SIU UPDATES

ASCO GU

ASCO GENITOURINARY CANCER SYMPOSIUM

# Neoadjuvant and adjuvant therapy: Current indications, trials, and patient selection

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# Disclosures

**Andrea Necchi:**

Consulting or Advisory Role: Company: Roche, Bayer, Merck & Co. Inc., Astra Zeneca, Janssen, Astellas/Seattle Genetics, Clovis Oncology, BioClin Therapeutics

Travel, Accommodations, Expenses: Company: Roche, Merck & Co. Inc., Janssen, PeerVoice

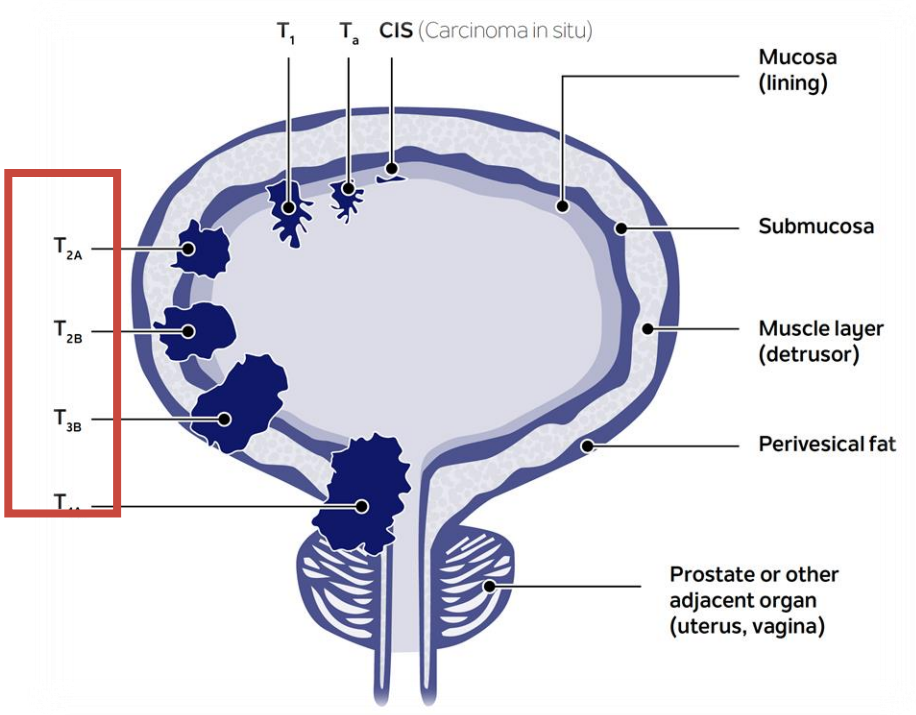
Research Funding (Institution): Company: Merck & Co. Inc., Astra Zeneca

**Thomas Powles:**

Honoraria: Bristol-Myers Squibb, Merck, Roche/Genentech

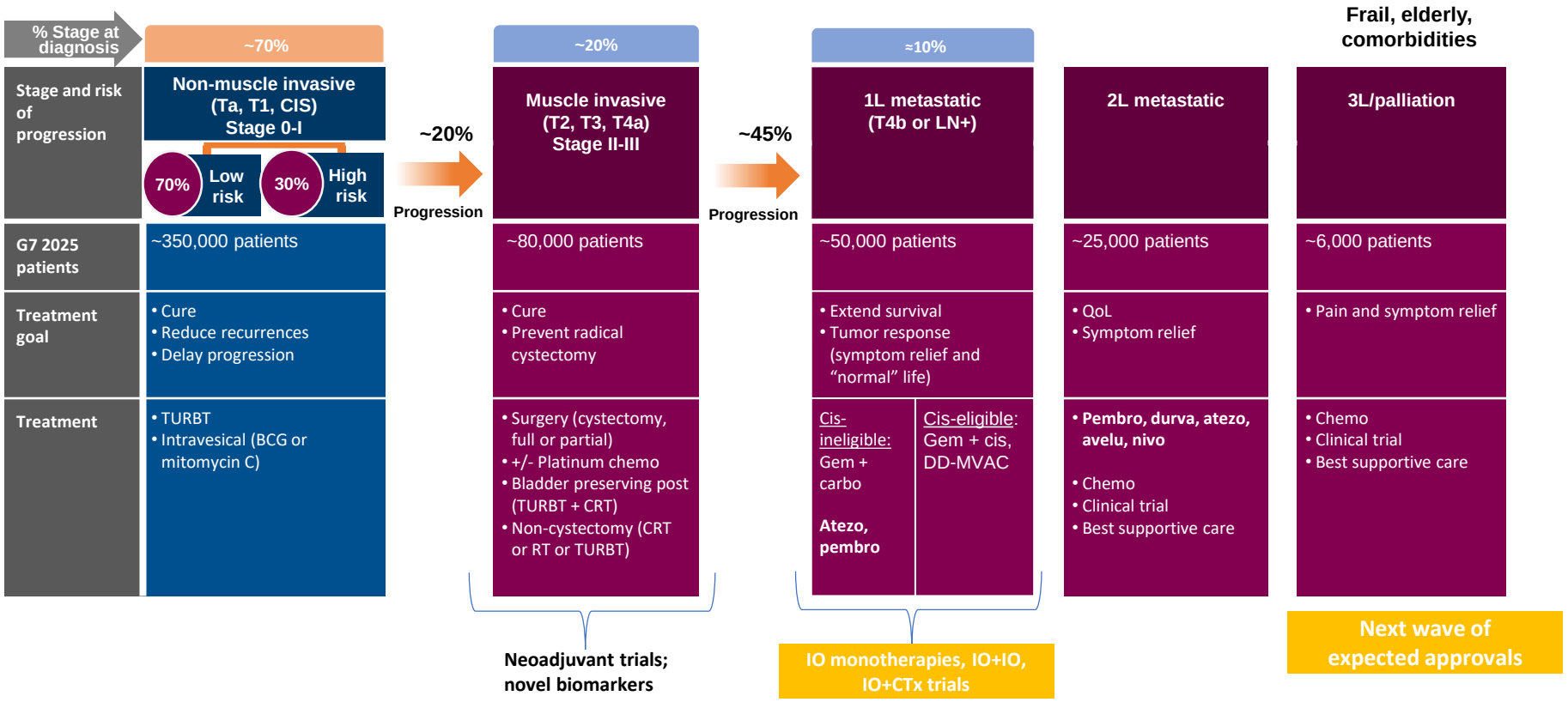
Consulting or Advisory role: Astra Zeneca, Bristol-Myers Squibb, Roche/Genentech, Merck, Novartis

