



Northwestern Medicine[®]
Feinberg School of Medicine

Role of Immunotherapy in Uterine Cancer

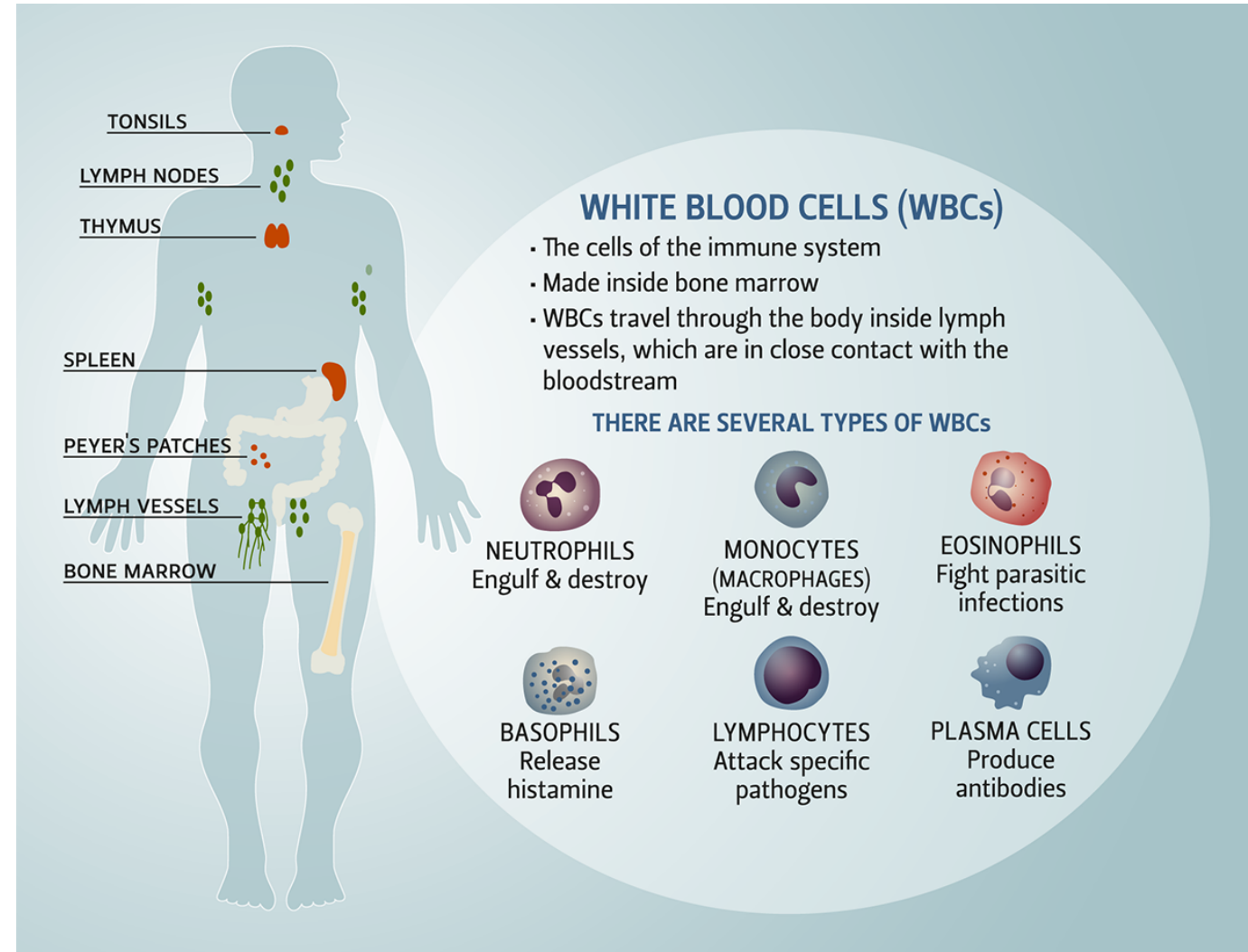
Survive & Thrive 2022
Patient & Caregiver Wellness

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What is the Immune System?

- Complex network of cells, tissues and organs
 - Defends the body from substances (antigens) it sees as harmful or foreign
 - Bacteria & viruses
 - Chemicals or toxins
 - Damaged cells (cancer)

