SITC Guidelines
Neoadjuvant Therapy

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Disclosures

- Clinical trials
  - Aura Bioscience, FKD, JBL (SWOG), Genentech (SWOG), Janssen (SWOG), Merck (Alliance), Surge Therapeutics, Vaxiion, Viventia
- Consultant/Advisory Board
  - Aura Bioscience, BMS, C2iGenomics, Ferring, Incyte, Pfizer/EMD Serono, Protara, UroGen, Vaxiion, Verity
- Patent – TCGA classifier
- Honoraria – Dava, Grand Rounds Urology, UroToday

Rationale for Neoadjuvant Systemic Therapy

- Muscle Invasive cancer is a systemic disease
- Measurable disease at time of treatment initiation
- Treat micro-metastatic disease up front
- Downstaging “unresectable” disease to “resectable”
- Disadvantages
  - Over-treatment for many patients
  - Ineffective chemotherapy delaying definitive local tx
- Guidelines recommend for all cisplatin eligible patients based on level I evidence

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We Must Improve Survival for Patients With MIBC

- Major challenge with current paradigm: one size does not fit all
- Up to one-half of patients are cisplatin ineligible
- Some tumors (10-15%) cured (pT0) by TURBT
- Some tumors (37%) cured by cisplatin-based NAC
- Many resistant to NAC and now adjuvant IO

- *Much of this heterogenous response may be secondary to molecular heterogeneity and lack of validated predictive and prognostic biomarkers*

Target Population for Clinical Trials

- cT2-4a, N0-1, M0
- Clinical staging
  - Pelvic EUA, TURBT, high quality CT or MRI
- Stratification covariates associated with risk for locally advanced dx
  - Tumor associated hydronephrosis
  - Variant histology – data lacking on impact on success NAC
  - T3b
  - LVI
  - Incomplete TURBT

Target Population for Clinical Trials

- Exclusions
  - Small cell or neuroendocrine histology – treat with difference chemo regimen
  - Minority urothelial histology < 25%

- Neoadjuvant therapy precedes definitive loco-regional therapy with radical or partial cystectomy (rarely indicated), or chemo-radiation

Neoadjuvant Therapy Trial Design

- Randomized, controlled PhIII
- SOC informed by current guidelines
  - Cisplatin eligible: 3-4 cycles cisplatin-based NAC + RC or CRT
    - CrCl ≥ 50-60 ml/min, PS < 2
    - Excludes: Grade ≥ 2 neuropathy; NYHA III/IV heart failure; grade ≥ 2-3 hearing loss
  - Non-cisplatin eligible: RC + adjuvant CPI or CRT
  - Cystectomy eligibility can be enrolled in both RC and CRT based trials
  - For CRT – no prior pelvic irradiation
  - CPI – patients with well- controlled HIV infection, treated hepatitis B or C infections, and well-controlled or remote autoimmune conditions

Neoadjuvant Therapy Trial Design

- Primary endpoints:
  - Path CR (not validated) and EFS – consider co-primary
  - For Bladder sparing cCR ad BIEFS (CRT)
    - CR determined by Cystoscopy, Bx/re-TURBT, cytology
    - Does not include CIS
    - Surveillance cysto, cytology following NMIBC guidelines for high risk dx
- Secondary endpoints
  - OS, DSS, MFS
  - TMT – NMIBC ad MIBC recurrences
  - NAC, surgery and CRT related toxicity, QOL

Neoadjuvant Therapy Trial Design

- Statistical assumptions
  - Effect size: 10% increase in EFS
  - Assume 3-year EFS of 50% in control arm
  - 344 events required
  - HR = 0.74
  - Alpha 0.05
  - Average follow up 3 years
  - Requires 766 patients

Neoadjuvant Therapy Trial Design

- Follow-up
  - Baseline – CT chest; CT or MRI prior to TURBT
  - Interim cystoscopy prior to RC an option but not required
  - Challenges with clinical staging requires explicit language in protocols detailing required elements and rigorous QC to harmonize across sites
- Recurrence events confirmed by independent review
- Patients should be followed for a minimum of 3 years.

