EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

Using immunotherapy for muscle invasive bladder cancer: why overtreat?

Vikram M. Narayan, MD, FACS

Disclosures

Consulting: Ciox Health/Target RWE, Valar Labs, Aura Labs, CG Oncology, Ferring Ventures

Research funding: Merck, Janssen (Johnson & Johnson Innovative Medicine), Ferring, CG Oncology

Outline

- ddMVAC efficacy: supporting data
- Selective adjuvant immunotherapy: evidence-based decision making
- Clinical advantages of risk-adapted therapy
- Practical considerations and real-world applicability
- Conclusions

Why neoadjuvant ddMVAC therapy?

- Proven efficacy in MIBC and standard of care
- Good pathologic complete response rates (pCR)
  - **Many patients are cured of their disease with NAC + surgery alone – should these folks also get immunotherapy?**
- Intensive schedule delivers rapid tumor reduction
- Robust evidence base over decades of experience
- Provides valuable pathologic staging at time of surgery for adjuvant decision-making

Grossman et al, **NEJM**, 2003

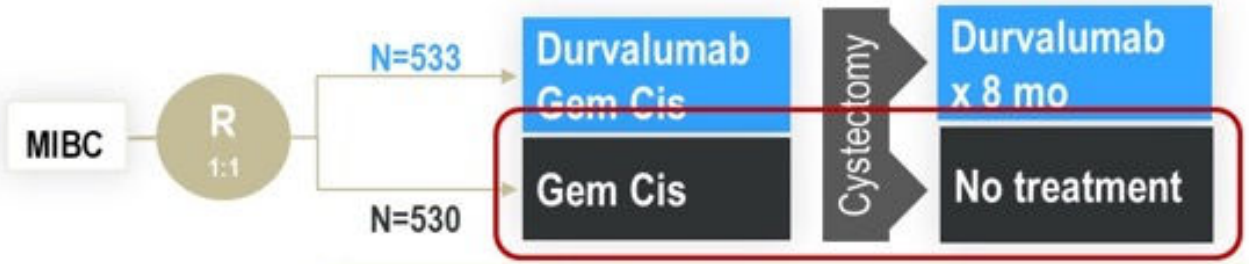
Plimack et al, **J Clin Oncol**, 2014

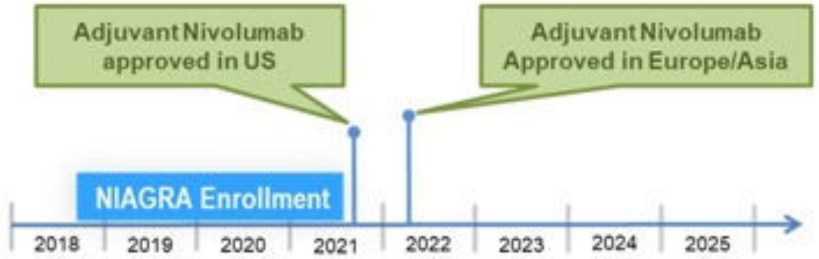
Evidence – pCR rates with ddMVAC

Study	pCR (ypT0)
Choueiri et al., 2014 (JCO)	**26%**
Plimack et al., 2014 (JCO)	**38%**
VESPER (Pfister et al, 2022 JCO)	**42%**

- Higher pCR directly correlates with improved survival outcomes.
- ddMVAC consistently demonstrates excellent pCR rates

