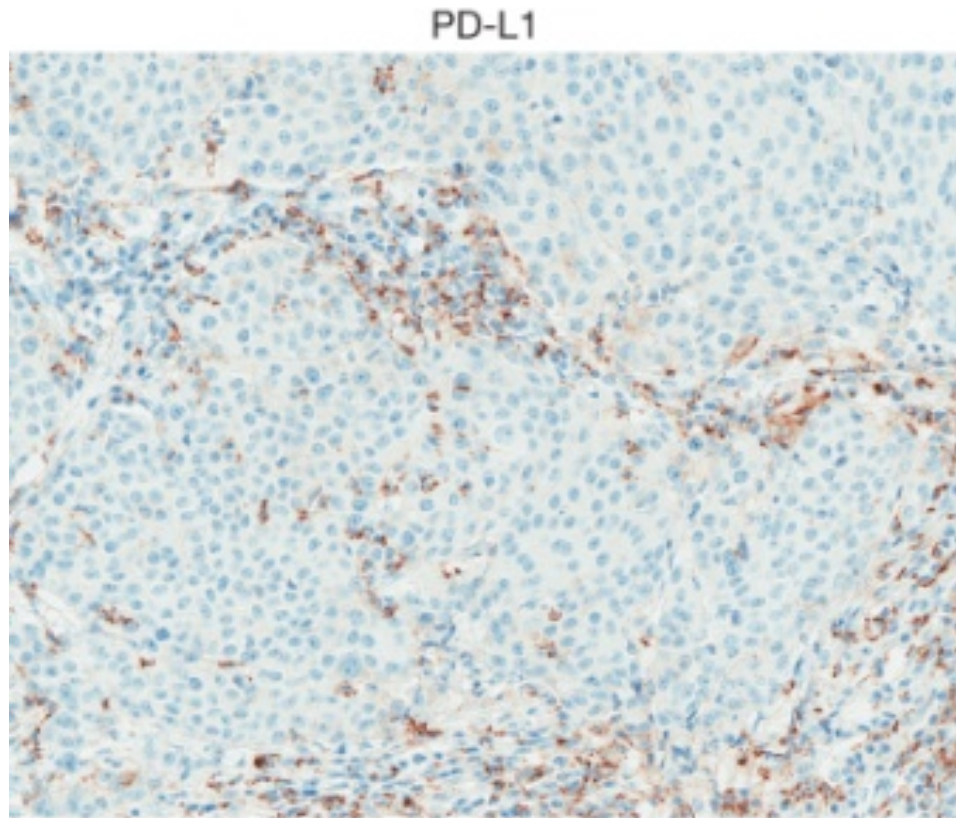


If PD-1 Is Mediating **Escape
Then Response Should Correlate with PD-L1
Expression in the Tumor Microenvironment**