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SWOG 8710

- Accrual goal 298 patients
- Registered and eligible n=307
- Power 80% to detect 50% or greater improvement in median survival
- Type I error 0.05

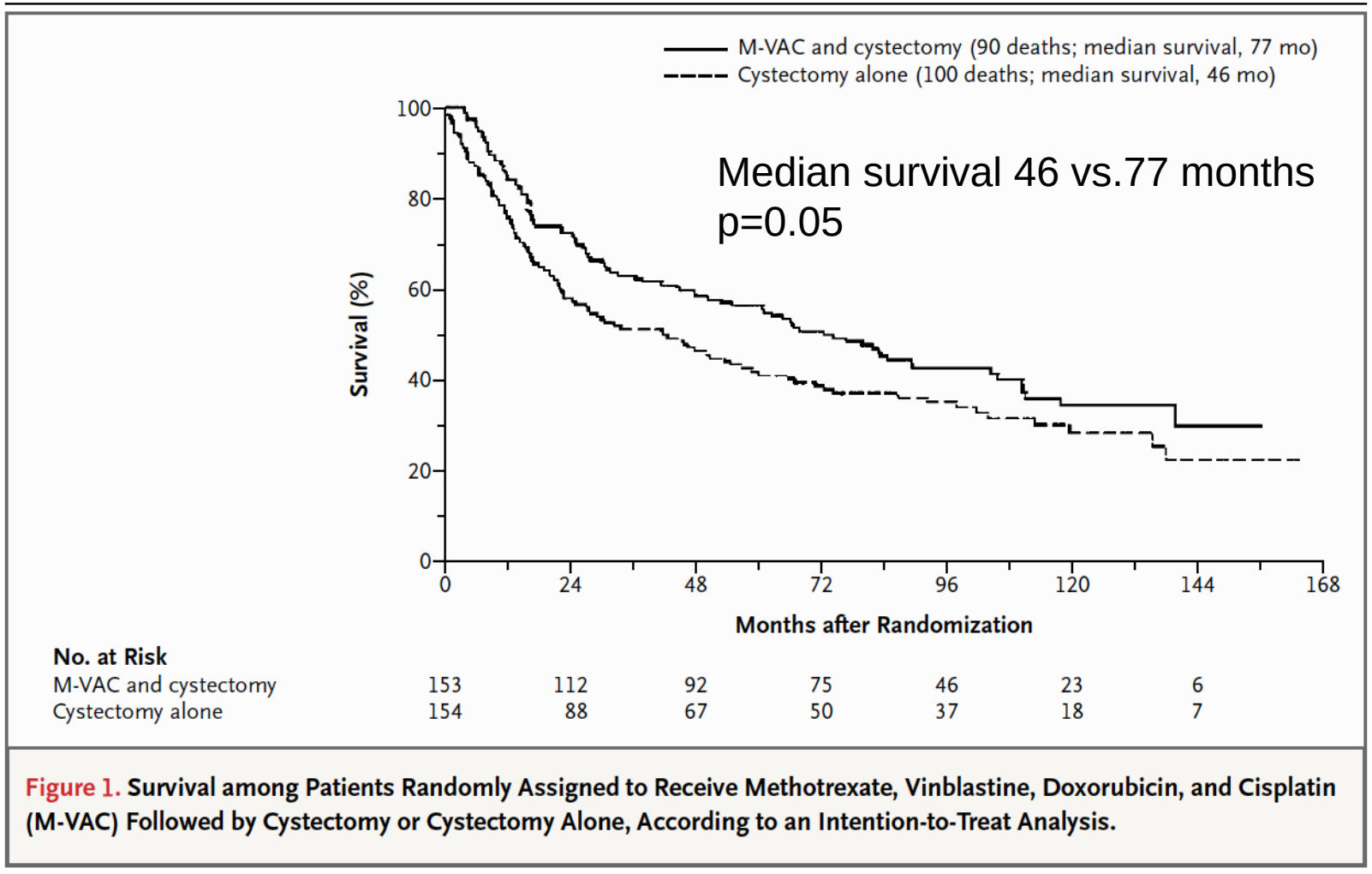