NIAGARA control arm does not reflect current standard of care



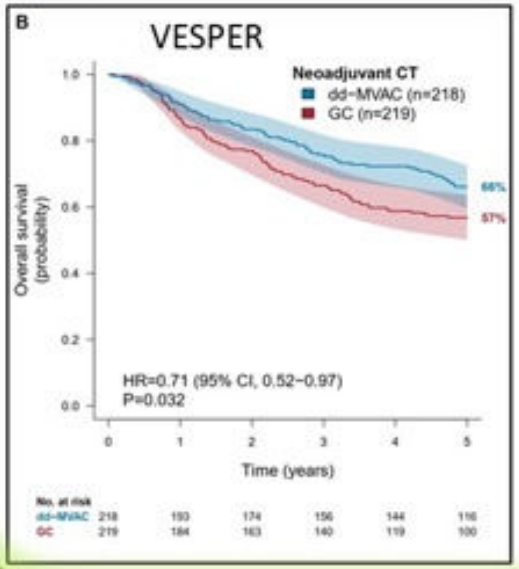


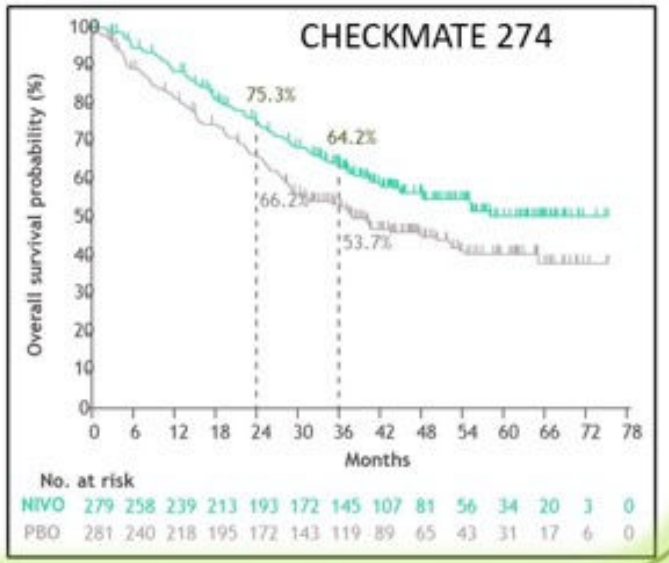
Standard of Care Now

ddMVAC OS benefit over GC 2023

Cystectomy

Adjuvant Nivolumab for high risk OS benefit vs no treatment 2021





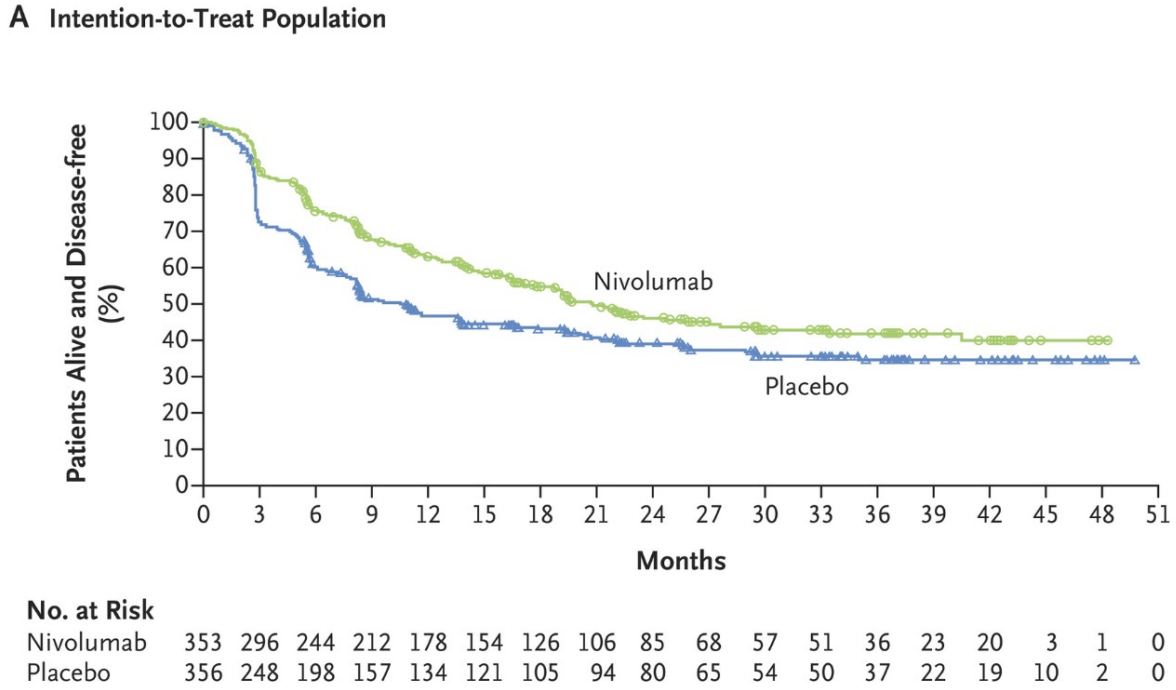
Few patients in the NIAGARA control arm would have had access to adjuvant nivolumab, which became standard of care in 2021

VESPER and COXEN OS data resulted in 2023, after NIAGARA had fully accrued

CHECKMATE 274 Milowsky et al. ASCO GU 2025
Powles et al. N Engl J Med 391, 1773-1786 (2024)
VESPER Pfister et al. LBA4507, ASCO 2023

Selective adjuvant immunotherapy – why this approach?

- Reserve immunotherapy for **high-risk pathological features**
  - Residual invasive disease (≥ypT2 or node-positive)
- Evidence-based approach from adjuvant IO trials
  - **CheckMate-274 (Bajorin et al., NEJM, 2021):**
    - Adjuvant nivolumab vs placebo: Improved DFS (HR: 0.70)
    - Greatest benefit in patients with residual disease post-neoadjuvant chemo
- Avoid unnecessary toxicity & financial burden in lower-risk patients cured by chemo alone



Evidence supporting selective adjuvant IO

Trial	IO agent	DFS Benefit (HR)	Subgroup Benefit
CheckMate-274	Nivolumab	0.70 (p<0.001)	Residual disease
IMvigor010	Atezolizumab	No overall DFS	Trend in residual dz
AMBASSADOR	Pembrolizumab	0.73 (p=0.003)	No difference in nodal, prior NAC, PD-L1 status

- CheckMate-274 provides strongest evidence favoring selective IO approach.
- **Lack of broad benefit in IMvigor010 underscores selective use**
- irAEs are not insignificant – why subject everyone to them?
- **Immature OS Data:** Long-term overall survival benefit still pending; DFS ≠ OS

Clinical advantages to a risk-adapted approach

Personalized medicine: Tailored to patient pathology

Reduces unnecessary overtreatment and immunotherapy-related adverse events (irAEs)

Decreases healthcare cost and patient burden

Real-world applicability: Aligns with clinical workflows and patient preferences

Practical advantages to a risk-adapted approach

Recovery after cystectomy: not all patients recover adequately to receive immediate post-operative IO

Neoadjuvant ddMVAC: shorter total duration, clinically feasible, manageable toxicity profile

Pathology-driven decisions: empowers clinicians and patients with clear prognostic information

Take Home Messages

- **ddMVAC neoadjuvant chemotherapy** is highly effective for MIBC (pCR ~38-42%)
- **Selective adjuvant immunotherapy** optimizes benefit, minimizes toxicity, and aligns with evidence-based practice
- Personalized approach best balances clinical efficacy, safety, and real-world application
  - ctDNA to help adjudicate decision making
- Supports informed decision-making with clear, actionable pathologic information post-surgery