



Alliance A031501: Phase III Randomized Adjuvant Study of MK-3475 (Pembrolizumab) in Muscle Invasive and Locally Advanced Urothelial Carcinoma (AMBASSADOR) vs Observation

Andrea B. Apolo, MD and Jonathan Rosenberg, MD

National Institutes of Health and Memorial Sloan Kettering Cancer Center

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Rationale

Rationale

Objective

Study Schema

QOL Measurements

Key Eligibility Criteria

Follow Up

- Patients with high-risk muscle-invasive bladder cancer (MIBC) have a poor prognosis.
- Radical cystectomy remains the standard treatment in the United States and much of Europe. Yet despite substantial improvements in surgical techniques, mortality from metastatic recurrence remains high.
- Although cisplatin-based neoadjuvant chemotherapy (NAC) has been shown to improve survival, a large number of patients are resistant to cisplatin-based chemotherapy or have persistent muscle-invasive disease despite aggressive chemotherapy.
- A large number of MIBC patients have persistent muscle-invasive disease despite neoadjuvant chemotherapy (NAC). These patients have a poor 5- year survival rate
- Almost half of MIBC patients are not cisplatin-eligible and thus we need additional treatment options.
- These two patient populations will be enrolled in this clinical trial of adjuvant MK-3475 (pembrolizumab).
- Pembrolizumab, a PD-1 inhibitor, has demonstrated significant activity and is FDA-approved for patients with advanced/chemotherapy-refractory metastatic urothelial carcinoma.

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Dual Primary

- To determine DFS and OS in all patients with muscle-invasive bladder and upper-tract urothelial carcinoma treated with adjuvant MK-3475 (pembrolizumab) vs. observation.

Secondary

- To determine DFS and OS in PD-L1 positive and negative patients with muscle-invasive bladder and upper-tract urothelial carcinoma treated with adjuvant MK-3475 (pembrolizumab) vs. observation.
- To characterize the safety and tolerability of MK-3475 (pembrolizumab) when administered in the adjuvant setting in patients with muscle-invasive bladder and upper-tract urothelial carcinoma.

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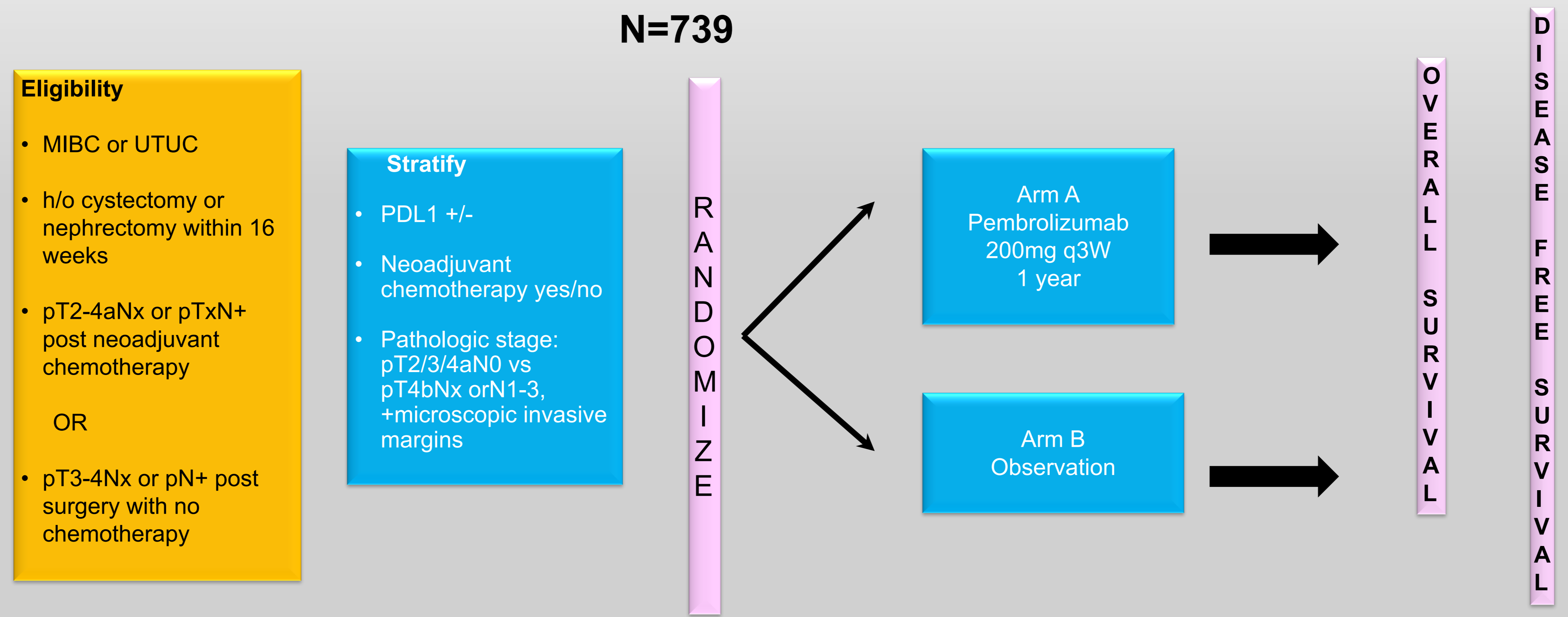
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Treatment is to continue until metastatic recurrence or unacceptable toxicity for up to one year. Metastatic recurrence is defined by a new lesion on CT scan. Patients will be followed for a total of 5 years from the date of registration or until death, whichever comes first.