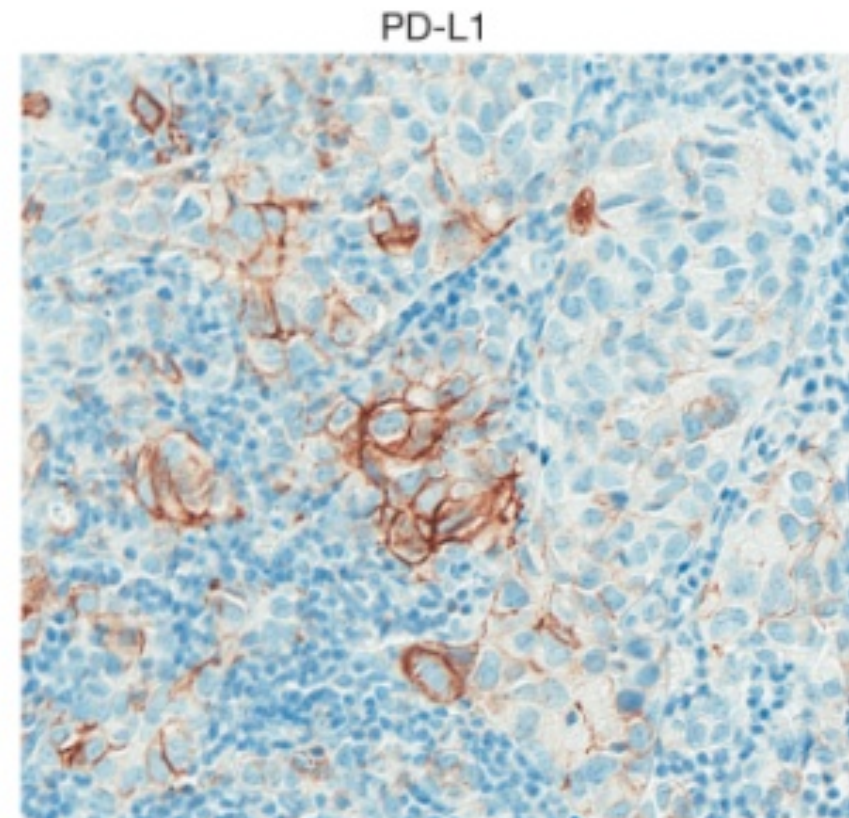


PD-L1 Expression on Tumor Cells OR
Myeloid Cells SENDS that Negative Signal

PD-L1 As a Predictive Biomarker



Tumour-infiltrating immune cells



Tumour cells

PD-L1 As a Predictive Biomarker

Anti-PD-L1 Post-Chemo

	Patients, n	Objective response rate, n (% [95% CI])	Complete response	Partial response	Stable disease	Progressive disease
RECIST version 1.1 criteria by independent review						
IC2/3	100	26 (26% [18–36])	11 (11%)	15 (15%)	16 (16%)	44 (44%)
IC1/2/3	207	37 (18% [13–24])	13 (6%)	24 (12%)	34 (16%)	107 (52%)
All patients	310	45 (15% [11–19])	15 (5%)	30 (10%)	59 (19%)	159 (51%)
IC1*	107	11 (10% [5–18])	2 (2%)	9 (8%)	18 (17%)	63 (59%)
IC0*	103	8 (8% [3–15])	2 (2%)	6 (6%)	25 (24%)	52 (50%)

PD-L1 As a Predictive Biomarker Anti-PD-L1 Platinum Ineligible

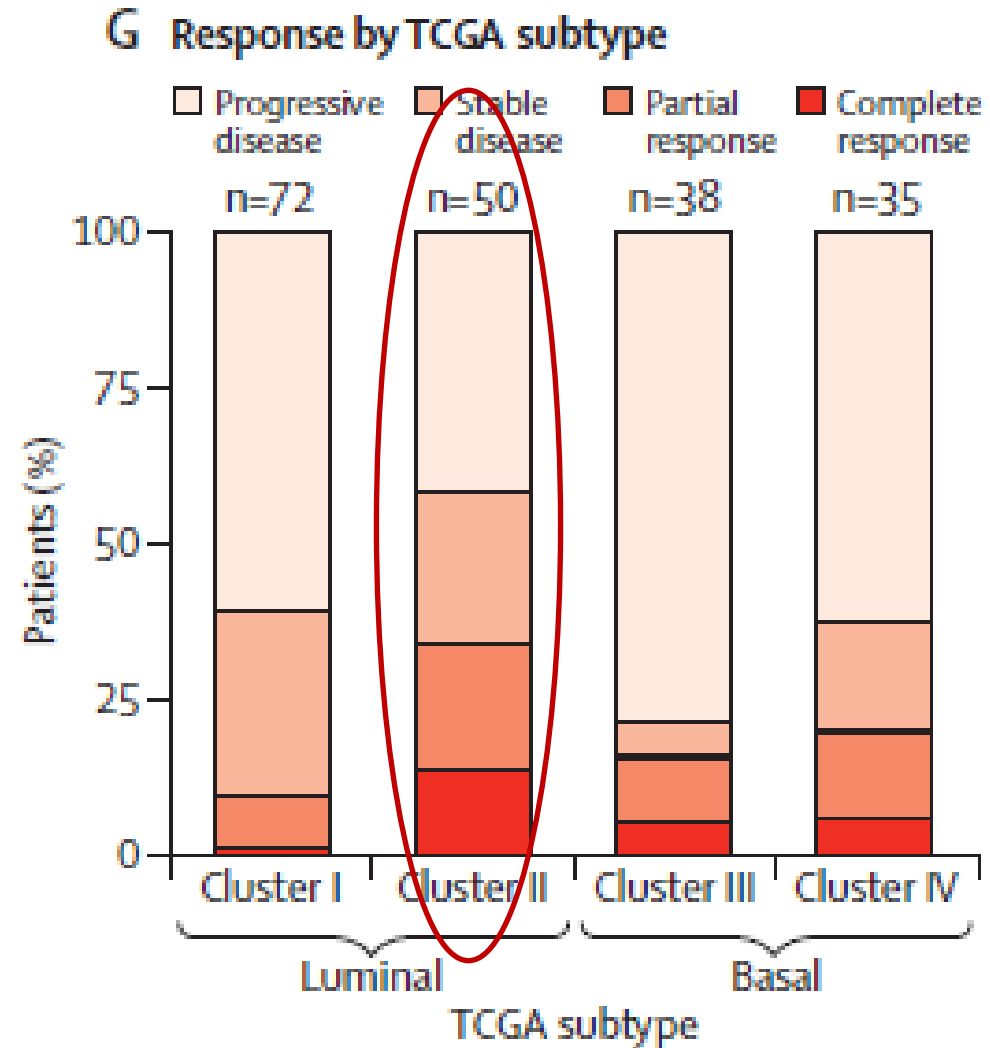
	Patients	Complete response	Partial response	Objective response, n (% [95% CI])*	Median duration of response (95% CI)
	119	11	16	27 (23% [16-31])	NE (14.1-NE)
IC2/3	32	4	5	9 (28% [14-47])	NE (11.1-NE)
IC1/2/3	80	8	11	19 (24% [15-35])	NE (NE-NE)
IC1	48	4	6	10 (21% [10-35])	NE (NE-NE)
IC0	39	3	5	8 (21% [9-36])	NE (12.8-NE)