Other relationship: Bristol-Myers Squibb, Ipsen



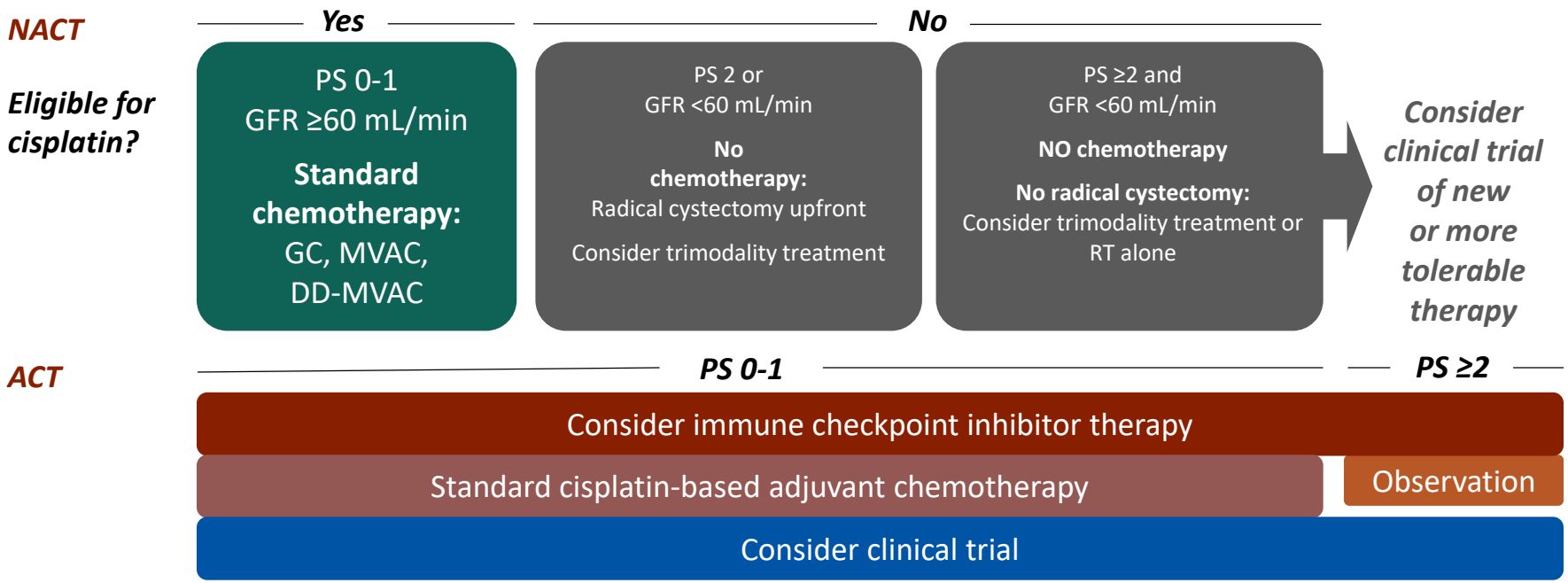

*From 2016 White Paper of Bladder Cancer*
*http://www.ecpc.org/da/pressroom/events/icalrepeat.detail/2016/04/20/60/119/launch-of-ecpc-paper-on-bladder-cancer*

# The UC Treatment Landscape Continues to Evolve




1L, first line; 2L, second line; BCG, Bacillus Calmette-Guerin; CRT, chemoradiation; CTx, chemotherapy; DD-MVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; QoL, quality of life; RT; radiation therapy; TURBT, transurethral resection of bladder tumor.

# How Emerging Clinical Data Will Impact the European Treatment Algorithm for MIBC



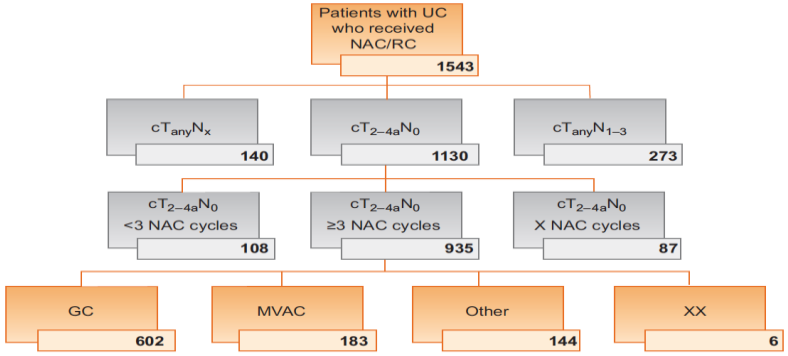

Available at: http://ime.peervoice.com/v/index.html?collection=505202977-2-2&presentationid=p1&Promocode=860#main

# Outcomes at 5 years after neoadjuvant chemotherapy and/or cystectomy in patients with muscle invasive bladder cancer*

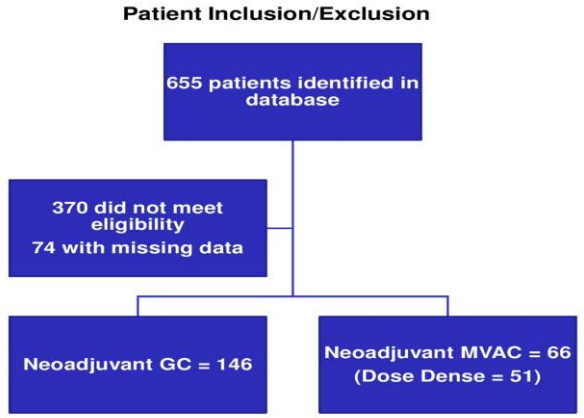
*data are derived from the Southwest Oncology Group (SWOG) trial 8710

Griffiths G, Hall R, Sylvester R, et al. J Clin Oncol. 2011;29:2171-2177
Galsky MD, Domingo-Domenech J. Clin Adv Hematol Oncol 2013;11:86-92

# Large retrospective data on the effectiveness of neoadjuvant chemotherapy in MIBC:




| | MVAC | GC | Other |
|---|---|---|---|
| Pathologic outcome, *n* (%) | | | |
| pT0N0 | 45 (24.5) | 144 (23.9) | 22 (15.3) |
| ≤pT1N0 | 82 (44.8) | 263 (43.7) | 36 (25) |
| Nodes removed, median (IQR) | | | |
| Extended LND | 27 (17-41) | 20 (13-29) | 15 (9-21) |
| Standard LND | 18 (11-25) | 14 (9-20) | 10 (5-15) |
| Positive nodes, median (range) | 0 (0-23) | 0 (0-50) | 0 (0-15) |
| Positive surgical margins, no. (%) | 14 (7.7) | 31 (5.1) | 19 (13.2) |
| Associated CIS, no. (%) | 62 (33.9) | 193 (32.1) | 45 (31.3) |

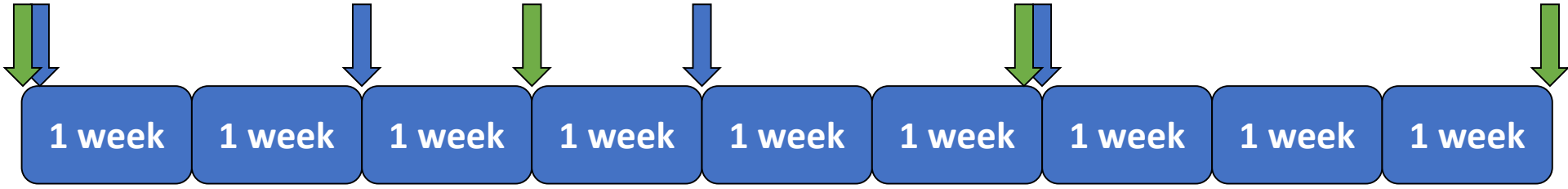



**Pathologic complete response rate for MVAC vs GC adjusted for propensity scores***

| | GC N=146 | MVAC† N=66 | Overall N=212 | OR [95% CI] P-value | OR* [95% CI] P-value | Imputed OR‡ [95% CI] P-value |
|---|---|---|---|---|---|---|
| **Path CR** | | | | | | |
| *Yes* | 45 (31%) | 19 (29%) | 64 (30%) | 0.91 [0.48-1.72] | 0.94 [0.48-1.83] | 0.95 [0.70-1.28] |
| *No* | 101 (69%) | 47 (71%) | 148 (70%) | P=0.77 | P=0.86 | P=0.74 |