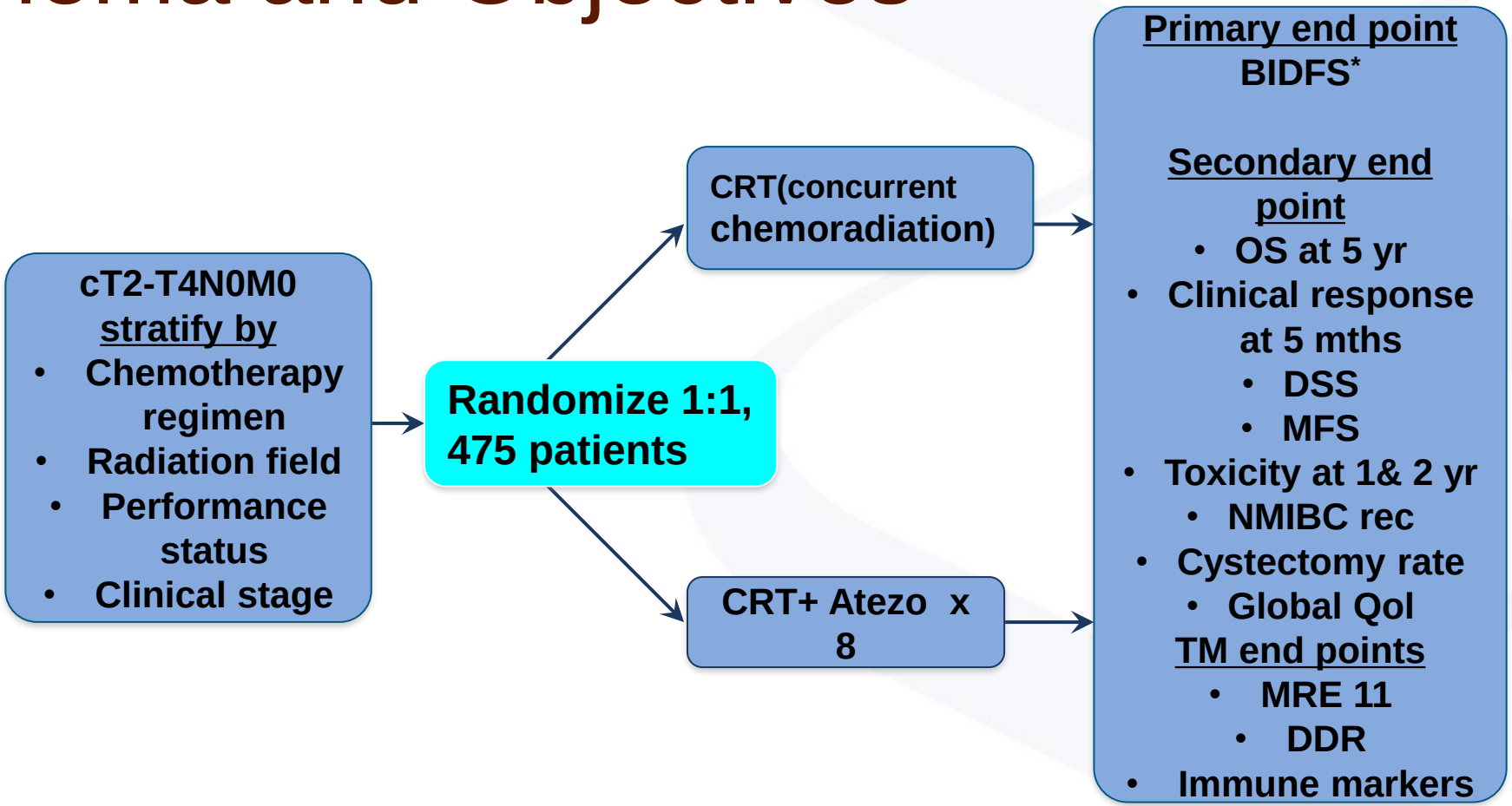


Figure 1. Survival among Patients Randomly Assigned to Receive Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Followed by Cystectomy or Cystectomy Alone, According to an Intention-to-Treat Analysis.