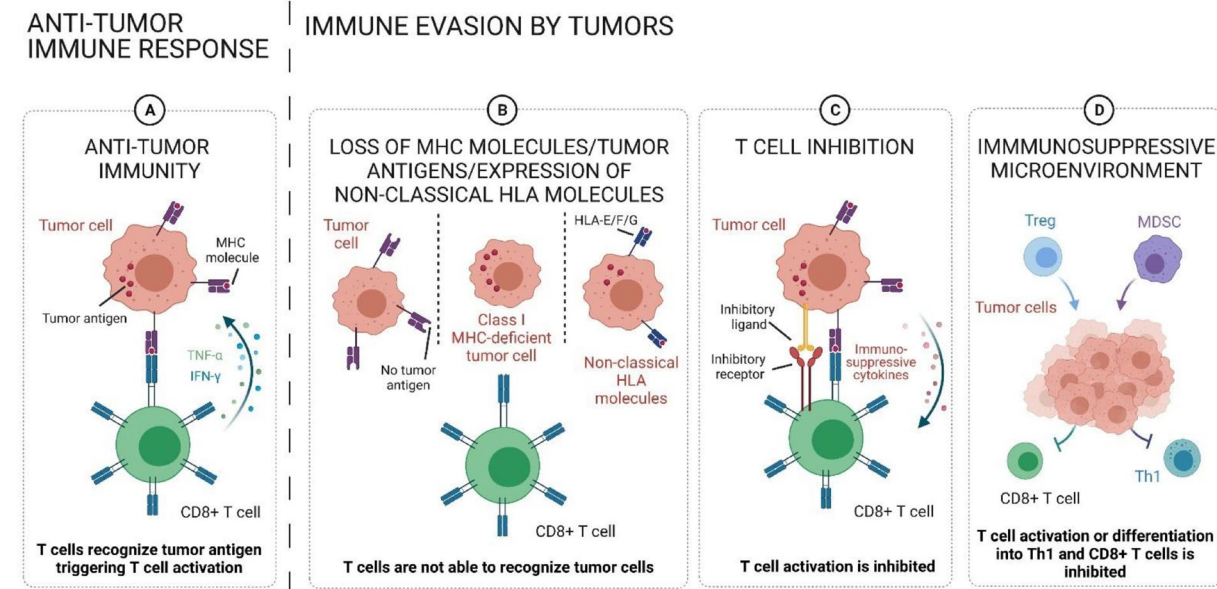
For the immune system to work, it has to recognize the harmful antigen



The Immune System & Cancer

- Evading the Immune System by Hiding in Plain Sight

- Genetic changes to avoid recognition
- Proteins that turn off immune cells
- Change the normal cells around the tumor so they can interfere with the normal immune response

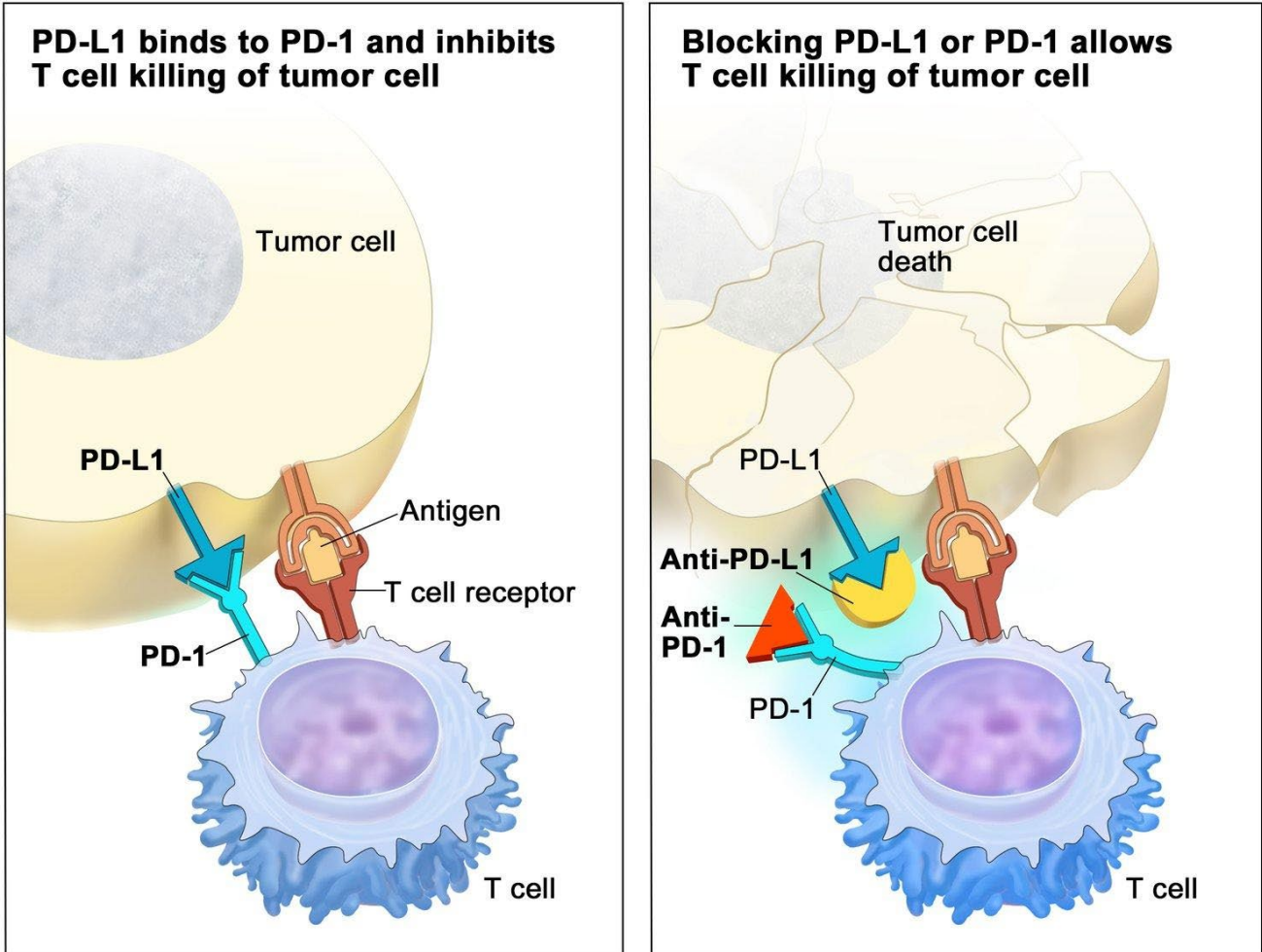


What is Immunotherapy?

