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Immunotherapy in Melanoma and Cutaneous Cancer

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American College of Surgeons

Disclosures

- None

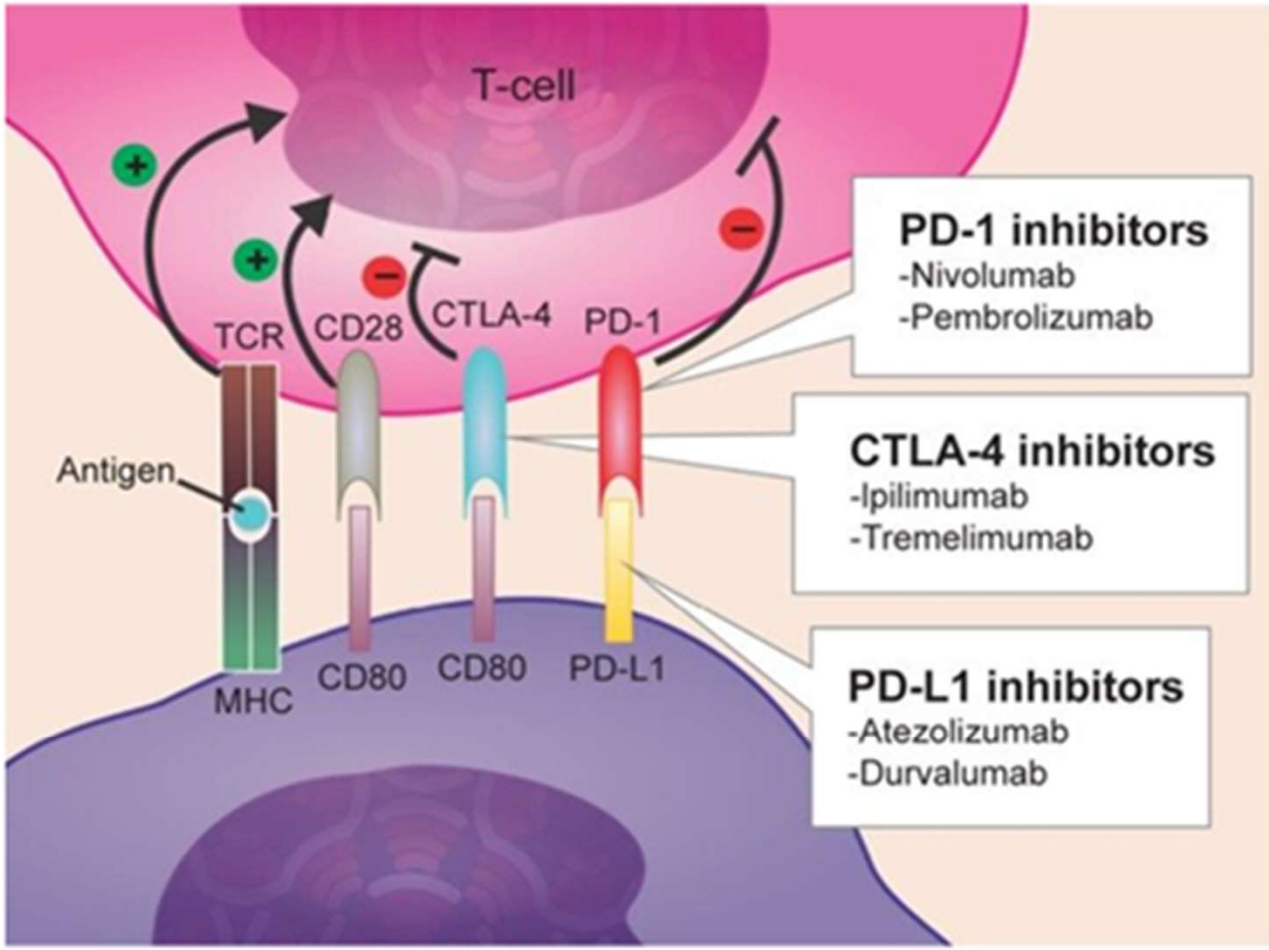
Immunotherapy

- Non-Melanoma Skin Cancer
  - Basal Cell Carcinoma
  - Squamous Cell Carcinoma

  CHECK POINT INHIBITORS
- Melanoma
  - Adjuvant and Neoadjuvant Check point inhibitors
  - TIL immunotherapy