Grossman, et al NEJM 349:859, 2023

SWOG/NRG S1806 Schema and Objectives



*BIDFS bladder intact disease free survival- includes
- muscle invasive recurrence in the bladder,
- regional pelvic soft tissue or nodal recurrence,
- distant metastases,
- bladder cancer or toxicity related death
- or cystectomy

Statistical Design

- Primary endpoint: BIDFS
  - Assume: Median BIDFS of CRT= 52%
  - Analysis: 85% power, 1-sided α=0.025 to detect, 12% improvement in BIDFS with HRa=1.46
  - Randomize: 1:1 (CRT vs CRT+ atezolizumab)
  - Sample size: n=432 eligible + 10% ineligible = 475 total

Enrollment	8-12/month
Accrual	4 years
Completion	7 years

- Interim analyses: to test efficacy and futility
- Contingency Plan: If slow accrual after 2 yr: n=232; HRa=1.67 (52% vs. 67% at 3 yrs)

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Conclusions

- SITC guidelines clearly describe eligibility and target population for neoadjuvant therapy trials in MIBC
- Addresses necessary statistical power to detect incremental but clinically significant improvements in EFS
- As more agents move from locally advanced/metastatic to clinically localized MIBC, SITC guidelines provide framework for trial design for “all comers” and covers patients undergoing cystectomy and bladder preservation

Keynote B15/EV 304

- MIBC T2-4aN0 and T1-4aN1
- Urothelial ≥ 50%
- Cisplatin eligible
- RC planned
- N= 784
- Arm A: EV + pembro x 4 followed by RC+PLND, followed by 5 cycles of adjuvant EV + 13 cycles of adjuvant pembro
- Arm B: GC x 4 followed by RC+PLND, followed by observation

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Keynote B15/EV 304

- Is GC an inferior regimen compared to MVAC (VESPER)?
- No adjuvant therapy in Arm B – not consistent with current SOC
- Comparing apples to oranges with adjuvant therapy in Arm A but not Arm B
- EV toxicity vs GC toxicity

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Keynote-905/EV303

- MIBC T2-4aN0 and T1-4aN1
- Urothelial ≥50%
- Cisplatin ineligible or decline cisplatin-based treatment
- RC planned
- N= 857
- Arm A: Pembro q3 weeks up to 3 cycles followed by RC + PLND and adjuvant pembro q3 weeks up to 14 cycles a
- Arm B: RC + PLND followed by observation
- Arm C: EV pembro q3 weeks up to 3 cycles followed by RC + PLND and adjuvant EV + pembro up to 6 cycles and adjuvant pembro 200 mg IV Q3W up to 8 cycles

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Keynote-905/EV303

- More of a fair fight
- Current SOC for cisplatin ineligible is definitive locoregional therapy without NAC
- Arm A and Arm C both have similar duration of adjuvant therapy
- How well will EV be tolerated?l

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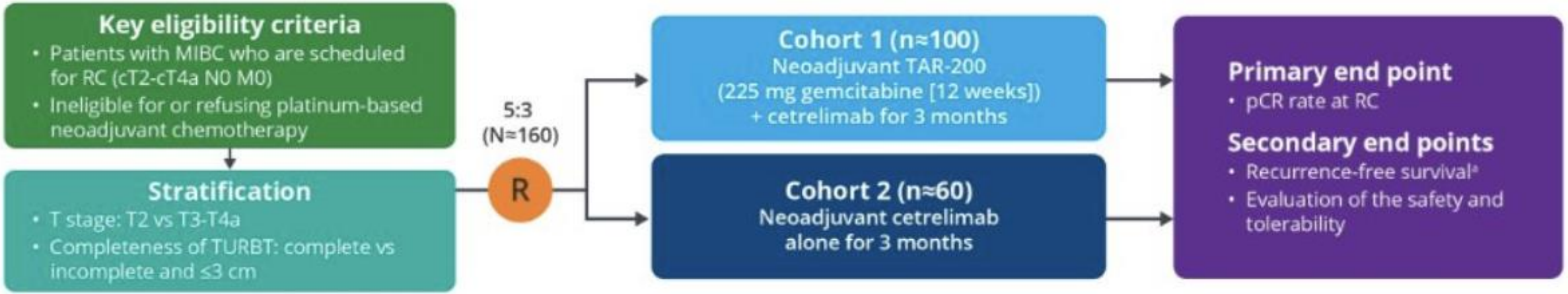
SunRISE-4