Zargar H, Eur Urol. 2015 Feb;67(2):241-249; Galsky MD, Cancer. 2015 Aug 1;121(15):2586-93

## Emerging concepts: neoadjuvant dose-dense chemotherapy

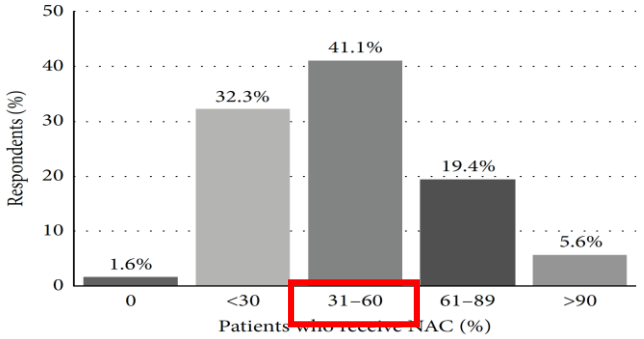


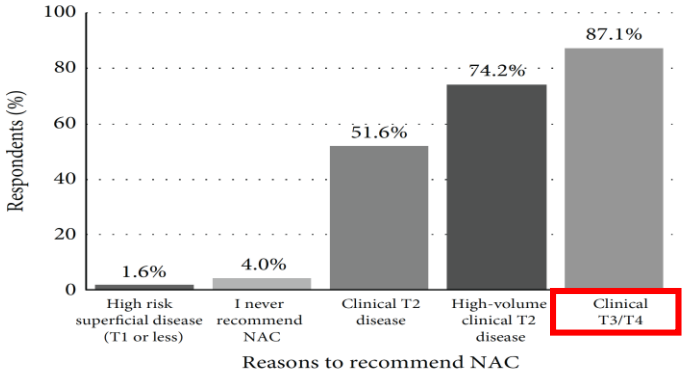

| Outcome | Standard dosing | Dose-dense schedule |
|---|---|---|
| pT0 | 25% | 17-28%[1,2] |
| pT<2 | 40-50% | 47-57%[1,2] |

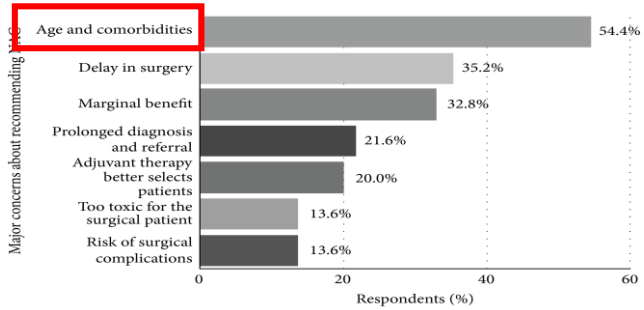
Dose-dense schedule
Standard dosing

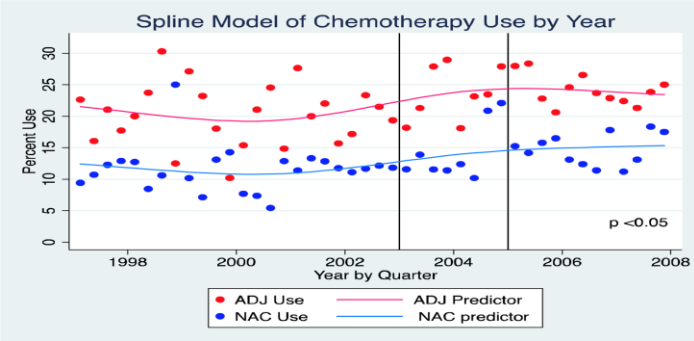

1. Choueiri TK, et al. J Clin Oncol 2014;32:1889-1894
2. Iyer G, et al. J Clin Oncol 2018 (Epub ahead of print)

# (Shifting) Use of neoadjuvant chemotherapy in the U.S.
# 1- results from the Urologic Oncology community




Cowan CG, et al. Adv Urol. 2014;2014:746298
See also Gray PJ et al. Eur Urol 2013;63:823-829

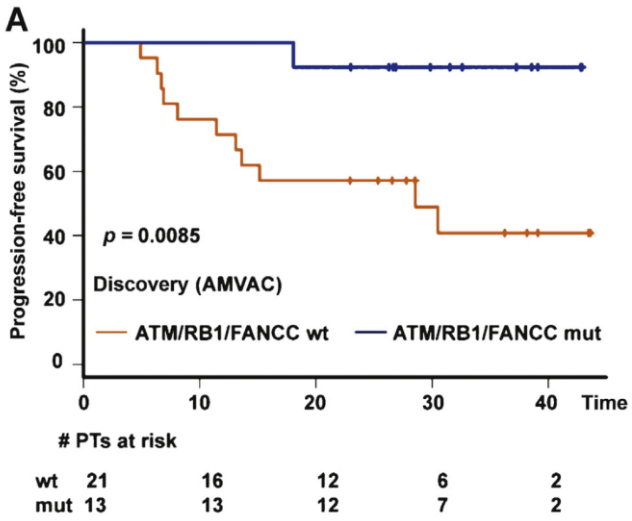
Keegan KA, et al. J Urol. 2012; 187:e216–7
See also NCDB data: Reardon ZD, et al. Eur Urol. 2015 Jan;67(1):165-70

Society of Urologic Oncology, Inc.