Immune checkpoints

- T lymphocytes have “checkpoints” (CTLA-4, PD-1, LAG-3, etc) to dampen immune response to prevent self-destruction
- Checkpoints can suppress the ability for the T cell to react to tumor cells
- Checkpoint inhibitors can “release the break” and allow T cells to kill target



(de Mello RA, *Oncotargets Ther* 2014)

Immunotherapy

- Nonmelanoma Skin Cancers (NMSC)

99% are Basal Cell Carcinoma and Squamous Cell Carcinoma

- Other rare NMSC:

Merkel Cell Carcinoma, Sebaceous Gland Carcinoma, Apocrine Adenocarcinoma, angiosarcoma and Dermatofibrosarcoma protuberans

Immunotherapy

Nonmelanoma Skin Cancers (NMSC)

- Majority are Basal Cell Carcinoma (BCC)
- Squamous Cell Carcinoma (SCC) – higher incidence rates with metastatic and mortality rates greater than BCC
  - 5 yr survival 90%

Squamous and Merkel Cell Carcinoma

Metastatic Squamous Cell Carcinoma Immunotherapy

- 2018 Cemiplimab (Libtayo) anti- PD-1 was approved for metastatic cutaneous SCC (62% OR)
- Pembrolizumab and Nivolumab are approved for the treatment of metastatic squamous cell carcinoma.

Merkel Cell Carcinoma: Avelumab, Pembrolizumab

These drugs are only utilized where surgery and or radiation cannot eradicate disease.