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Quality of Life (QOL) Measurements

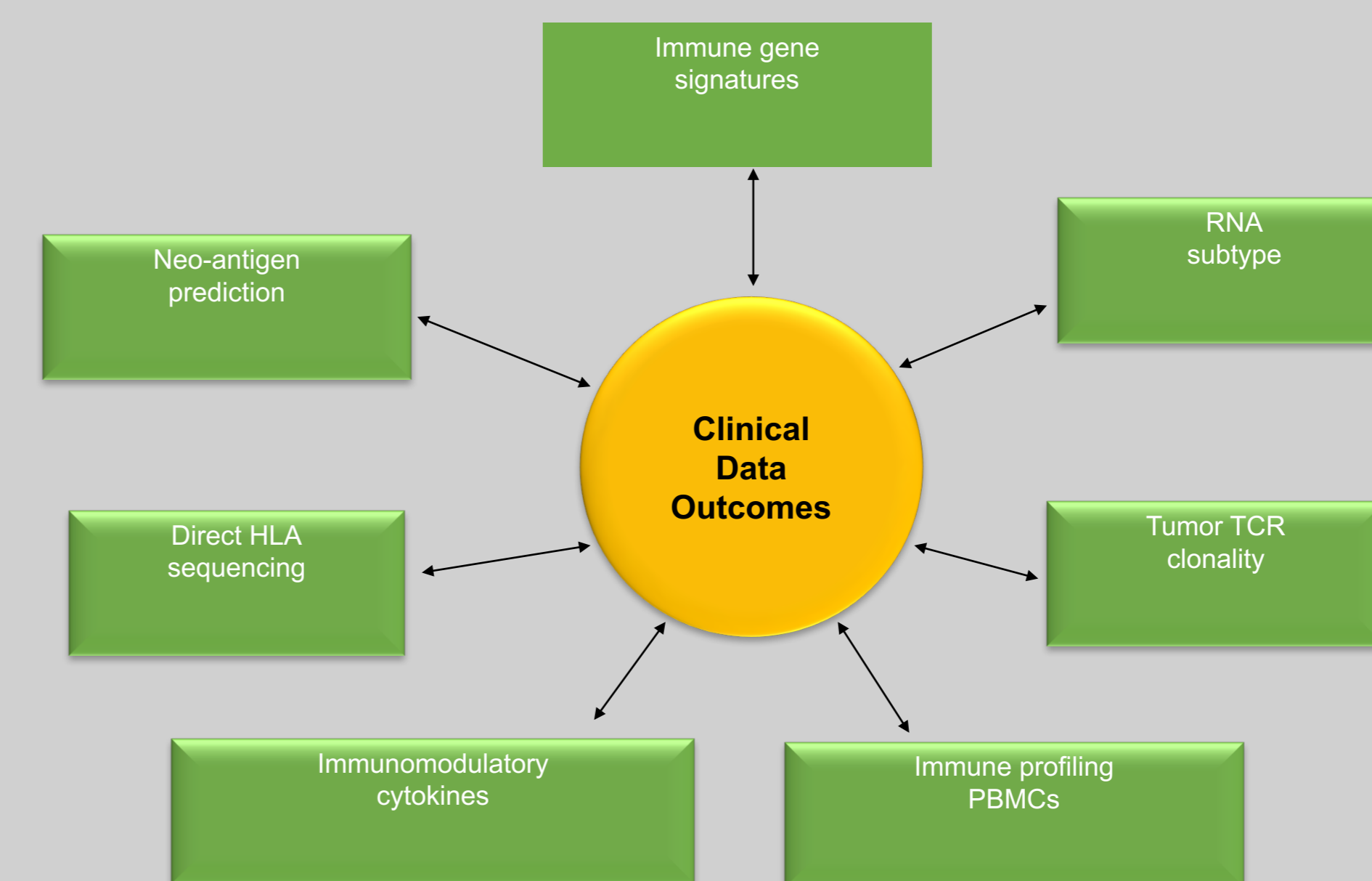


QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates. It will take approximately one minute to complete this measure.²⁻⁴

Quality of Life Correlative Study Objectives

- To compare health-related quality of life (HRQL) as assessed by the EORTC QLQ-C30 between patients randomized to MK-3475 (pembrolizumab) vs. observation.
- To compare urinary symptoms as assessed by EORTC QLQ-BLM30 between patients randomized to MK-3475 (pembrolizumab) vs. observation.
- To compare patient-reported fatigue, diarrhea, and pain between patients randomized to MK-3475 (pembrolizumab) vs. observation.
- To compare health utilities and QALYs between patients randomized to MK-3475 (pembrolizumab) vs. observation.
- To compare other scale scores of the EORTC QLQ-C30, EORTC QLQ-BLM30, and EQ5D-5L between patients randomized to MK-3475 (pembrolizumab) vs. observation.
- To compare global quality of life, symptoms, health utilities, QALYs, and other scale scores of the three questionnaires between patients randomized to MK-3475 (pembrolizumab) vs. observation within subgroups defined by each of the stratification factors.

Correlatives



2 - Tan, A., et al. A patient-level meta-analytic investigation of the prognostic significance of baseline quality of life (QOL) for overall survival (OS) among 3,704 patients participating in 24 North Central Cancer Treatment Group (NCCTG) and Mayo Clinic Cancer Center (MC) oncology clinical trials. *in ASCO Annual Meeting Proceedings. 2008.*
3 - Sloan, J., et al. A patient-level pooled analysis of the prognostic significance of baseline fatigue for overall survival (OS) among 3,915 patients participating in 43 North Central Cancer Treatment Group (NCCTG) and Mayo Clinic Cancer Center (MC) oncology clinical trials. *in ASCO Annual Meeting Proceedings. 2009.*