# Can we predict response and survival after neoadjuvant chemotherapy?

| Biomarker | N | Translational relevance | Reference |
|---|---|---|---|
| ERCC2 mutation | 50 | Association with pathologic response | *Van Allen EM et al, Cancer Discov 2014* |
| ERCC2 mutation | 48+54 | Association with improved OS in 2 independent cohorts of cisplatin-treated MIBC patients | *Liu D et al. JAMA Oncol 2016*<br>*Plimack ER et al, Eur Urol 2015*<br>*Plimack ER et al, ASCO 2014* |
| ATM/RB1/FANCC mutations | 34 | Association with improved pT<2 response and OS | *Plimack ER et al, Eur Urol 2015* |
| ATM/RB1/FANCC mutations | 25 | Association with improved pT<2 response | *Anari F et al, Eur Urol Oncol 2018* |
| ERBB2 mutations | 71 | Association with pT0 response | *Groenendijk FH et al, Eur Urol 2015* |
| DNA damage response (DDR) gene alterations | 46 | Association with pT<2 response and RFS with dose-dense GC | *Iyer G et al, J Clin Oncol 2018* |
| Single-sample genomic subtyping classifier | 343 | Basal tumors benefited the most from neoadjuvant chemotherapy administration | *Seiler R et al, Eur Urol 2017* |

# Can we predict response to neoadjuvant chemotherapy?
## ATM/RB1/FANCC (Discovery and validation cohorts)



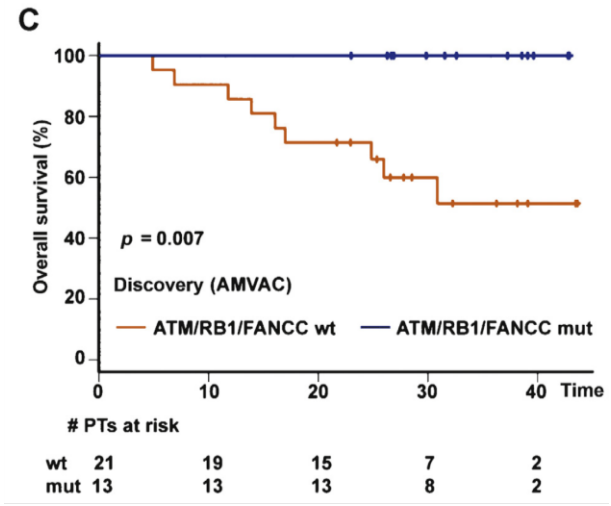



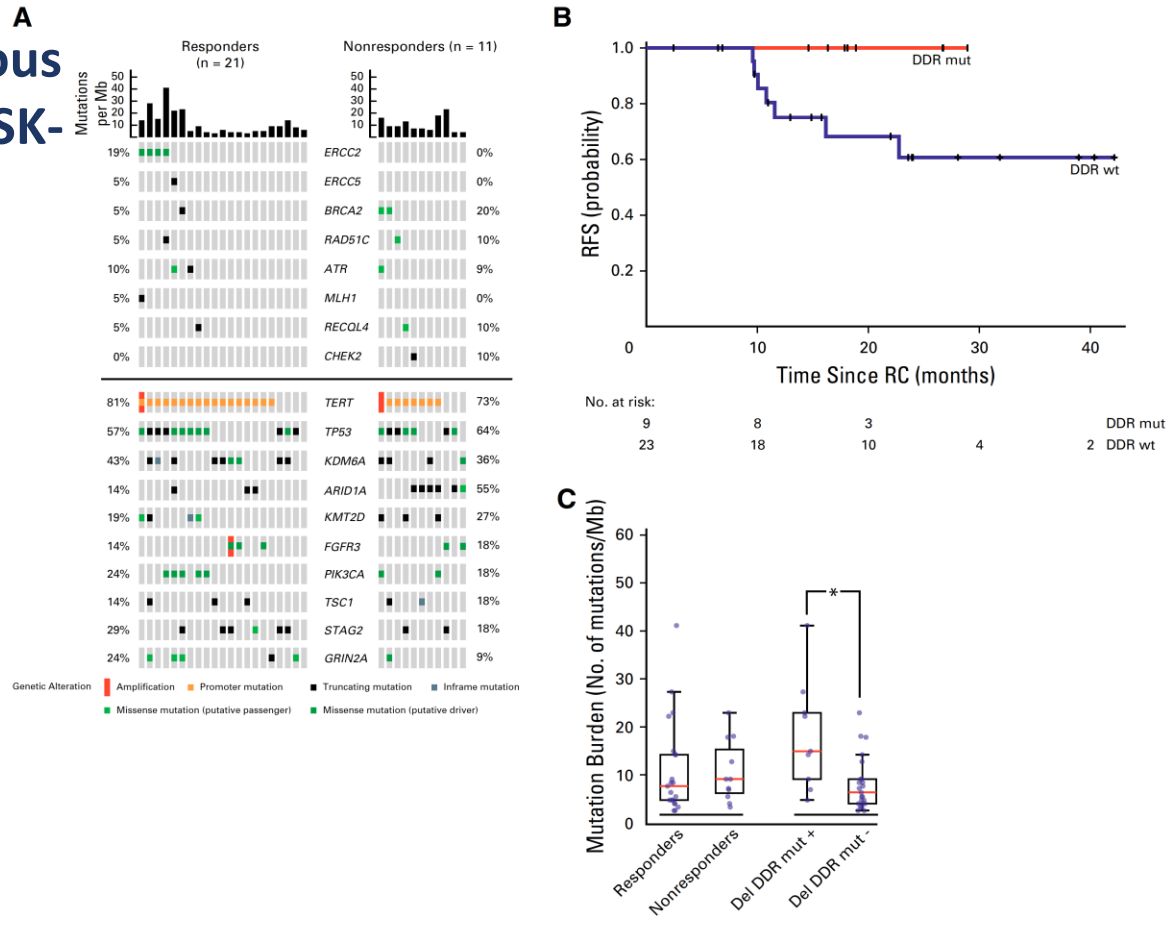

**Table 3 – Number of alterations as a predictor of response**

| Set | Response definition | RSPs ($n$) | NRSPs ($n$) | Mean alterations, $n$ (median) {range} | | $p$ value |
|---|---|---|---|---|---|---|
| | | | | NRSPs | RSPs | |
| Discovery ($n$ = 34) | pT0pN0cM0 | 14 | 20 | 18.65 (16) {8–32} | 25.36 (27) {11–39} | 0.024 |
| Discovery ($n$ = 34) | ≤pT1pN0cM0 | 15 | 19 | 18.58 (16) {8–32} | 25.00 (26) {11–39} | 0.030 |
| Validation ($n$ = 24) | pT0pN0cM0 | 9 | 15 | 15.33 (13) {7–29} | 22.67 (22) {14–35} | 0.018 |
| Validation ($n$ = 24) | ≤pT1pN0cM0 | 11 | 13 | 16.15 (15) {7–29} | 20.36 (21) {8–35} | 0.181 |

RSPs = responders; NRSPs = nonresponders.