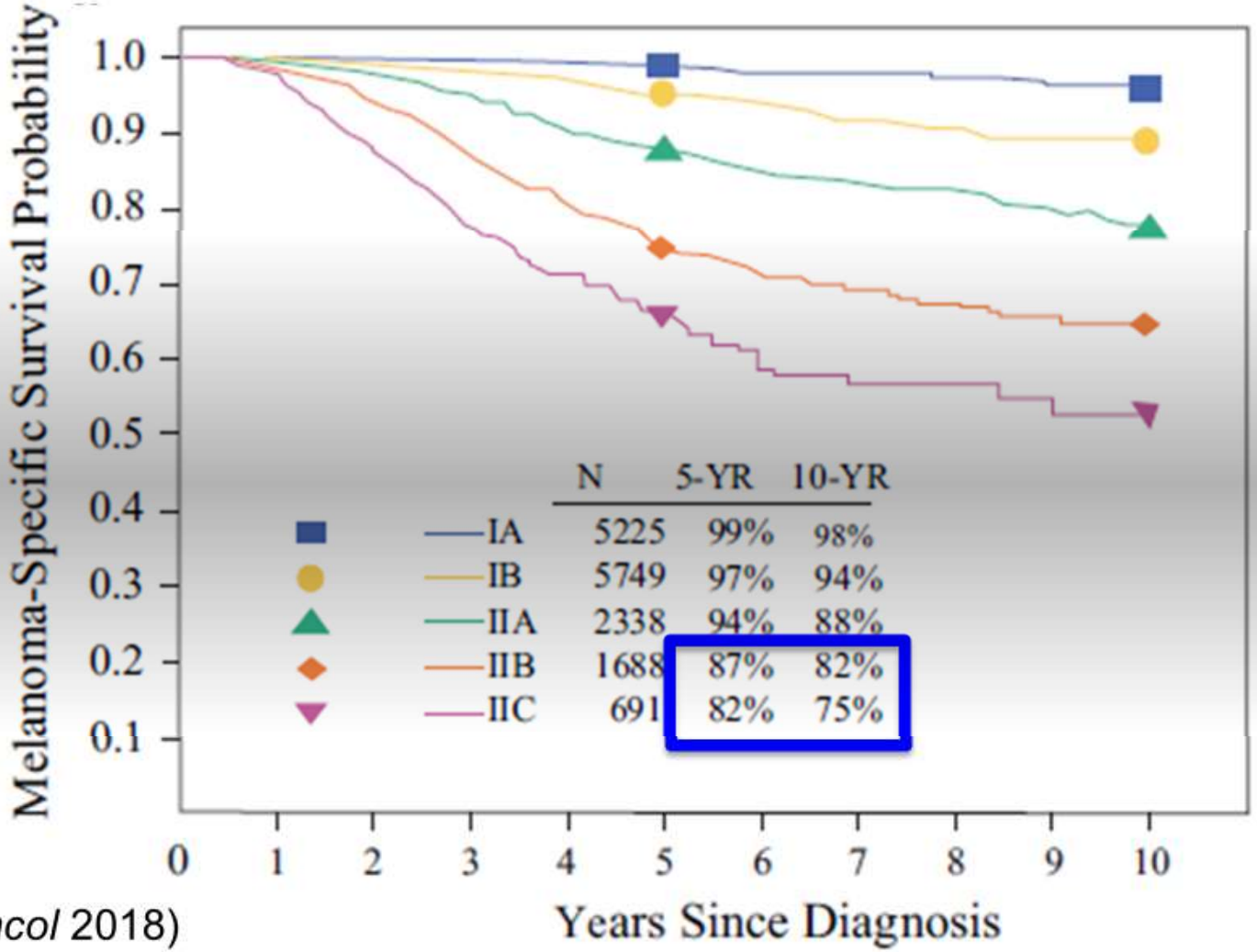
Immunotherapy for Melanoma

- Melanoma and Prognosis
- Check point Inhibitors- adjuvant and neoadjuvant therapy
- Tumor Infiltrating Lymphocytes

Survival rates for stage I and II (AJCC 8th)

- IA/IB: pT1a - pT2a
- IIA: pT2b or pT3a
- IIB: pT3b or pT4a
- IIC: pT4b

- Survival correlates with stage
- Substantial decrease in survival for stages IIB & IIC

