Phase II Trial of Concurrent Nivolumab and Radiation Therapy in Chemotherapy Ineligible Muscle Invasive Bladder Cancer [NUTRA trial]

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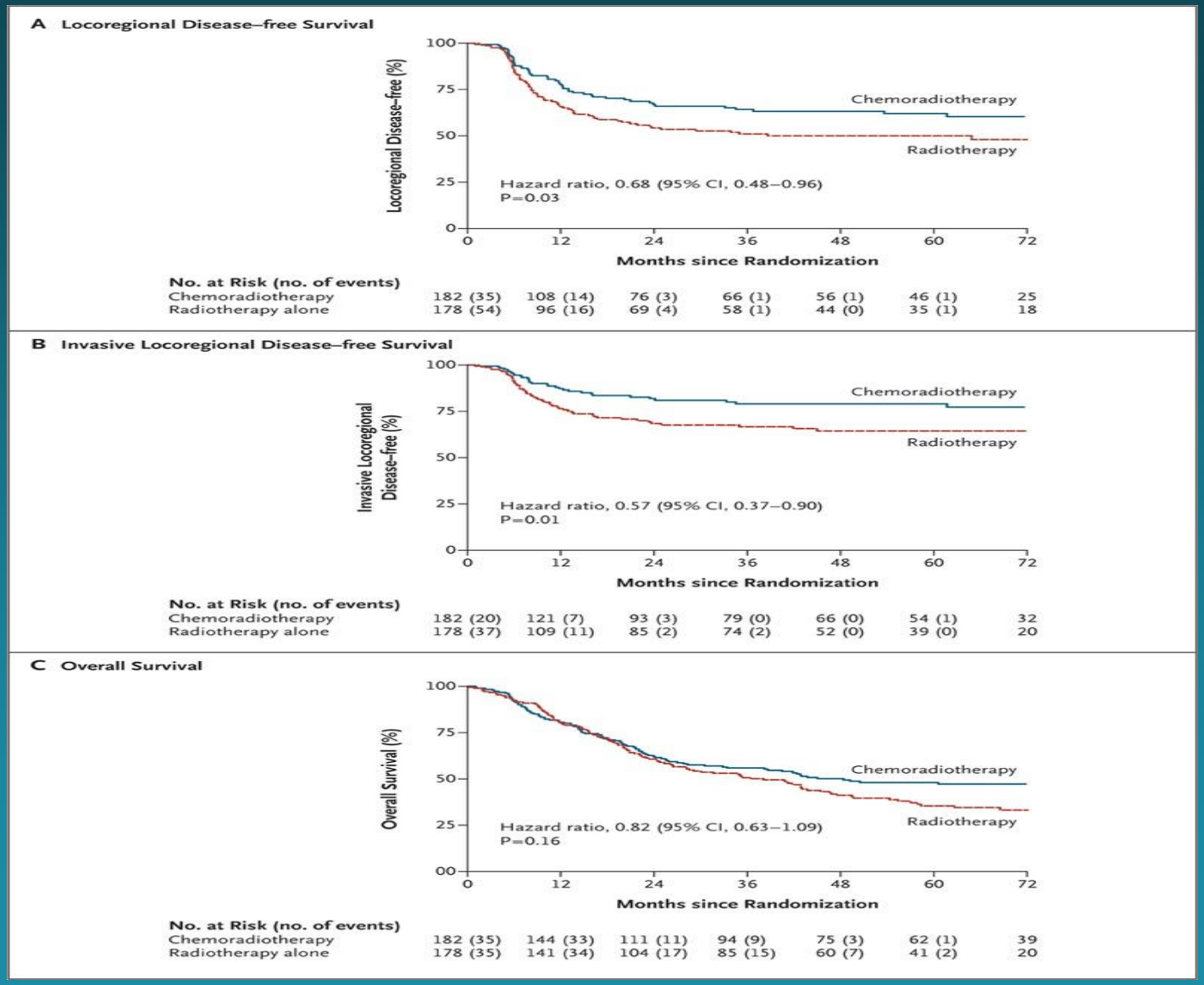
ChemoRT vs RT alone in Bladder Ca

James N, et al N Engl J Med 2012



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Background

- Bladder cancer is increasing in incidence in the elderly
- Pts > 75 years with muscle invasive bladder cancer (MIBC) had a mortality of 48% in cystectomy group and 61% in RT group at median follow up of 10 months [Tripathi A, et al. JCO 2017 and Taylor JA et al. Nat Clin pract urol 2009]
- Many patients are not candidates for chemotherapy due to comorbid conditions, performance status, or having received prior chemotherapy with progression.
- Patients with comorbidities and elderly pts are underrepresented in prospective clinical trials.
- Finding therapy options for chemotherapy and cystectomy ineligible patient population is a huge unmet need.
- We have previously reported on use of capecitabine and RT in localized urothelial cancer in an elderly and sick population with 61% remission rate at 10 months. [Patel B, et al. Int J Rad Oncol Biol Phys 2005]
- We conducted a phase II trial in this patient population of concurrent nivolumab and radiation therapy