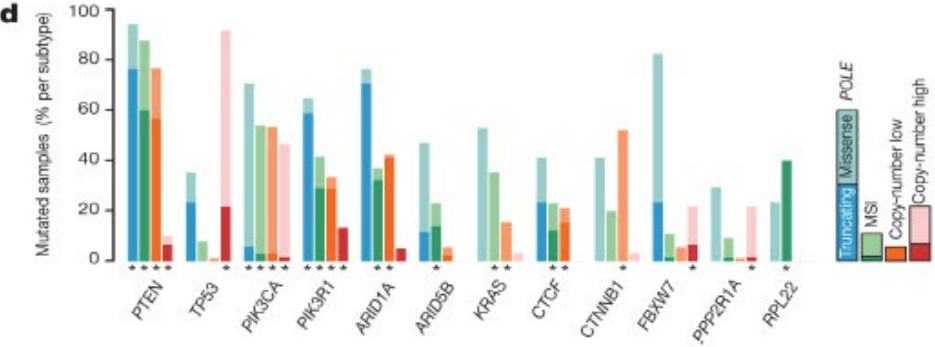
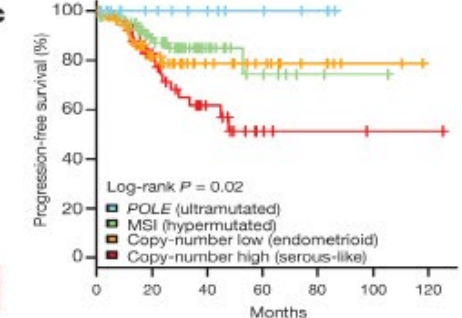
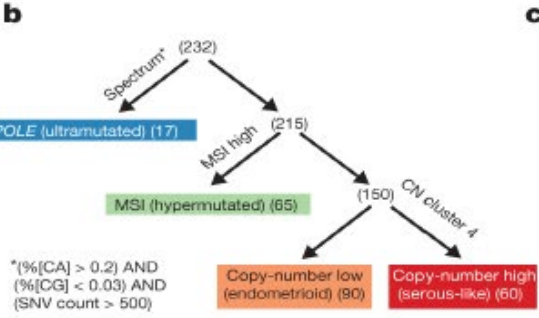
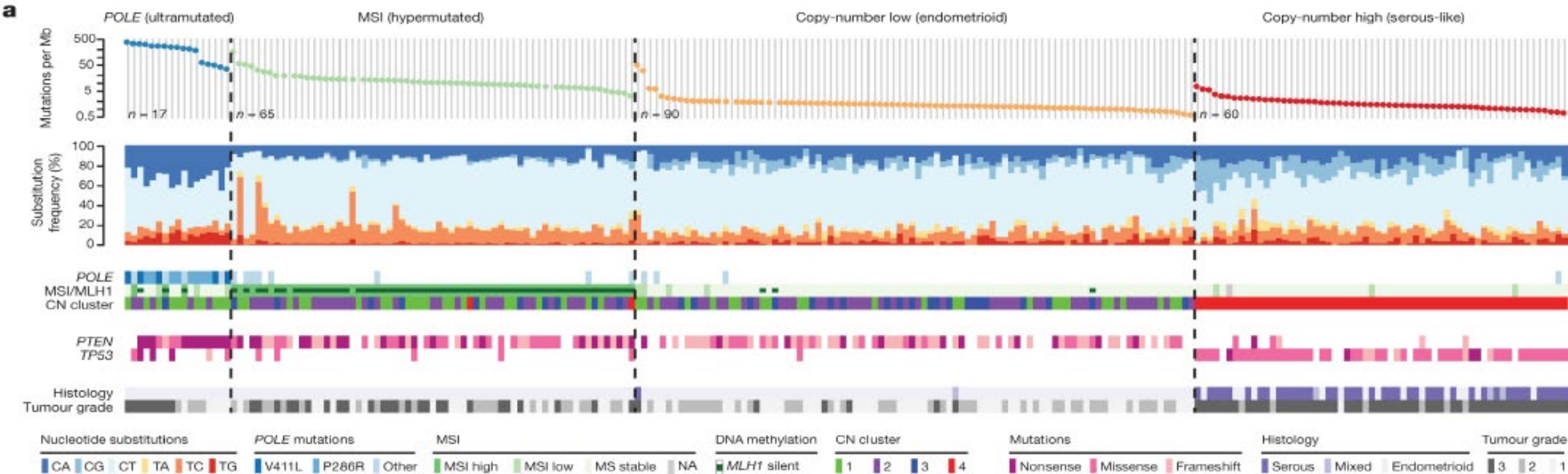
- Treatment that helps your immune system recognize and kill cancer cells
 - **Checkpoint inhibitors** → Allow immune cells to respond more strongly to cancer
 - **T-Cell Transfer Therapy** → Removal of tumor immune cells, selection of most active ones and injected back into the body
 - **Monoclonal antibodies** → Attach to cancer cells and make them better targets for immune system
 - **Treatment vaccines** → Boosting the immune system response to cancer cells

