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Updates in Endometrial Cancer

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Division of Gynecologic Oncology

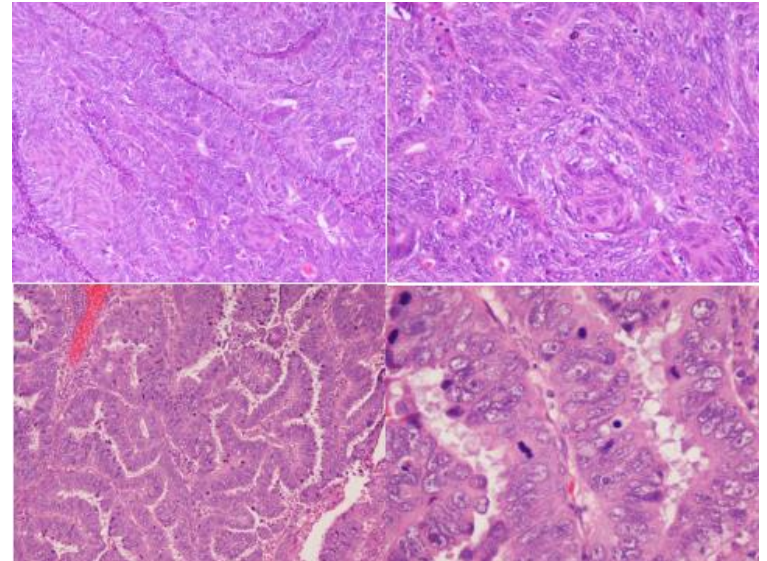
Survive and Thrive 2024

Disclosures

- Speakers bureau – Immunogen/Abbvie

What is cancer classification?

- Classification – grouping cancers together that act similarly
 - Allows for better decision-making regarding the best treatment options
- Many different approaches to grouping cancer
 - Pathology
 - Grade
 - Stage
 - Molecular features



Endometrial Cancer: Type I vs Type II

- Traditionally, endometrial cancer was classified into two pathologic groups using a combination of these features

Characteristic	Type I	Type II

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Stage	Often early	Often advanced
Etiology	Unopposed estrogen	Sporadic

Endometrial Cancer: Type I vs Type II

- This classification system:
 - Grade and histopathology is not always reproducible
 - This can lead to heterogeneity in not only classification, but also research and clinical trials
 - Somewhat more limited ability to risk stratify patients

Can we do better?

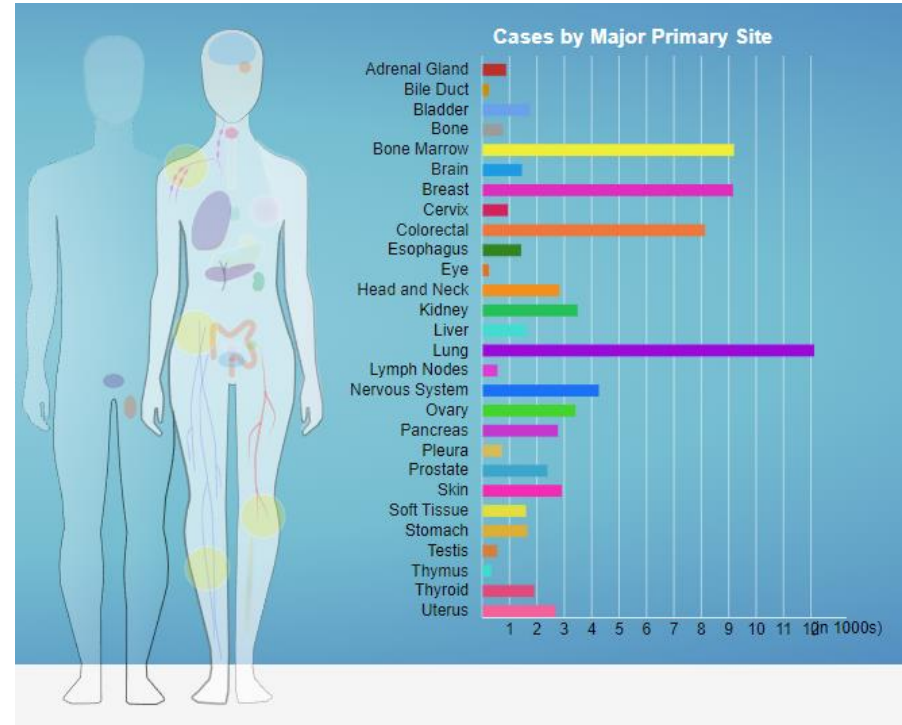
An aerial photograph of Northwestern University's campus in Chicago. The image shows several large, modern buildings with glass facades and flat roofs. In the background, the blue waters of Lake Michigan are visible under a clear sky. The foreground is dominated by a large, semi-transparent purple graphic that contains the text.