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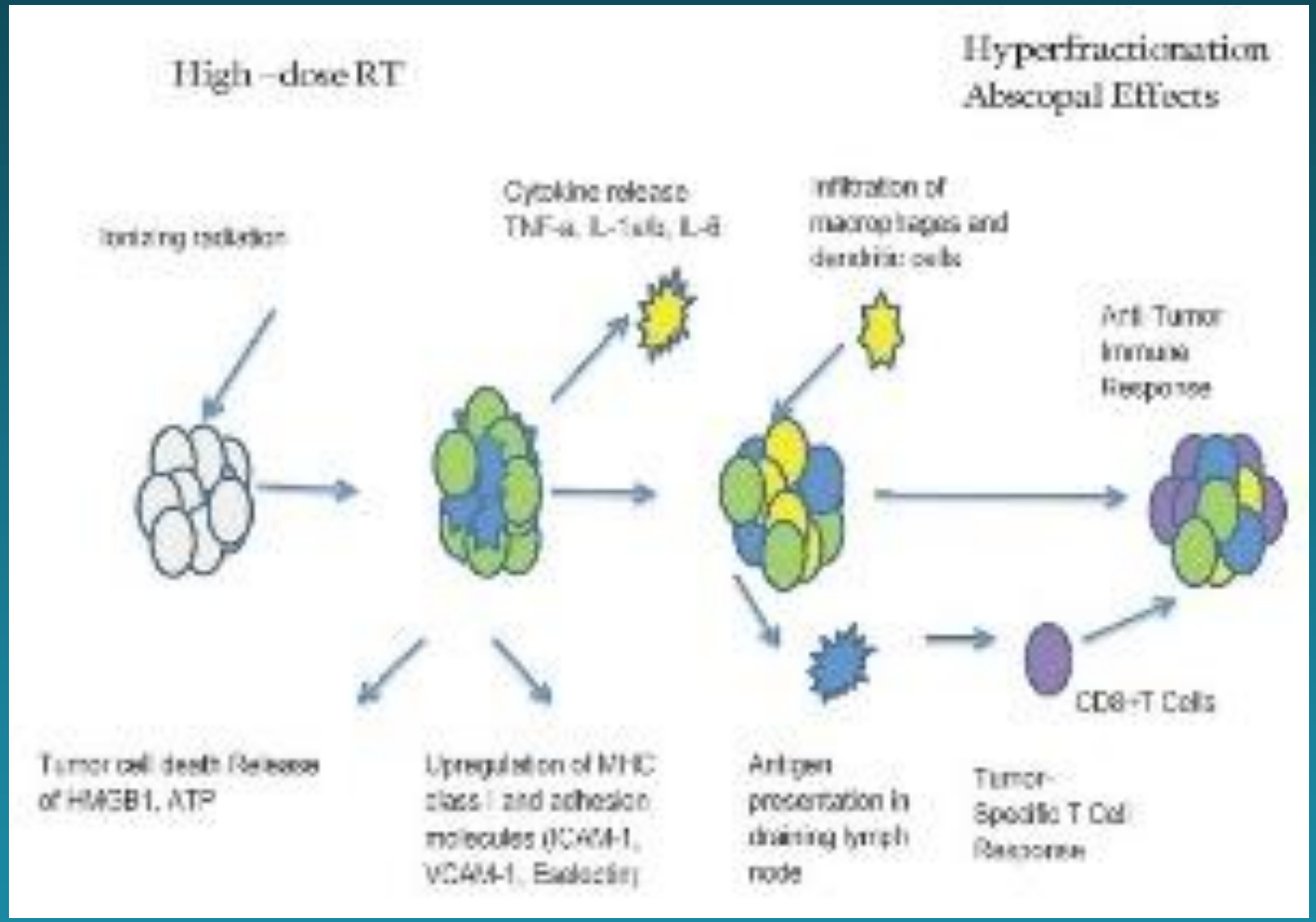
Rationale for Immunotherapy and RT

Asna N et al Curr Oncol 2018



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Objectives

- **Primary objective:**
- To compare the 12-month rate of progression-free survival achieved with the combination of nivolumab, a programmed death (PD-1) inhibitor, and radiation therapy in localized/locally advanced urothelial cancer patients, to a historical control reference rate.
- **Secondary Objectives:**

1) To assess the toxicity of concurrent nivolumab and radiation therapy in urothelial cancer.
2) To determine overall response rate (ORR).
3) To determine metastasis-free survival (MFS).
4) To determine overall survival (OS).
5) To evaluate the quality of life and bladder functioning during and after the therapy.
6) To explore the relationships of PD-1 expression, PDL-1 expression, and the Th1/Th2 cytokine ratio to clinical outcomes (response, PFS, MFS, and OS).