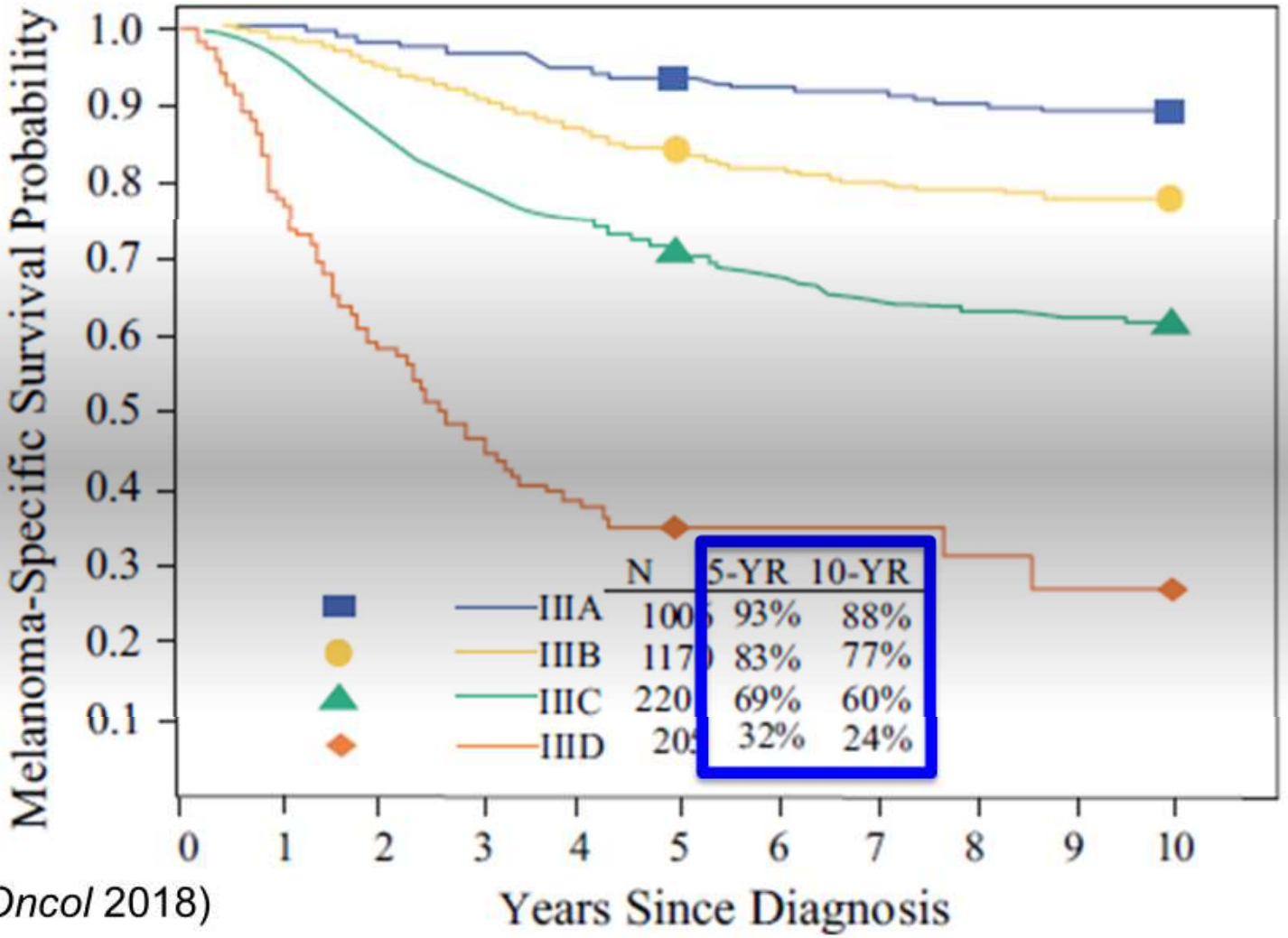


(Gershenwald JE, *Ann Surg Oncol* 2018)

Survival rates for stage III (AJCC 8th)

- IIIA: ≤ pT2a +SLN
- IIIB/C/D: in-transit, clinically-detected, or ≥ pT2b +SLN

- Survival correlates with stage
- Stage IIIA (93%) similar to stage IIA (94%)



(Gershenwald JE, *Ann Surg Oncol* 2018)

Adjuvant for Stage III

- Checkmate 238 Randomized resected stage IIIb/C and stage IV to anti PD-1 Nivolumab or anti-CTLA-4 Ipilimumab. They evaluated RFS.

  Weber JS NEJM 2017 52% Nivo 41%, Ipi at 48 months

  Larkin L Clin Cancer Res 2023 50% Nivo, 39% Ipi at 60 months

- EORTC 1325-MG Keynote -054: Phase III trial randomizing resected stage III A/B/C melanoma to adjuvant Pembrolizumab vs Placebo. There was significant ($p<.0001$) improvement in distant metastatic free survival with Pembrolizumab. Lancet Oncol 2021
  - 2019 approval with FDA

Pembrolizumab Versus Placebo as Adjuvant Therapy in Resected Stage IIB or IIC Melanoma: Final Analysis of Distant Metastasis-Free Survival in the Phase III KEYNOTE-716 Study