Plimack ER et al, Eur Urol 2015

# Dose-dense GC and deleterious DDR genomic alterations (MSK-IMPACT)

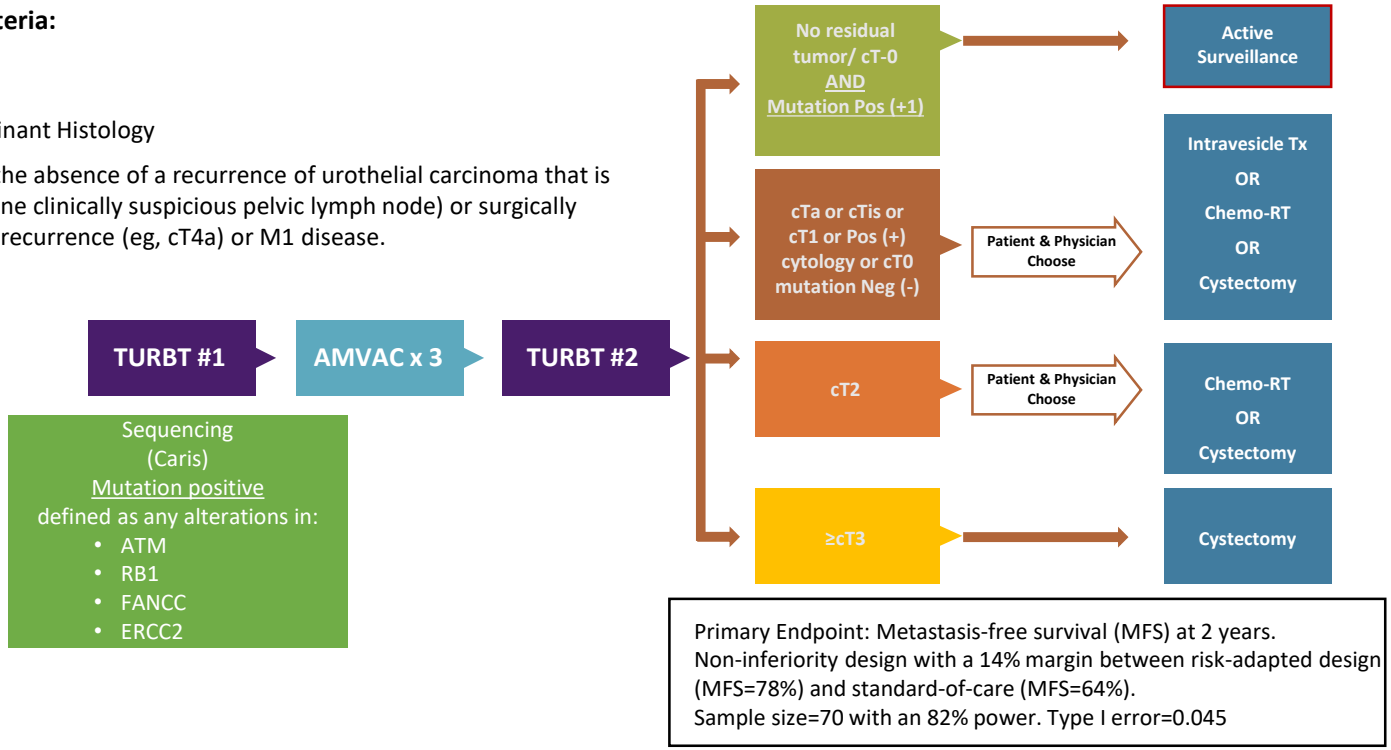



Iyer G, et al. J Clin Oncol 2018 (Epub ahead of print)

# A Phase II Trial of Risk Enabled Therapy After Initiating Neoadjuvant Chemotherapy for Bladder Cancer (RETAIN BLADDER) NCT02710734

**Major Inclusion Criteria:**

- cT2-T3 N0M0
- ECOG 0-1
- Urothelial Predominant Histology
- MFS is defined as the absence of a recurrence of urothelial carcinoma that is >cN1 (more than one clinically suspicious pelvic lymph node) or surgically unresectable local recurrence (eg, cT4a) or M1 disease.

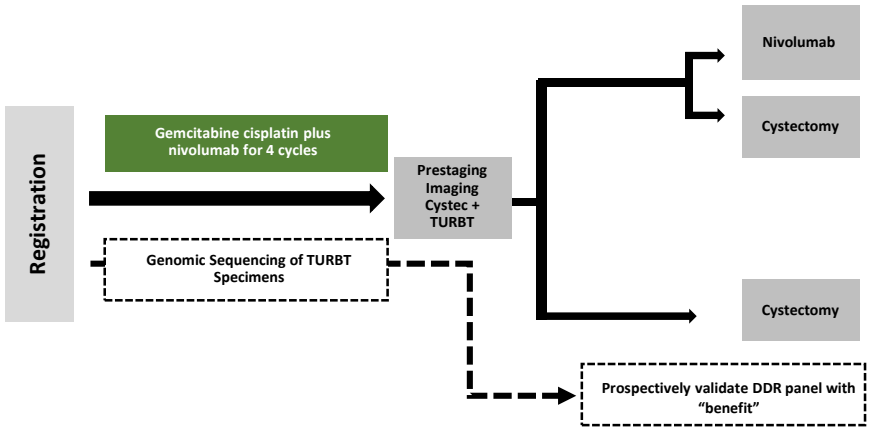



Study NCT02710734. ClinicalTrials.gov website. Accessed May 25, 2018

# Other risk adapted neoadjuvant studies in development

## Systemic Therapy: Gem Cis Nivolumab
## Biomarker: ATM, FANCC, ERCC2, or High TMB

**HCRN 16-257: Neoadjuvant gemcitabine, cisplatin, plus nivolumab in patients with muscle-invasive bladder cancer with selective bladder sparing**