PD-L1 As a Predictive Biomarker For Anti-PD-1 (Pembrolizumab) Post-Chemo

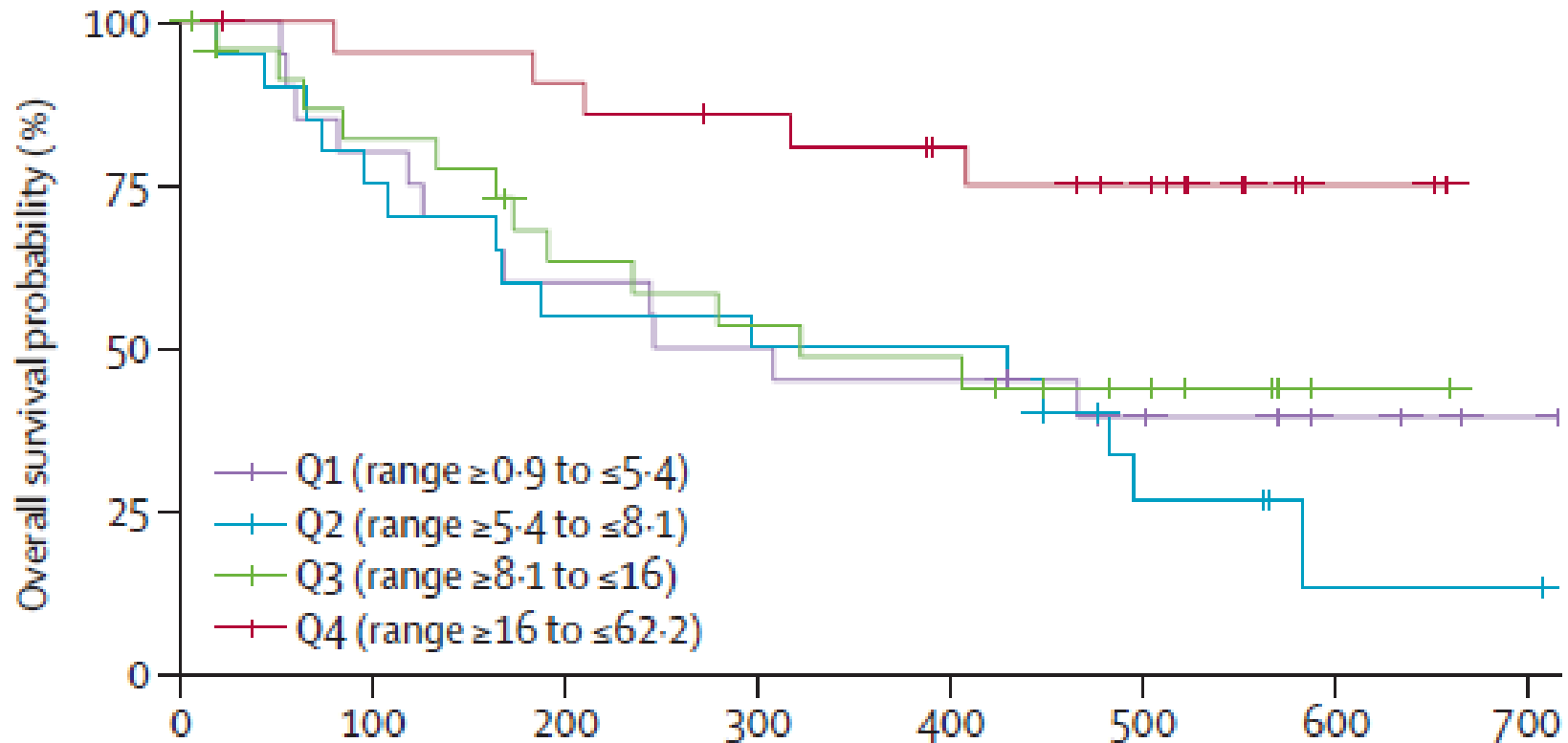
Table S4. Summary of Response in the Total and PD-L1 Combined Positive Score Intention-to-Treat Populations.*