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Molecular Classification

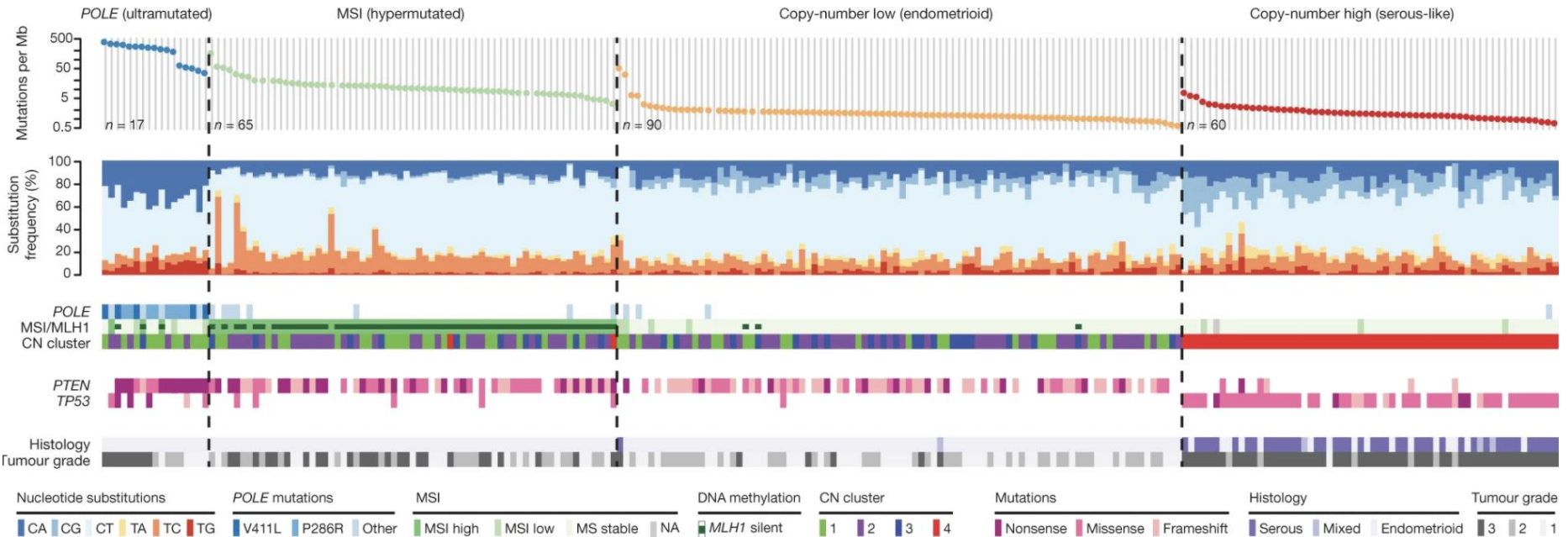
The Cancer Genome Atlas (TCGA)