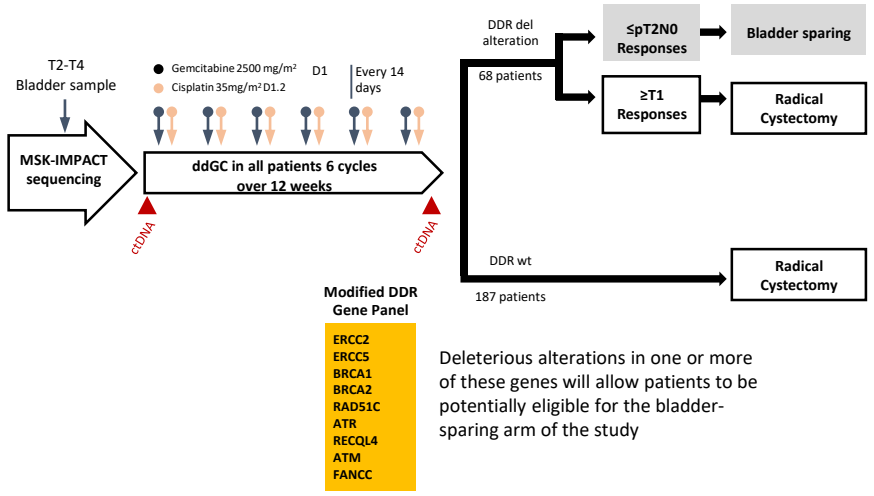



PI: Matt Galsky

Plimack E, AACR 2018 Oral presentation

## Systemic Therapy: ddGem Gem Cis
## Biomarker: DDR panel from the literature

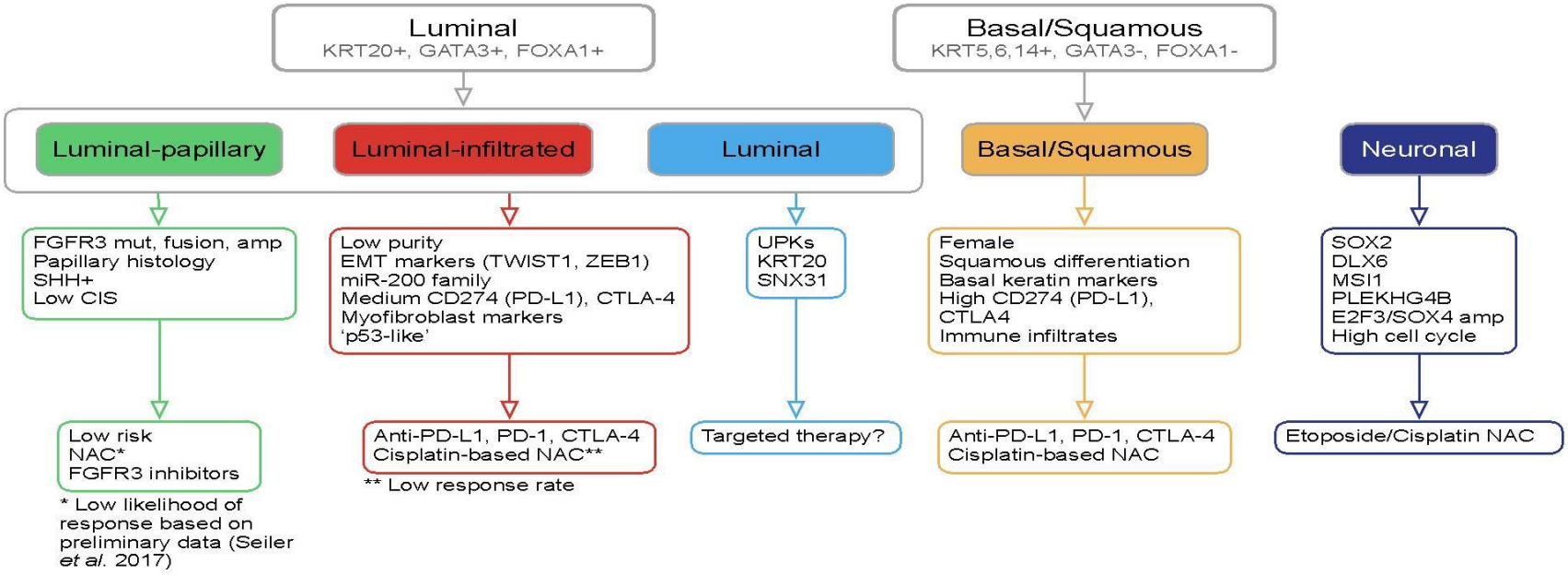
**AO31701: A phase II study of dose-dense Gemcitabine plus Cisplatin in patients with muscle-invasive bladder cancer with bladder preservation for those patients whose tumors harbor deleterious DNA damage response (DDR) gene alterations**




Gupta I, et al. J Clin Oncol 2018; 10.1200/JCO.2017.75.0158. [Epub ahead of print]

# Future Treatment Paradigm for MIBC (?)

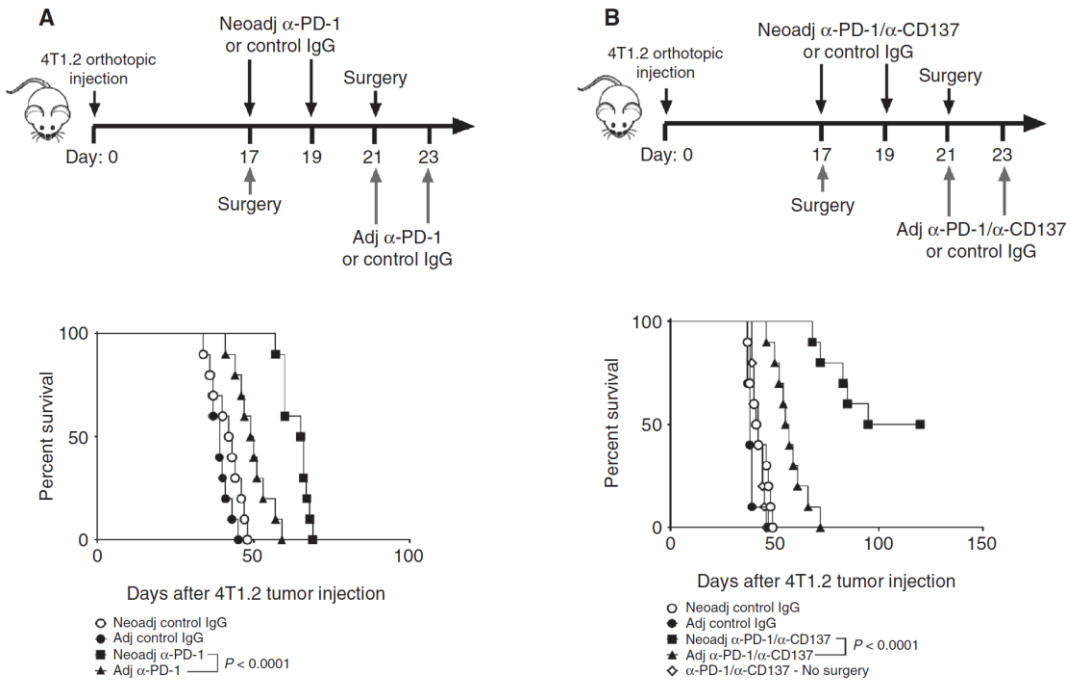
TCGA (n=412)




Robertson, Kim, et al Cell 171:540, 2017

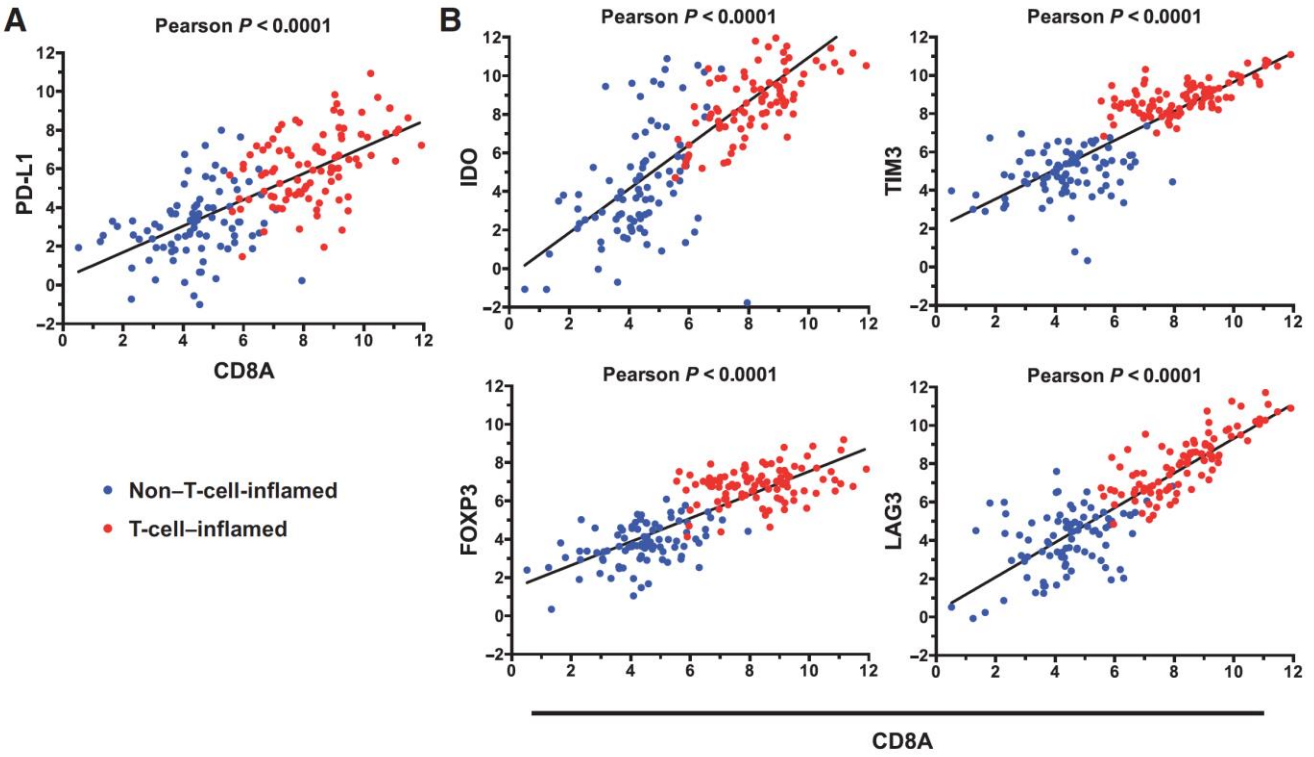
# Neoadjuvant trials as models for clinical research in MIBC