Immunotherapy in Uterine Cancer

Immune Checkpoint Inhibitors (ICI)



Relevance of Endometrial Cancer Molecular Sub-Types

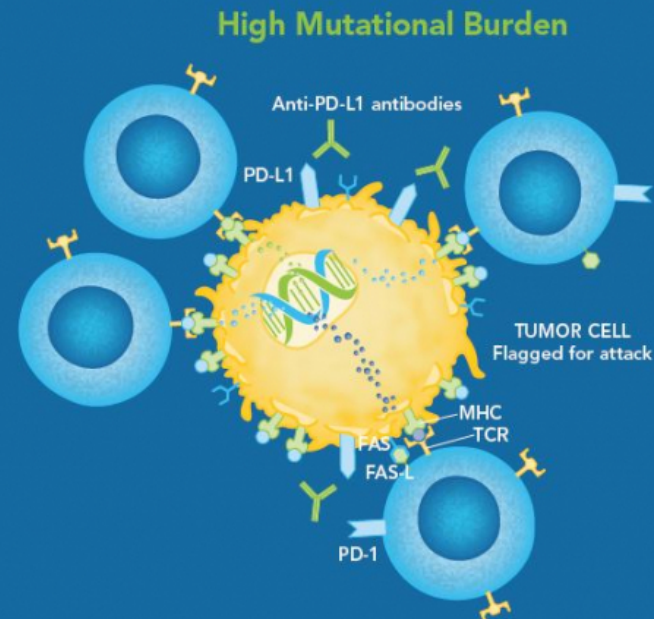
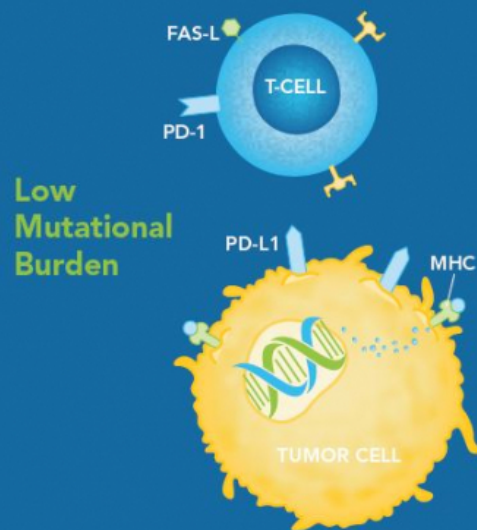


Microsatellite Instability (MSI) = High Mutational Burden



Enhanced Immune Cell Recognition

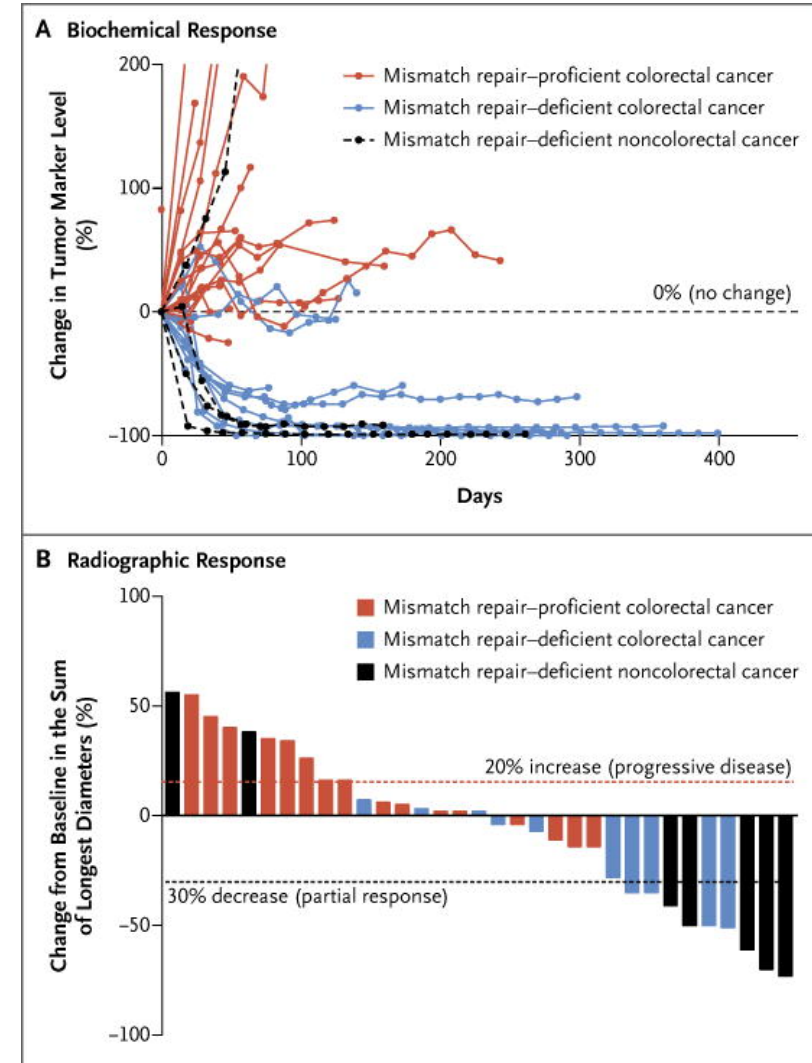
Compared to TMB low tumor cells, higher TMB may be associated with enhanced immune cell recognition, which are therapeutically predictive of favorable response to checkpoint inhibitors. High TMB levels (>10 mutations/ megabase) are now an FDA-approved indication for Pembrolizumab administration, irrespective of tumor type.