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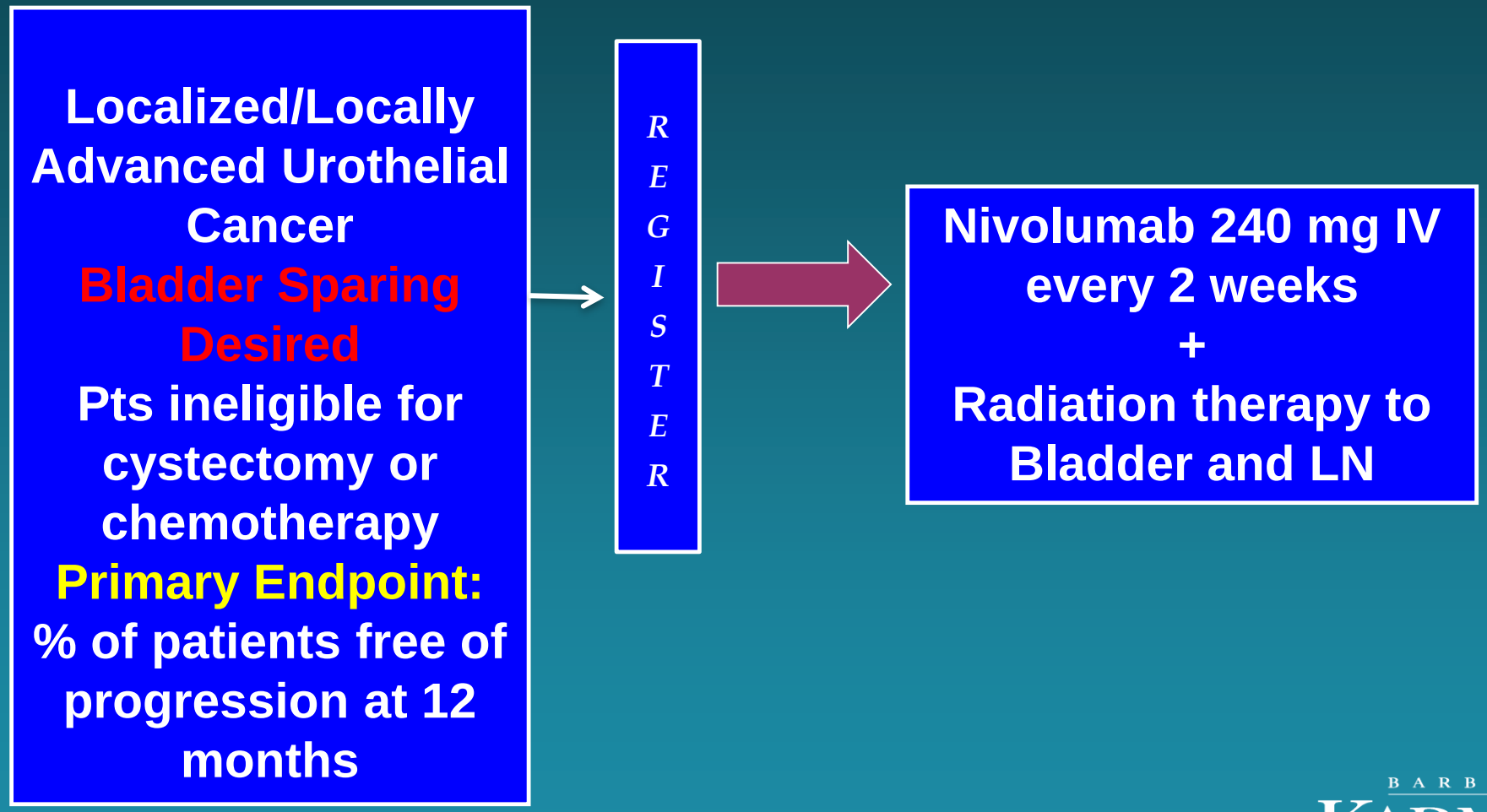
STUDY DESIGN



