Introduction

- Pembrolizumab + chemotherapy is standard of care for early-stage TNBC (KEYNOTE-522).
- ICIs use may cause immune-related adverse events (irAEs) that vary with age in other cancers.
- Age-specific pembrolizumab toxicity patterns in TNBC are **unknown**.
- No real-world studies have evaluated age-related differences in irAE incidence, severity, and survival in TNBC.

Methods

- Retrospective cohort study using TriNetX (2016-2024).
- Adult female TNBC patients receiving pembrolizumab.
- Exclusions: pre-existing autoimmune disease, other pembrolizumab-treated cancers.
- Age groups: **Younger ≤54 yrs**, **Older ≥55 yrs**
- Patients were 1:1 propensity score matched based on sex, race, and comorbidities, resulting on **1,661 patients per cohort**.
- irAEs defined using composite ICD-10 codes (endocrine, hepatic, pulmonary, hematologic, GI).
- Markers of severity: **corticosteroid use** and **hospitalization**.
- Outcomes assessed at **1, 3, 6, 12 months** post-treatment.
- Primary outcomes included all-cause mortality, overall survival (Kaplan-Meier, log-rank test, hazard ratios), and use of daratumumab.

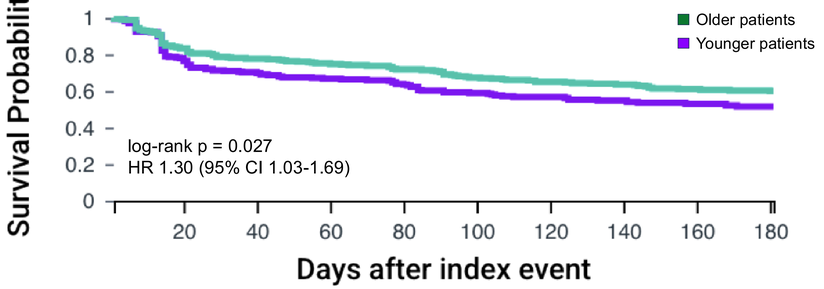
Results

- Older patients had more early irAEs (comparing younger vs. older):
  - **1 month:** OR 0.70 (95% CI 0.497–0.999); *p=0.048*
  - **3 months:** OR 0.70 (95% CI 0.56–0.90)*; p=0.0049*
- Driven by higher **thyroiditis** in older group:
  - OR 0.6 (95% CI 0.47–0.93); *p=0.017*
- Differences **not significant** at 6 or 12 months.

- Steroid exposure and hospitalization were integrated into a composite endpoint because these interventions represent meaningful, high-grade toxicity not fully captured by diagnostic codes.

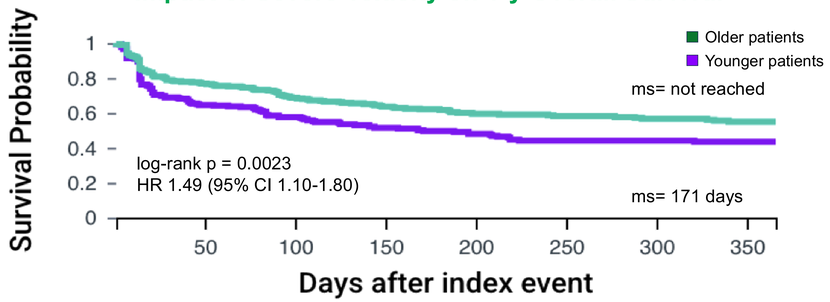
- **Younger patients showed higher severe-toxicity burden from the earliest timepoint.**
  - **1 month:** OR 1.45 (95% CI 1.03–2.17); p=0.03
  - Associated with worse early survival: HR 1.30 (95% CI 1.01–1.90), log-rank p=0.04.
  - **3 months:** OR 1.57 (95% CI 1.13–2.10); p=0.0087.
  - Survival: HR 1.40 (95% CI 1.08–1.88), log-rank p=0.0105.
  - **6 months:** OR 1.38 (95% CI 1.0–1.9); p=0.048
  - Survival: HR 1.30 (95% CI 1.03–1.69), log-rank p=0.027.

Impact of Severe Toxicity on 6-m Overall Survival



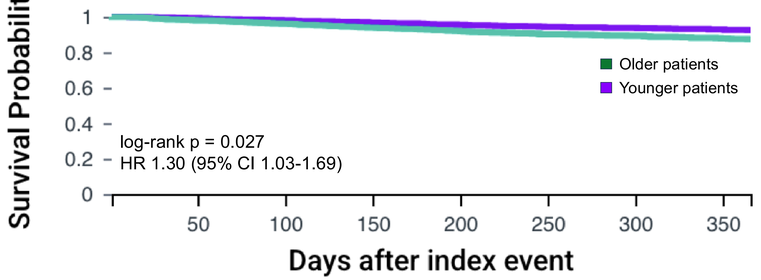
- **At 12 months, the cumulative toxicity gap was even more pronounced.**
  - OR 1.57 (95% CI 1.13–2.1)
  - Median survival: **younger 171 days vs. older not reached,** HR 1.49 (95% CI 1.10–1.80), log-rank p=0.0023.

Impact of Severe Toxicity on 1-y Overall Survival



- All-cause mortality was higher in older patients (*expected for age*)

All-cause mortalitly on 1-y Overall Survival



Conclusion

- Older patients had **more early irAEs**, mainly thyroiditis, but these were generally low-grade and not associated with worse survival.
- Younger patients showed fewer irAEs but **more severe toxicity**, reflected by higher steroid use + hospitalization at every timepoint.
- Severe toxicity in younger patients correlated with **consistently worse survival**, despite their expected age advantage.
- These findings imply that **younger immune systems may generate more intense or rapidly progressive inflammatory toxicity**, requiring earlier escalation of care.
- Using a composite marker of **steroids + hospitalization** provides a clearer measure of true toxicity burden and better explains survival differences.
- Further investigation is warranted to elucidate the immunologic mechanisms of aging in the context of ICI use and safety to guide toxicity monitoring and supportive care strategies.