Sharabi A, Kim SS, Kato S, et al. Exceptional Response to Nivolumab and Stereotactic Body Radiation Therapy (SBRT) in Neuroendocrine Cervical Carcinoma with High Tumor Mutational Burden: Management Considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center. *Oncologist*. 2017;22(6):631-637. doi:10.1634/theoncologist.2016-0517

Therapeutic Implications

- Five single arm clinical trials
 - 149 patients with 15 different dMMR or MSI-H cancer types
 - 40% of patients had measurable tumor shrinkage
 - 11 complete responses
 - 48 partial responses
 - 78% of responders had sustained shrinkage or stable tumor size for ≥ 6 months



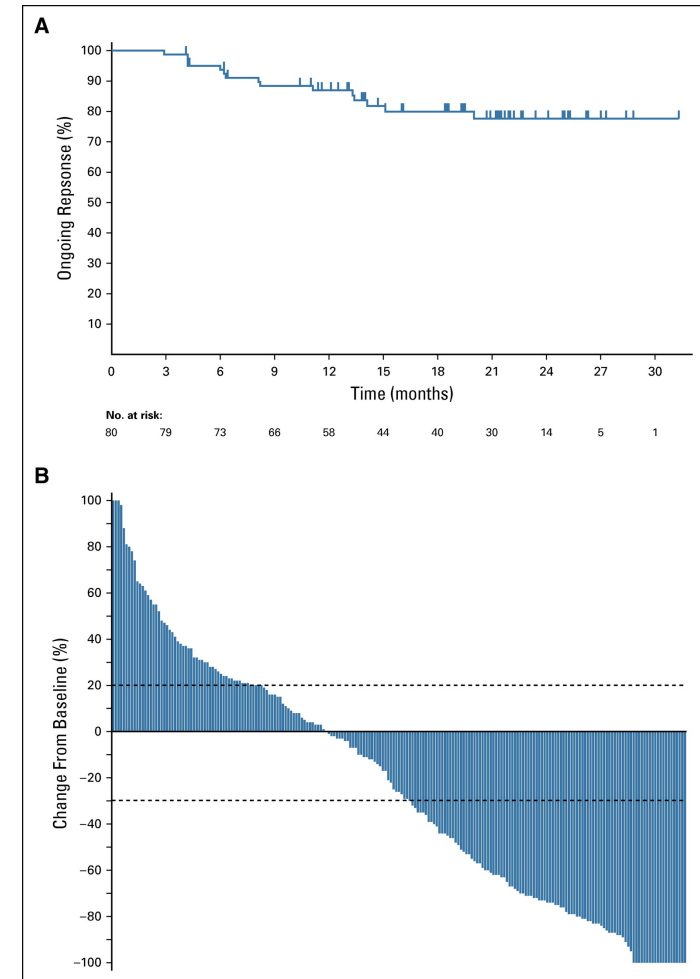
Pembrolizumab

- Accelerated approval on May 23, 2017
 - Adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having MSI-H or dMMR
 - First drug approved a cancer treatment based on a common biomarker rather than the location in the body