- Landmark cancer genomics program
 - National Cancer Institute
 - National Human Genome Research Institute
- Molecularly characterized multiple cancer types with matched normal samples
 - 2664 cases of uterine cancer
 - Multiple histologies

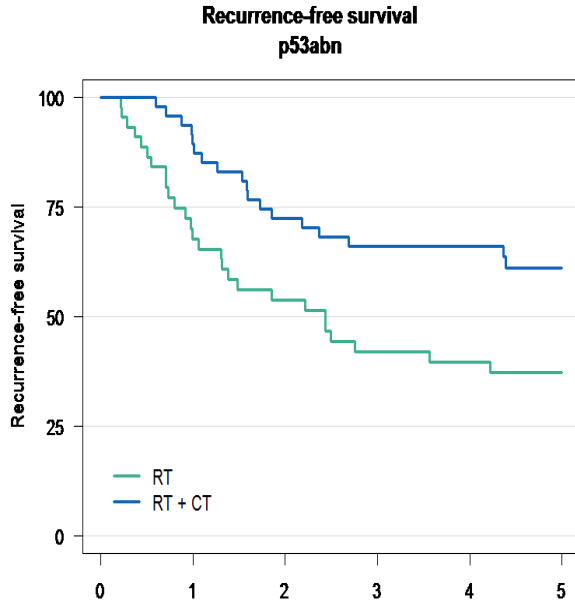


TCGA Molecular Classification

- Grouping endometrial cancer based on molecular characteristics rather than pathologic characteristics



TCGA Molecular Classification: Copy number high



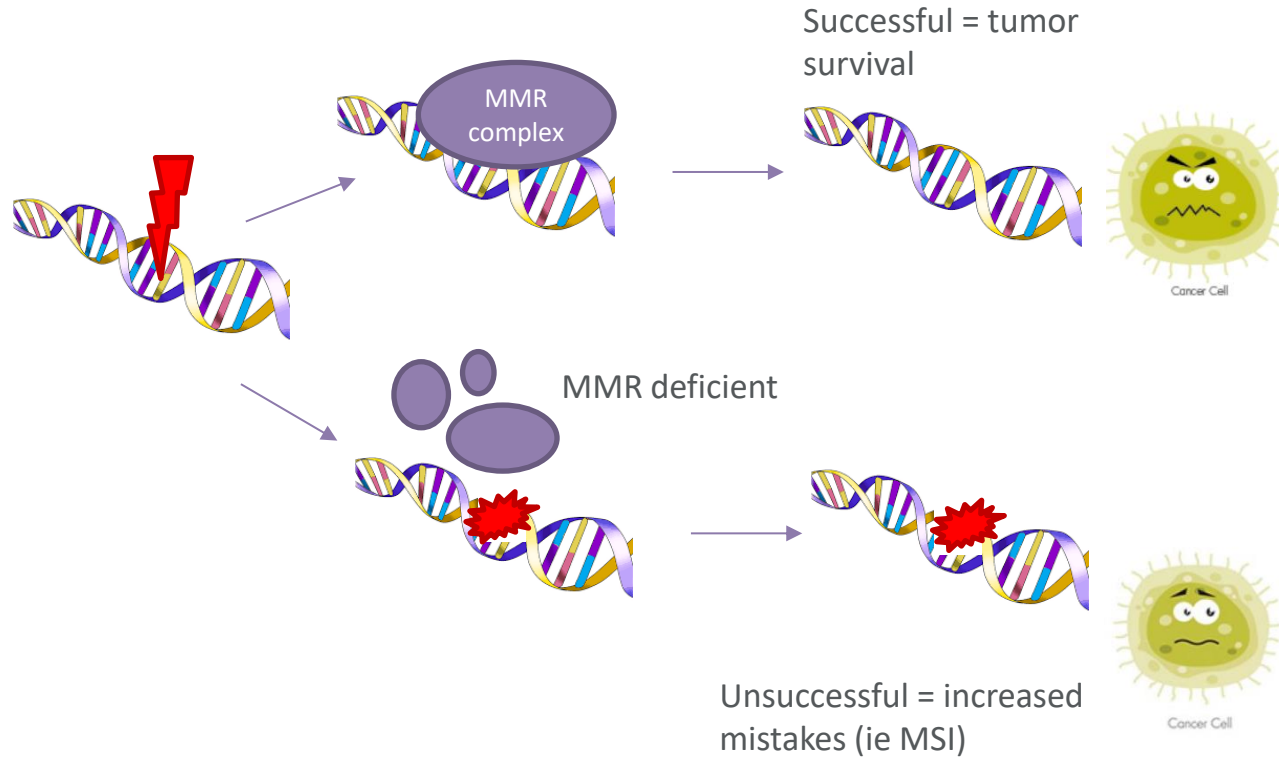
- “Serous-like” (73% in this group are serous histology)
- Aggressive, poorer prognosis
- P53 mutated
 - Chemotherapy may have greater benefit for these patients than others in the adjuvant setting