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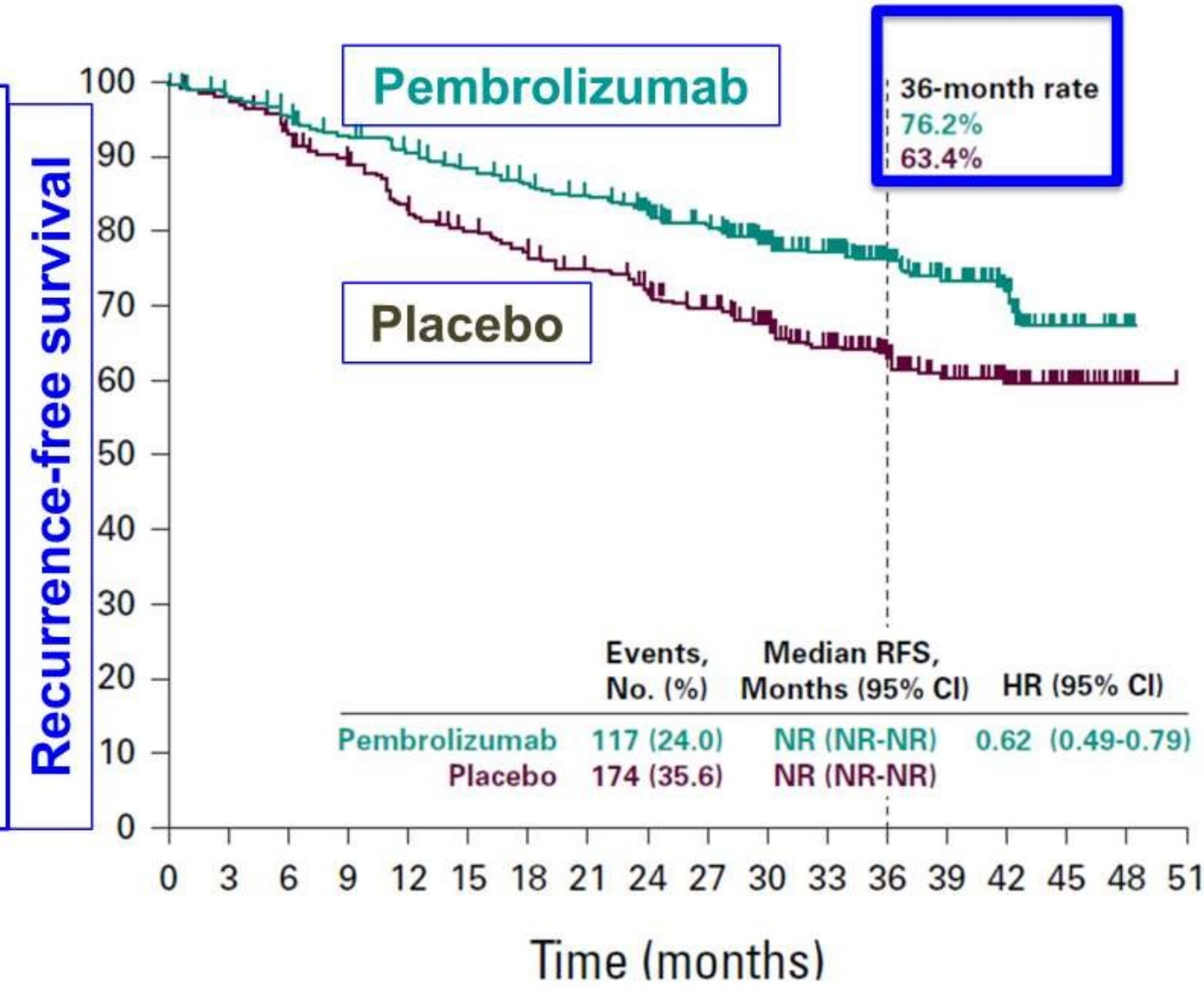
- 976 patients with resected stage IIB and IIC melanoma randomized
  - 487 patients: adjuvant pembrolizumab (anti-PD-1 inhibitor)
  - 489 patients: placebo
- Patients followed for recurrence-free survival & distant metastasis-free survival

(Luke JJ, *J Clin Oncol* 2024) (Long GV, *Lancet* 2022)

Adjuvant therapy for Stage IIB & IIC:

- Significant difference in recurrence rate **76.2%** vs. **63.4%** at 36 months
- FDA approval for pembrolizumab for stage IIB/IIC in December 2021



(Luke JJ, *J Clin Oncol* 2024)

Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

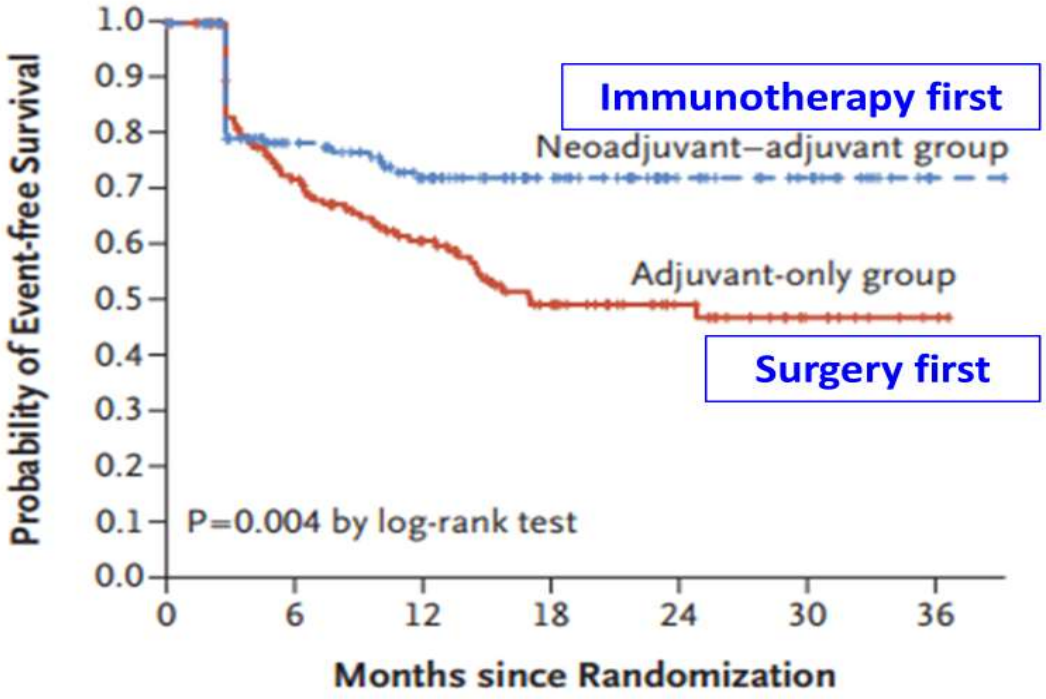
S.P. Patel, M. Othus, Y. Chen, G.P. Wright, Jr., K.J. Yost, J.R. Hyngstrom, S. Hu-Lieskovan, C.D. Lao, L.A. Fecher, T.-G. Truong, J.L. Eisenstein, S. Chandra, J.A. Sosman, K.L. Kendra, R.C. Wu, C.E. Devoe, G.B. Deutsch, A. Hegde, M. Khalil, A. Mangla, A.M. Reese, M.I. Ross, A.S. Poklepovic, G.Q. Phan, A.A. Onitilo, D.G. Yasar, B.C. Powers, G.C. Doolittle, G.K. In, N. Kokot, G.T. Gibney, M.B. Atkins, M. Shaheen, J.A. Warneke, A. Ikeguchi, J.E. Najera, B. Chmielowski, J.G. Crompton, J.D. Floyd, E. Hsueh, K.A. Margolin, W.A. Chow, K.F. Grossmann, E. Dietrich, V.G. Prieto, M.C. Lowe, E.I. Buchbinder, J.M. Kirkwood, L. Korde, J. Moon, E. Sharon, V.K. Sondak, and A. Ribas

- 313 patients with resectable stages IIIB/C to stage IV randomized
- 154 patients: Surgery Adjuvant pembrolizumab x 12 months
- 159 patients: Neoadjuvant pembrolizumab x 3 cycles followed by surgery, then adjuvant pembrolizumab
- Patients followed for recurrence-free survival

Patel, SP NEJM 2023

Neoadjuvant vs. adjuvant pembrolizumab

- Patients who receive neoadjuvant immunotherapy before surgery have improved progression-free survival at 2 years (**72%** vs. **49%**)
- No unexpected/new adverse event



(Patel SP, *NEJM* 2023)

Patel, SP NEJM 2023

Neoadjuvant Immunotherapy

- New Standard of care is **NEOADJUVANT** check point inhibitor prior to surgery for resectable stage IIIB/C and stage IV melanoma
- 3 cycles of Pembrolizumab followed by surgery and adjuvant therapy
- Underscores the importance of multidisciplinary teams

Melanoma TIL

- Developed over many years and started prior to availability of Check Point Inhibitors
- Tumor Infiltrating Lymphocytes from resected Tumors
- Grown to large volume and infused back to the patient like an “autologous transplant” with preparative regimen
- They cannot over come the immunosuppressive environment in the tumor without assistance.

Surgeons are needed for the resection to develop this treatment.

MACON & JOAN BROCK VIRGINIA HEALTH SCIENCES
Eastern Virginia Medical School
AT OLD DOMINION UNIVERSITY

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