Multicenter trial.: KCI and Roswell park, 14 of 30 patients enrolled

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Statistical Design

- 1-arm 1-stage survival type design focused on the primary endpoint of the 12-month PFS rate.
- The study design assumptions are:
- 1) A population reference value of 50% 12-month PFS rate from standard of care with RT alone
- 2) A hypothesized 75% 12-month PFS rate for patients treated with Nivolumab+RT;
- 3) Accrual time of 24 months;
- 4) Significance level alpha = 0.025 (1-sided, due to the directional hypothesis);
- 5) Power = 0.95 (high due to the unmet need for improved therapy options for study eligible patients).
- **Sample size of 30 evaluable patients**

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Patient Eligibility

- Histologically confirmed muscle invasive urothelial carcinoma
- No e/o distant metastasis
- Serum creatinine < 1.5 X institutional ULN
- Not candidates for surgery or standard chemoradiation strategy due to any of the following;

---Zubrod performance status of 2

---creatinine clearance $\leq$ 60ml/min

---cardiac disease

--neuropathy

---intolerance to previous treatment

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Radiation Therapy

- Radiation Therapy (RT) had to be started within +/- 3 days of nivolumab administration.
- RT would be administered at a total dose of 64 Gy in 32 fractions over a 6-8-week period in all patients.
- Inclusion of external iliac, internal iliac, perivesical, presacral and obturator nodes, as well as, the prostate in male patients, is at the discretion of the treating physician.
- In node positive disease, the pelvic lymph nodes had to be included in the initial treatment field.
- The total PTV64 Gy dose delivered will be 64 Gy in 2 Gy per fraction.

Study Plan

- The primary endpoint is progression free survival rate at 12 months.
- Nivolumab is started within 3 days of radiation therapy and is administered at the dose of 240 mg intravenously every 2 weeks for a maximum of 6 months.
- Radiation therapy is per standard of care for bladder cancer.
- Imaging and cystoscopy and biopsy evaluation is required at months 3, 6 and 12 and then annually until progression.

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Correlative Analyses

- PD-1, PDL-1, TILs
- Serum cytokines: Th1/Th2
- Correlation with PFS

Patient Reported Outcomes:

- FACT-IT Questionnaires
- Bladder Symptom Index Questionaires

Results: Patient Characteristics

Characteristic	N=14 (%)
Median age	71years [54-95 years]
Gender : Male/Female	12 (86%) /2 (14%)
Race : AA/CA	3 (21%) /11 (79%)
T stage: T3, T4/ T2	2 (14%) /12 (86%)
Prior intravesical BCG therapy	3 (21%)
Prior Chemo	2 (14%)
Lymph Node Metastases	1 (7%)

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Toxicities

Adverse Events	N=14 (Grade)
Rash	1(Grade 3)
Diarrhea	4 (Grade 2)
Dehydration	2 (Grade 2)
Hypothyroidism	2 (Grade 2)
Immune/RT Cystitis	3 (Grade 2)
Fatigue	4(Grade 2)
Transaminitis	1 (Grade 3)
Urinary Infection	2 (Grade 2)
Anemia	3 (2 Grade 2 and 1 Grade 3)
Steroid Use	9 (64.2%)

Efficacy Results

- 8 patients are evaluable at 6 month assessment
- 5 patients demonstrated complete remission
- 1 showed residual CIS
- 4 of 11 patients had PDL-1 combined positive score (CPS) of 5, 10, 15 and 40%. Of the non responders only 1 had CPS of 5%, all others were 1% or less.
- Preliminary immune evaluation results indicate an improvement in CD4:CD8 ratio, natural killer (NK) cell expansion as well as enhanced expression of T cell and NK cell activation markers.

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Conclusions

- Concurrent nivolumab and radiation therapy is tolerable
- Promising efficacy is noted even in an elderly population with multiple comorbidities.
- The regimen is worthy of investigation in this patient population with urothelial cancer
- The pretherapy CPS maybe a potential biomarker for selection of patients who will not benefit and should be directed to chemotherapy with RT.

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Acknowledgements

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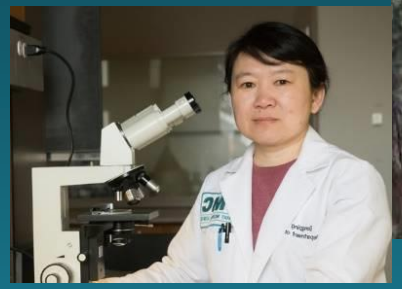
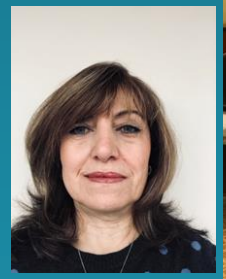
  Dr Saby George and the Roswell Park Team
- Radiation and Med Oncology team at Karmanos/McLaren
- Clinical trials office staff
- **Patients and their Families**





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