p=0.015, HR 0.50 (95%CI 0,28-0,88)

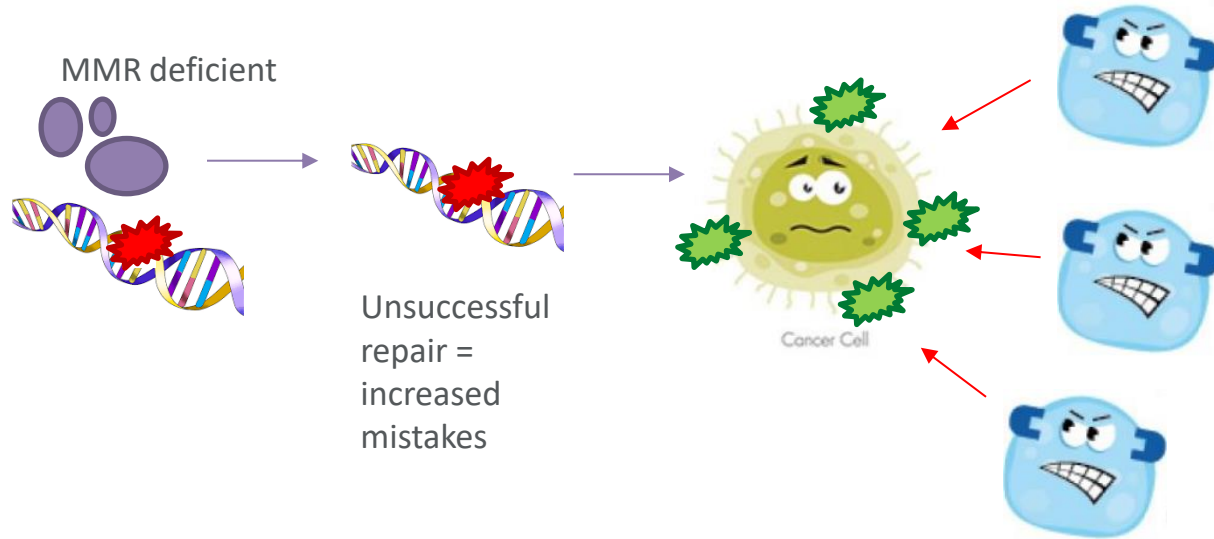
TCGA Molecular Classification: Immune SUSCEPTIBLE

- POLE Mutation
 - 4-8% of endometrial cancers
 - Very high mutational burden
 - Excellent prognosis
 - Decreased recurrence risk
- Mismatch repair:
 - MSI = microsatellite instability
 - dMMR = deficient mismatch repair
- 20-40% of endometrial cancer
- Intermediate prognosis group
 - Predictive of response to immunotherapy