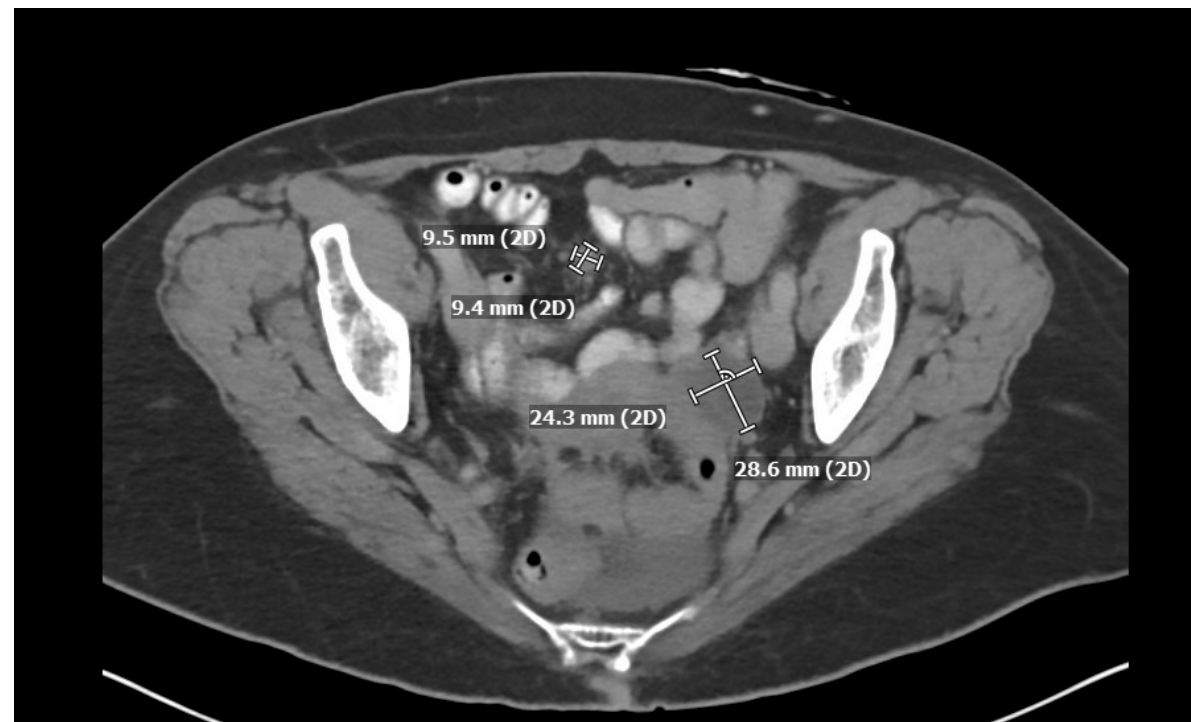
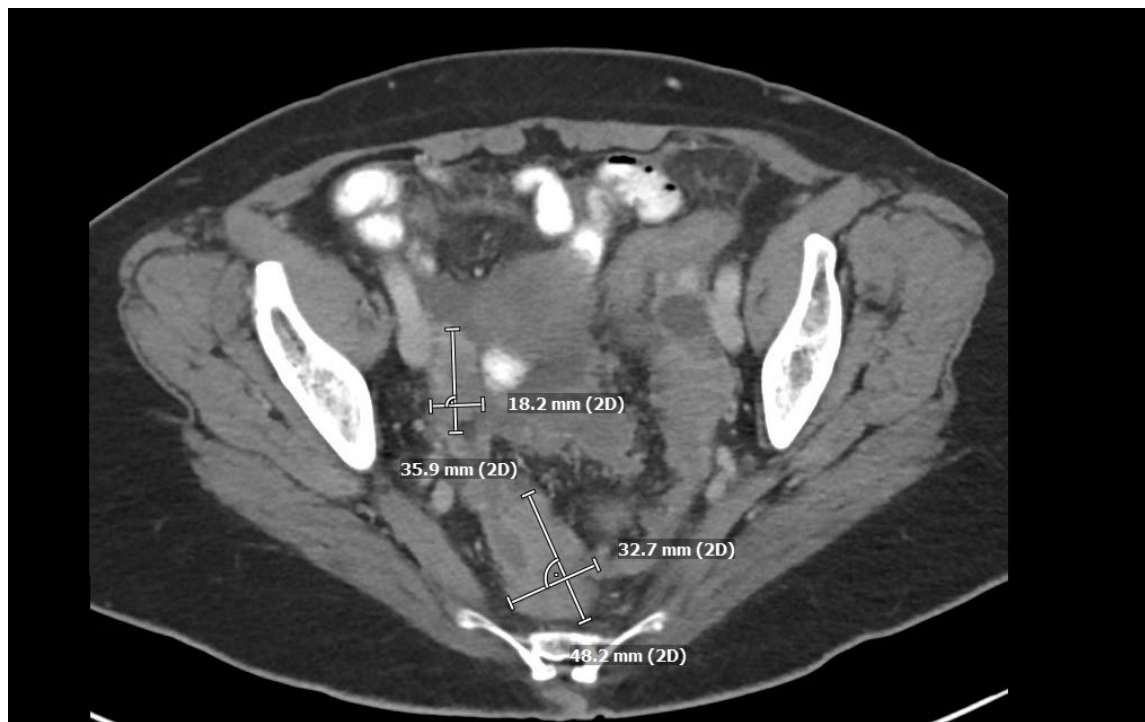
Pembrolizumab & Endometrial Cancer

- KEYNOTE-158
 - 49 patients (21%) endometrial cancer
 - Advanced recurrent disease, prior treatment
 - 57% objective response rate
 - 20 partial response
 - 8 complete response
 - Median PFS – 25.7 months
 - Median OS – NR
 - Median DOR - NR