- MIBC T2-4aN0
- Stratified by completeness of TURBT (visibly complete vs incomplete and ≤3 cm) and tumor stage (cT2 vs cT3-4a)
- RC planned
- TAR 200 is pretzel with Gemcitabine
- CET – Cetrelimab anti-PD-1

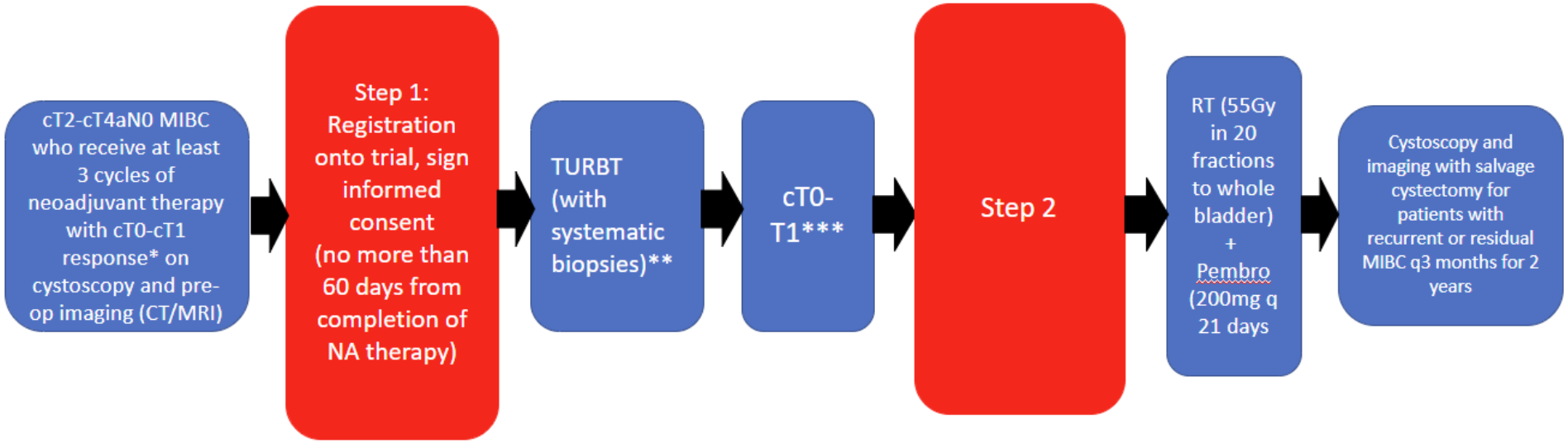
FIGURE 2: SunRISe-4 study schema



pCR, pathologic complete response; TURBT, transurethral resection of bladder tumor.
[a]Per Response Evaluation Criteria In Solid Tumors 1.1 or histologic evidence.

Treatment/Schema

Must have initial TURBT path diagnosing MIBC at time of registration



*Patients who receive NAC as their NAT must have at least 3 cycles of a cis-based regimen
**Patients found to have>T1 disease on TURBT will proceed to SOC cystectomy
***Diffuse cis patients will be excluded (>3cm area of contiguous cis or >3 separate locations of cis on TURBT (anterior/posterior/left/right/trigone)

Courtesy Leslie Ballas

Statistics

Study Design:

- The standard of care for this patient population is cystectomy. We would not be interested if the 3-year BIEFS were 45%, but we would be interested if it were 60% or better.
- With 112 eligible and evaluable patients we will have 82% power to declare that a regimen with a 60% BIEFS rate at 3 years is favorably active, and an 11% chance of declaring the regimen with a 3-year BIEFS of 45% is an active agent (false positive rate).

Courtesy Leslie Ballas