Immunogenic: Mismatch repair



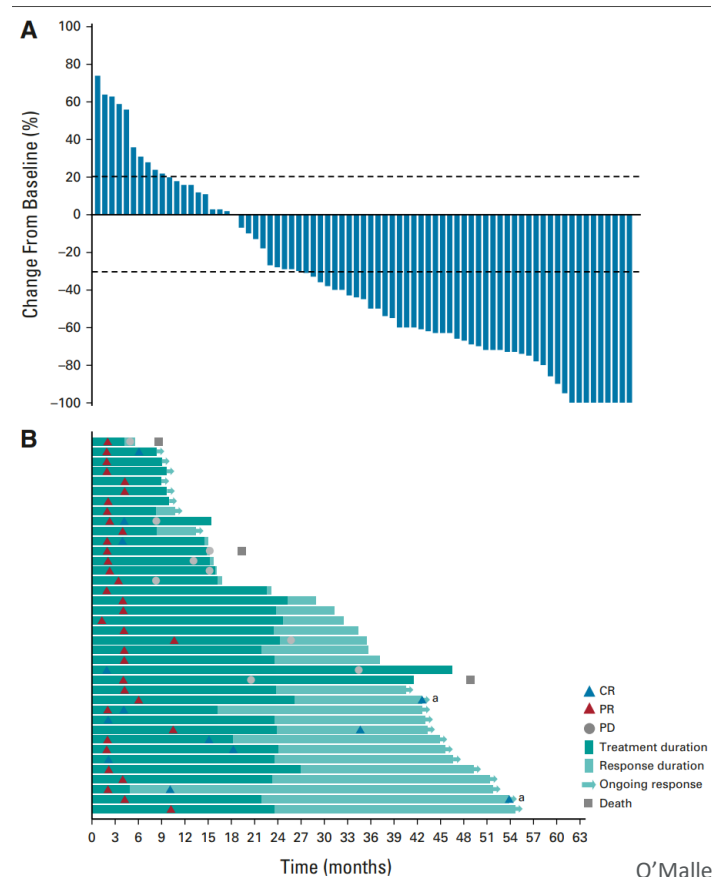
Immunogenic: Mismatch repair



In RECURRENT endometrial cancer:

- Keynote – 158
 - 79 Patients
 - 48% Response Rate

- 2/3 of patients have a response duration of > 3 years



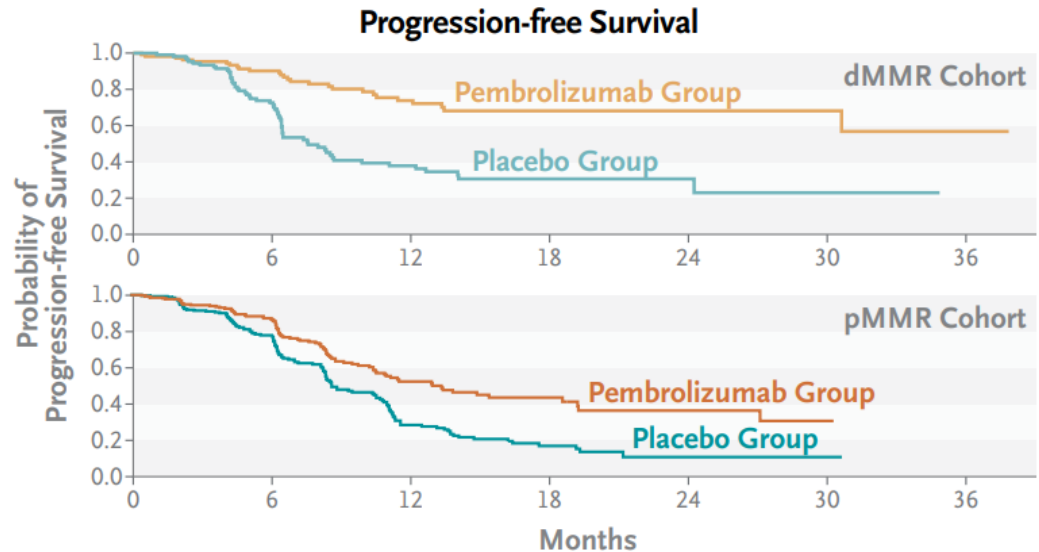
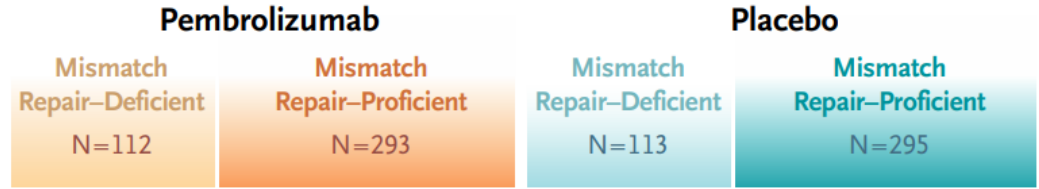
In UPFRONT endometrial cancer:

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavcansky, M.D., Charles A. Leath III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O’Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.



In UPFRONT endometrial cancer:

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ORIGINAL ARTICLE

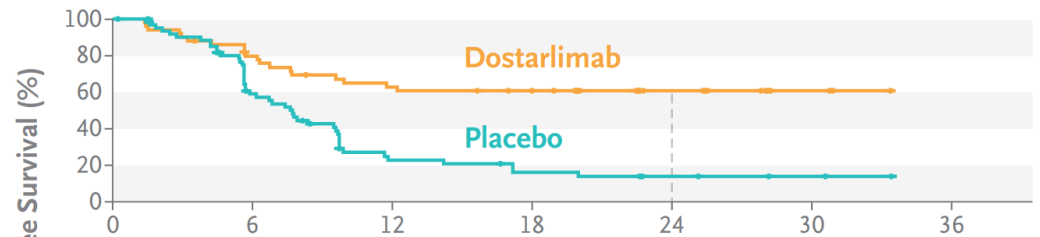
Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

M.R. Mirza, D.M. Chase, B.M. Slomovitz, R. dePont Christensen, Z. Novák, D. Black, L. Gilbert, S. Sharma, G. Valabrega, L.M. Landrum, L.C. Hanker, A. Stuckey, I. Boere, M.A. Gold, A. Auranen, B. Pothuri, D. Cibula, C. McCourt, F. Raspagliesi, M.S. Shahin, S.E. Gill, B.J. Monk, J. Buscema, T.J. Herzog, L.J. Copeland, M. Tian, Z. He, S. Stevens, E. Zografos, R.L. Coleman, and M.A. Powell, for the RUBY Investigators*

Progression-free Survival at 24 Mo

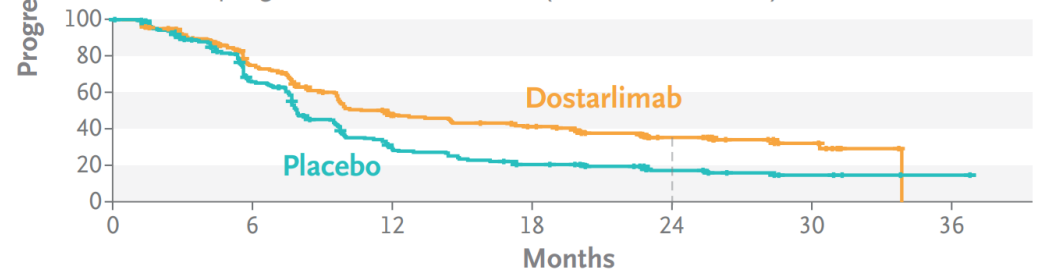
dMMR–MSI-H Population

HR for progression or death, 0.28 (95% CI, 0.16–0.50); $P < 0.001$



Overall Population

HR for progression or death, 0.64 (95% CI, 0.51–0.80); $P < 0.001$



What about patients WITHOUT this immune sensitivity?