4 - Galsky, M.D., et al., Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. *J Clin Oncol, 2011. 29(17): p. 2432-8.*



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Pre-Registration

- Histologically confirmed muscle-invasive urothelial carcinoma of the bladder or upper tract; variant histology allowed as long as urothelial carcinoma is predominant; pure small-cell carcinoma is excluded
- Paraffin tissue samples obtained by transurethral resection of muscle-invasive bladder tumor, upper tract resection, cystectomy/nephrectomy/ureterectomy, or nephroureterectomy; specimen submission is mandatory prior to registration
- Patient must fit into one of the following three categories:
 - Patients who received neoadjuvant chemotherapy and pathologic stage at surgical resection is \geq pT2 and/or N+, or +microscopic invasive margins **OR**
 - Patients who are not cisplatin-eligible (according to \geq 1 of the following criteria: Eastern Cooperative Oncology Group [ECOG] performance status of 2, creatinine clearance $<$ 60 mL/min, grade \geq 2 hearing loss, grade \geq 2 neuropathy, or New York Heart Association class III heart failure) and pathologic stage at surgical resection is \geq pT3 or pN+, or +microscopic invasive margins **OR**
 - Patients that decline adjuvant cisplatin-based or other systemic chemotherapy based on an informed discussion with the physician and pathologic stage at surgical resection is \geq pT3 or pN+, or +microscopic invasive margins

Registration

- Results of central PD-L1 testing available; Q2 Solutions will forward the PD-L1 results to the statistical center and the statistical center will notify the site that the result is available; the notification from the Alliance registration/randomization office will serve as a confirmation of this eligibility criteria; after sites receive the confirmation e-mail from Alliance they can register the patient.

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