## Neoadjuvant compared with adjuvant anti-PD-1 + anti-CD137 therapy is more efficacious in eradicating metastatic disease (TNBC model)




Liu J, et al. Cancer Discov 2016

# Expression of PD-L1 is positively correlated with expression of CD8A and other immune-inhibitory molecules in UBC

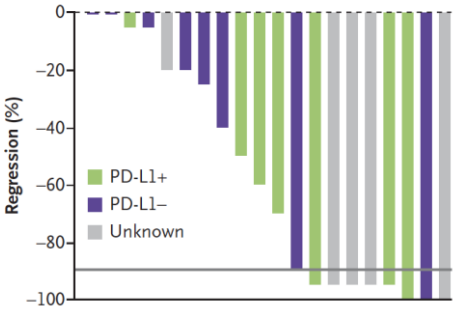


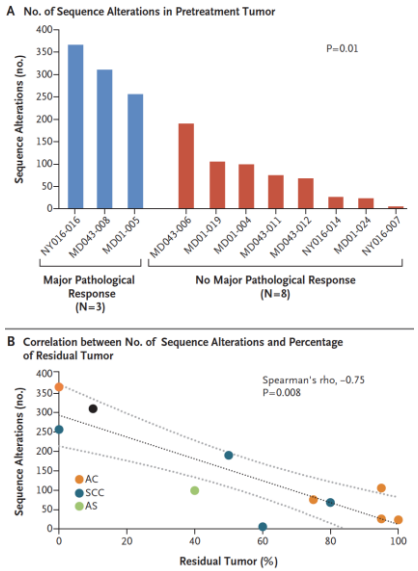

Sweis RF, et al. Cancer Immunol Res 2016;4(7):563-8

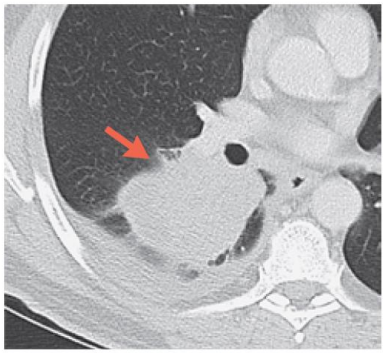
ORIGINAL ARTICLE

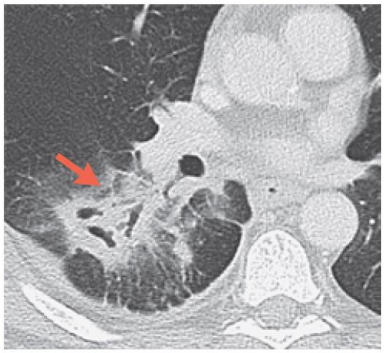
# Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

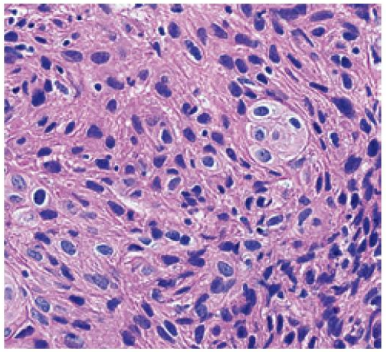
P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

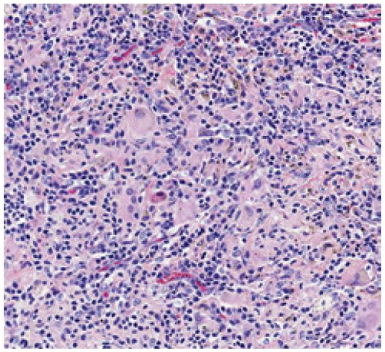


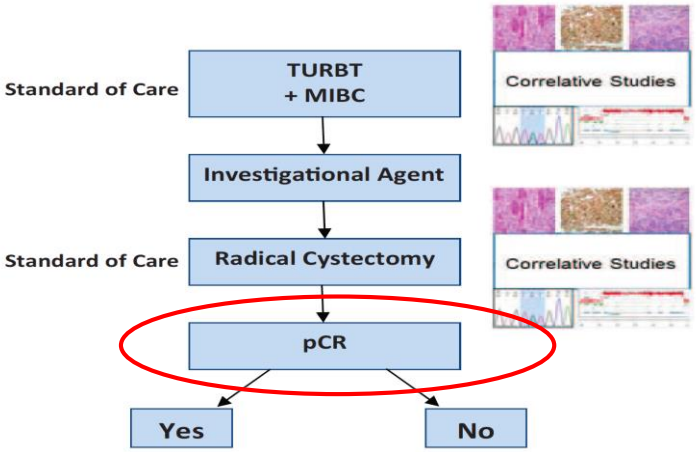


Pretreatment Imaging


Week 4 (before surgery)


Pretreatment Tumor Biopsy


Resection Specimen

Forde PM, et al. N Engl J Med 2018




Chism DD, Oncologist 2013

Kassouf W, Eur Urol 2007
Grossman HB, N Engl J Med 2003
Rosenblatt R, Eur Urol 2011
Sonpavde G, Cancer 2009

| Actuality | | Recommend Yes | Recommend No |
|---|---|---|---|
| Px≤P0 | | Incorrect | Correct |
| | **P0 = 20%** | | |
| P0<Px<P1 | | OK | OK |
| | **P1=40%** | | |
| Px≥P1 | | Correct | Incorrect |

| | pCR% | Cystectomy | Randomized | CR-ITT (95% CI) |
|---|---|---|---|---|
| MVAC | 38 | 126 | 150 | 32% (25-40) |
| CMV | 32 | 206 | 246 | 27% (21-33) |
| GC (retrospective) | 23-31 | 602-146 | - | 23-31 |
| MVAC (retrospective) | 24-29 | 183-66 | - | 24-29 |

Zargar H et al, Eur Urol 2014
Galsky MD et al, Cancer 2015

- Fit and planned for cystectomy
- Predominant (i.e. 50% at least) UC histology
- cT≤3bN0 stage
- Residual disease after TURB (surgical opinion, cystoscopy or radiological presence)
- GFR ≥20 ml/min (Cockcroft – Gault formula)
- ECOG-PS 0-1