TCGA Molecular Classification: Copy number low

- Also known as “no specific molecular profile” (NSMP)
- 40-50% of endometrial cancer
- Intermediate prognosis group
- Hormone receptors
- Further molecular characterization in order to stratify
 - CTNNB1
 - L1CAM

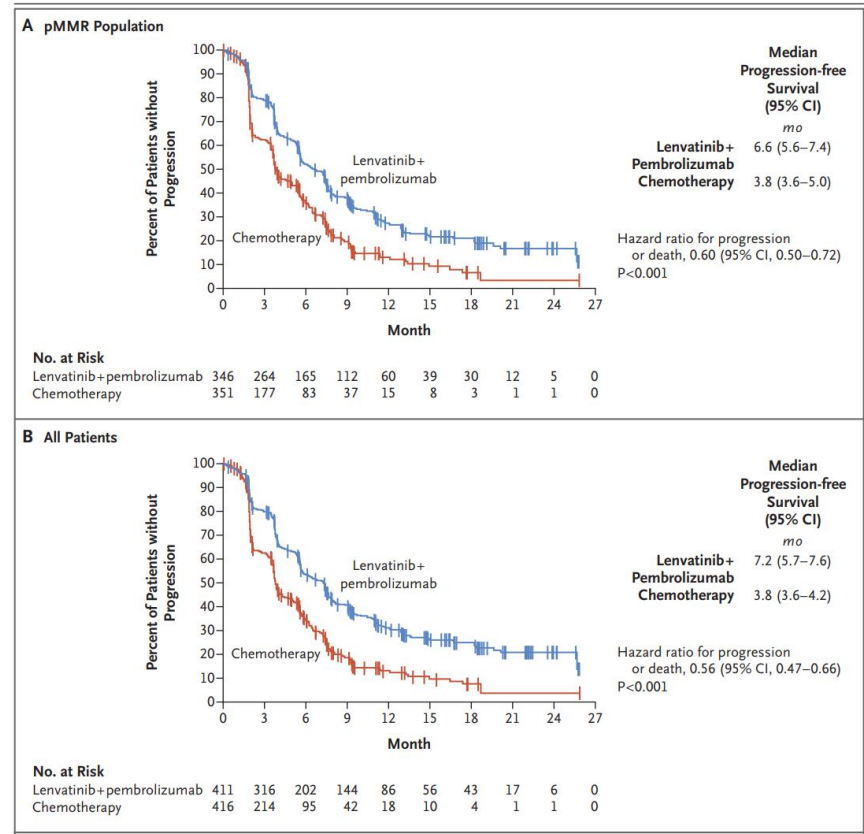
But what about patients WITHOUT this immune sensitivity?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer

V. Makker, N. Colombo, A. Casado Herráez, A.D. Santin, E. Colomba, D.S. Miller, K. Fujiwara, S. Pignata, S. Baron-Hay, I. Ray-Coquard, R. Shapira-Frommer, K. Ushijima, J. Sakata, K. Yonemori, Y.M. Kim, E.M. Guerra, U.A. Sanli, M.M. McCormack, A.D. Smith, S. Keefe, S. Bird, L. Dutta, R.J. Orłowski, and D. Lorusso, for the Study 309–KEYNOTE-775 Investigators*