Variable	Total Population		CPS \geq 10% Population	
	Pembrolizumab Group (N=270)	Chemotherapy Group (N=272)	Pembrolizumab Group (N=74)	Chemotherapy Group (N=90)
Objective response†				
No. of patients	57	31	16	6
% (95% CI)	21.1 (16.4 to 26.5)	11.4 (7.9 to 15.8)	21.6 (12.9 to 32.7)	6.7 (2.5 to 13.9)

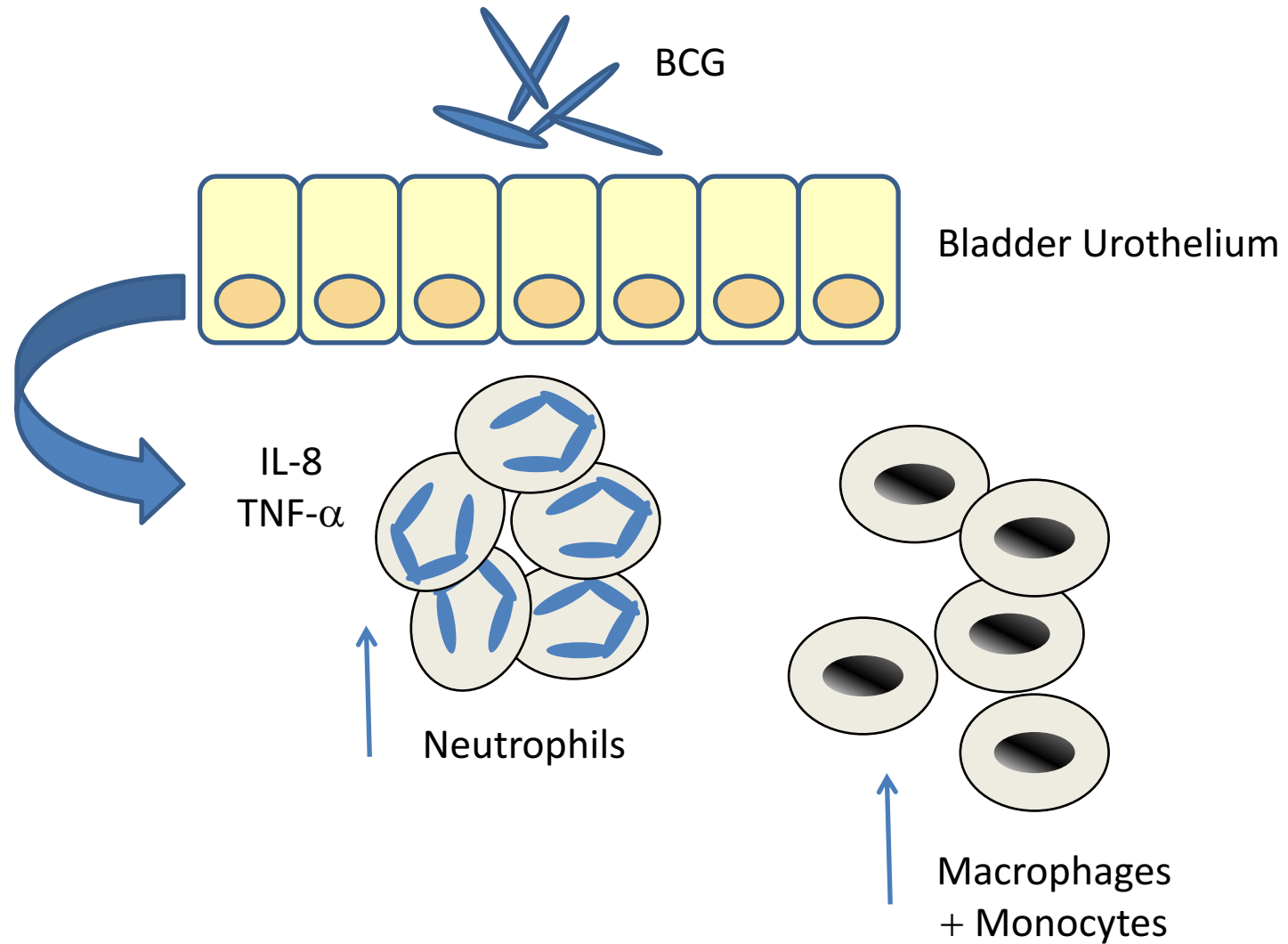
Tumor Subtype as a Predictive Biomarker



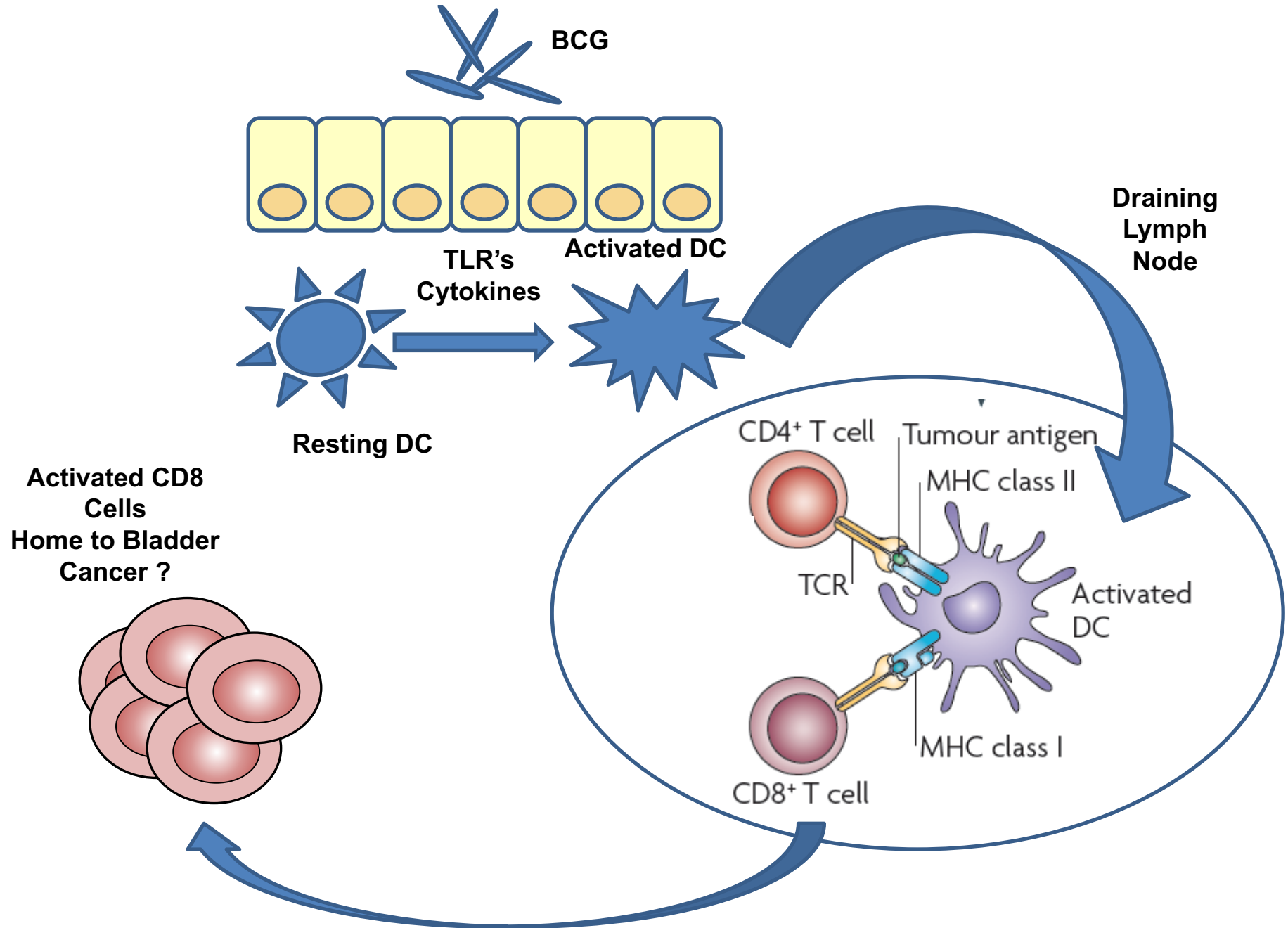
Mutational Load As a Predictive Biomarker (A Threshold Effect ?)



BCG Initiates an Innate Immune Response



An Innate Response Can Lead To An Adaptive Response



Summary

- Four PD-1 or PD-L1 blocking antibodies are approved and one is close to approval for bladder cancer
- PD-L1 is NOT a consistent predictive biomarker
- Nor is TCGA subtype
- Mutational burden = promising, requires validation