65 yo patient with Stage IV Endometrial Cancer

MMR-d treated with pembrolizumab

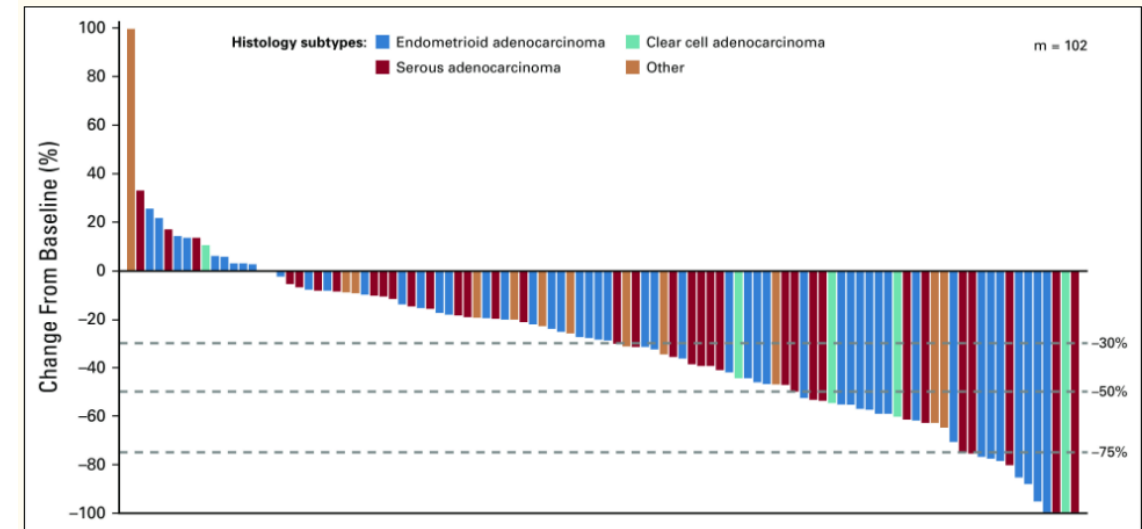
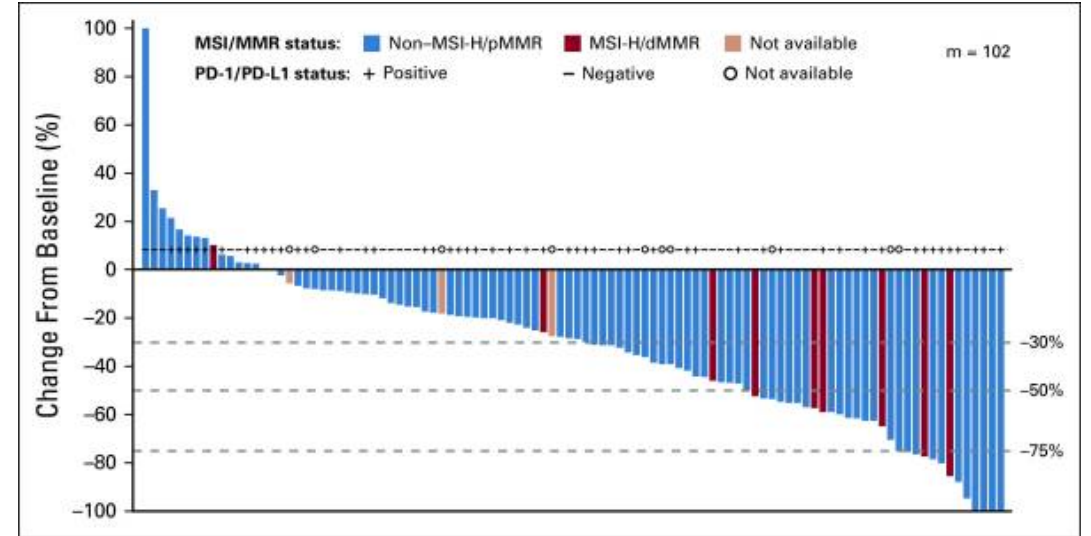


No Cancer Identified on pathology from surgery

What About MMR-Proficient Tumors?

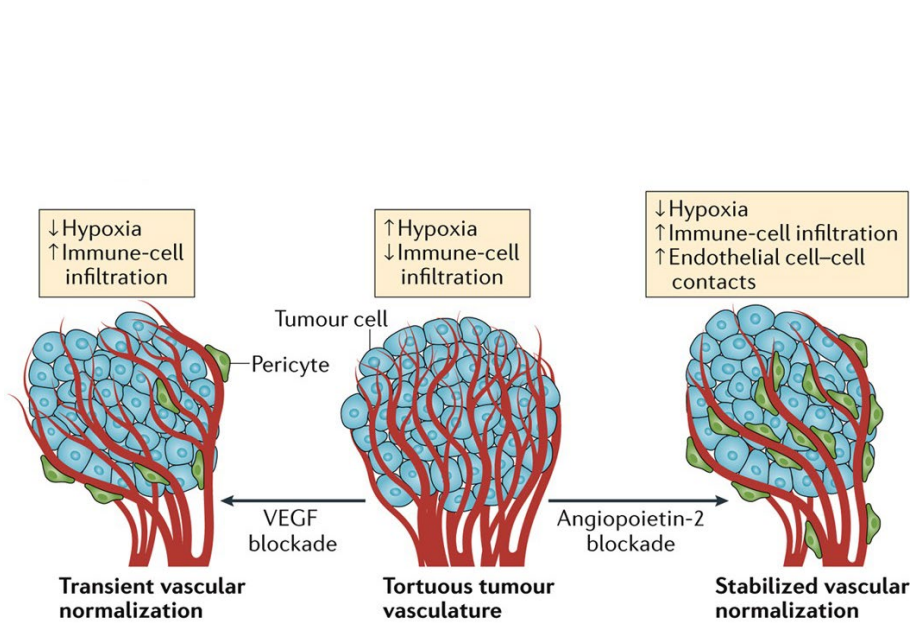
Study 111/KEYNOTE-146

- Phase 2, single arm, open label
- 94 patients with MMR-p EC
- Patients with progression following at least one prior systemic therapy
 - Pembrolizumab 200 mg IV Q3 weeks
 - Lenvatinib (VEGF receptor inhibitor) 20 mg PO daily
- ORR 37.2 %
 - CR 7.4%
 - PR 29.8%
 - Response duration ≥ 6 months – 85%