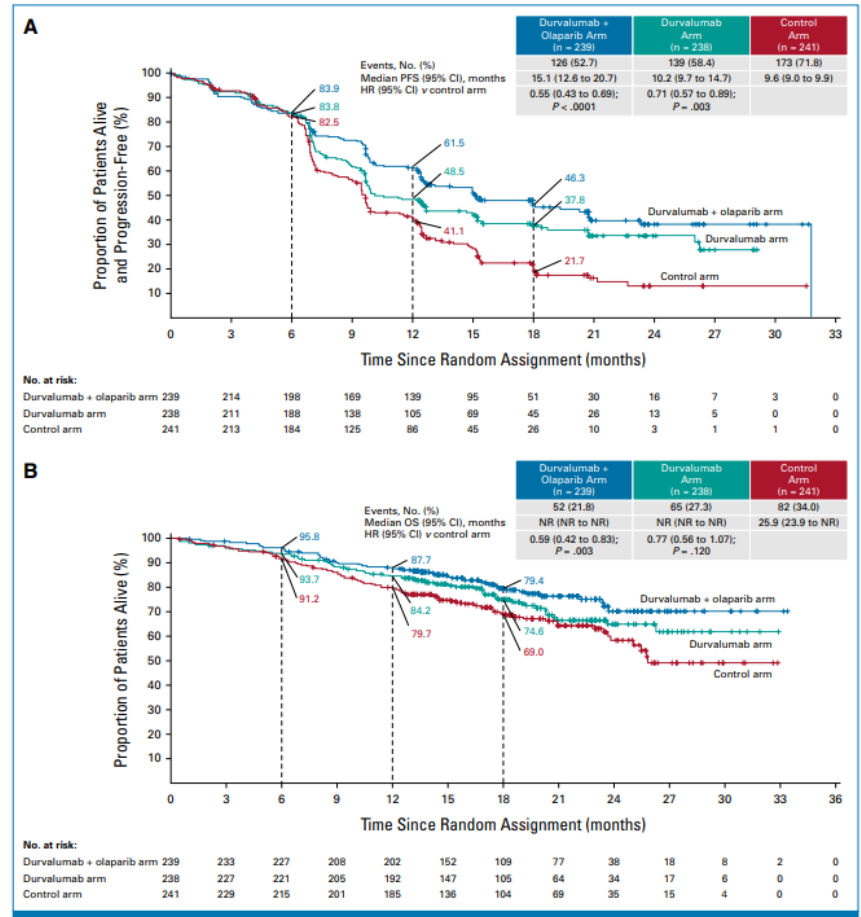


But what about patients WITHOUT this immune sensitivity?

Original reports | Gynecologic Cancer

③ Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial

Shannon N. Westin, MD, MPH¹; Kathleen Moore, MD²; Hye Sook Chon, MD³; Jung-Yun Lee, MD⁴; Jessica Thomes Pepin, MD⁵; Michael Sundborg, MD⁶; Ayelet Shai, MD, PhD⁷; Joseph de la Garza, MD⁸; Shin Nishio, MD⁹; Michael A. Gold, MD¹⁰; Ke Wang, MD¹¹; Kristi McIntyre, MD¹²; Todd D. Tillmanns, MD¹³; Stephanie V. Blank, MD¹⁴; Ji-Hong Liu, MD¹⁵; Michael McCollum, MD¹⁶; Fernando Contreras Mejia, MD¹⁷; Tadaaki Nishikawa, MD¹⁸; Kathryn Pennington, MD¹⁹; Zoltan Novak, MD, PhD²⁰; Andrea Cristina De Melo, MD²¹; Jalid Sehouli, MD²²; Dagmara Klasa-Mazurkiewicz, MD²³; Christos Papadimitriou, MD²⁴; Marta Gil-Martin, MD²⁵; Birute Brasiuniene, MD, PhD²⁶; Conor Donnelly, PhD²⁷; Paula Michelle del Rosario, MD²⁸; Xiaochun Liu, MD, PhD²⁹; and Els Van Nieuwenhuysen, MD³⁰; on behalf of the DUO-E Investigators



In summary...

- We are learning more and more about how endometrial cancer acts and responds to treatment
- Molecular classification represents a new way of grouping these cancers, and gives a more nuanced view
 - This will hopefully allow us to better tailor treatment to each woman's specific tumor
- Immunotherapy has dramatically changed the treatment, and outcomes, for endometrial cancer
 - Both upfront and recurrent endometrial cancer
 - Are there other patients who can benefit:
 - Immunotherapy combinations?
 - Early stage endometrial cancer?
 - Immunotherapy VERSUS chemo?

Thank You!

Any questions?