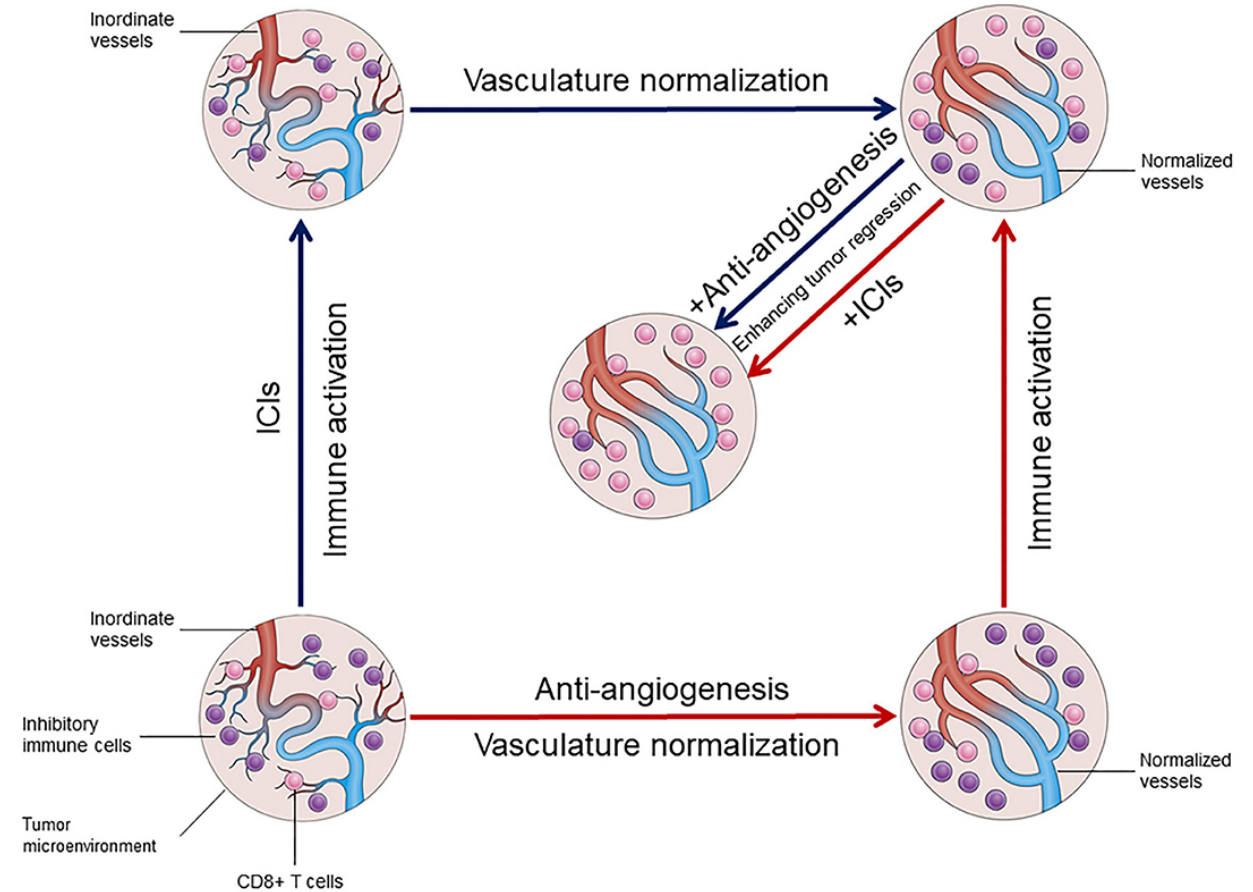


How Does Lenvatinib Enhance Immune Response?

Vascular Remodeling



Nature Reviews | Clinical Oncology



Lenvatinib + Pembrolizumab

Toxicities

- TRAEs
 - Drug interruption of one or both drugs in 72% of patients
 - Lenvatinib dose reduction in 65% of patients
 - Drug discontinuation in 19%
 - Most common Grade ≥ 3 TRAE were HTN (32%), Fatigue (7%) and diarrhea (7%)

September 17, 2019, the US FDA granted accelerated approval of the combination

Conclusion

- Immunotherapy plays an important role in the management of endometrial cancer
- Ongoing clinical trials evaluating combination of chemotherapy with ICI
- Unanswered questions remain
 - Timing of ICI
 - Duration of treatment

Questions?