**3×3 weekly cycles of pembrolizumab 200 mg IV**

Pre-post treatment tissue/blood sample collection for biomarker analyses

Pre-post treatment imaging: multiparametric bladder MRI (mpMRI); $^{18}$FDG-PET/CT scan, T/A CT scan

**Additional DD-MVAC x 4 cycles in non-responding pts (investigator choice)**

- Cystectomy
- Post-cystectomy management according to EAU guidelines
- Survival data collected until 2-y post cystectomy

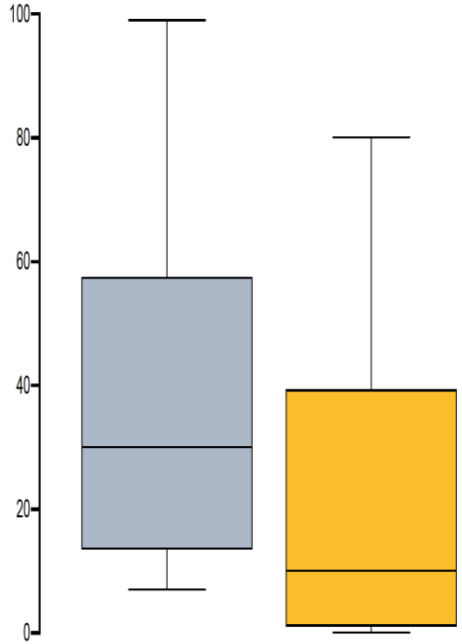
# All treated patients
# N=43



*Pathologic response to Pembro>CT:

- pTispN0: n=2 (40%); pT2pN2: n=1 (20%); pT3pN1: n=2 (40%)

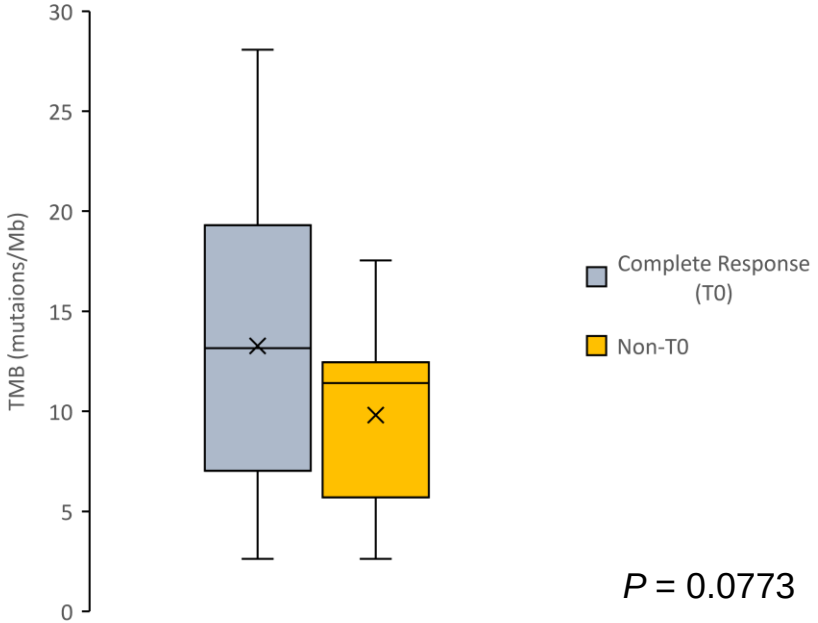
## Pathologic response and PD-L1 CPS




*P* = 0.0549

Median CPS pT0: 30%
Median CPS non-pT0: 10%

## Pathologic response and TMB




*P* = 0.0773

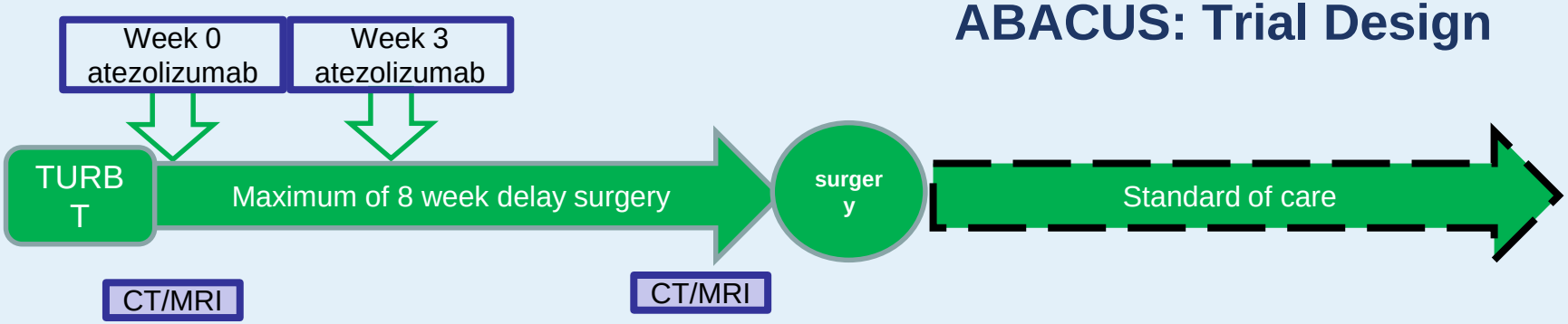
Median TMB pT0: 13.16 Mut/Mb
Median TMB non-pT0: 11.41 Mut/Mb

| | All treated patients N=43 | PD-L1 CPS ≥20% N=22 | DDR and/or *RB1* GA N=25 | PD-L1 CPS ≥20% AND DDR/*RB1*-GA N=10 |
|---|---|---|---|---|



GA: genomic alterations

# ABACUS: Trial Design




## Eligibility

- T2-T4aN0M0 bladder cancer
- Transitional histology
- Residual disease post TURBT
- Not fit for / reject cisplatin chemotherapy

## Endpoints

- Co-primary endpoints: pCR (>20%) and increase in CD8 count
- Secondary endpoints: safety and radiological response
- IDMC met in Jan ’18, resulting in interim presentation of results

Powles T, et al. For presentation at: American Society of Clinical Oncology Annual Meeting; *J Clin Oncol*. 2018;36(Suppl). Abstract 4506.

## ABACUS: A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer

- Ph2, single-arm study of atezolizumab (2 cycles, 1200mg Q3W) prior to cystectomy in MIBC
  - Primary endpoint: pCR ≥ 20%; Co-primary endpoint:  biomarker analysis on sequential tissue
  - pT0 (23%), Tis (6%), T1 (10%), T2 (21%), T3 (24%), T4 (16%)
  - 39% patients were downstaged to non-muscle invasive disease
  - 17% of pCR patients had pT3/4 disease at baseline
- G3/4 TRAEs (12%)
- G3/4 surgical complications (31%) (n=69)

| | All Comers | PD-L1 Positive | PD-L1 Negative |
|---|---|---|---|
| **pCR** | **29%** (95% CI: 19-42) | **40%** (95% CI: 21-62) | **16%** (95% CI: 5-34) |

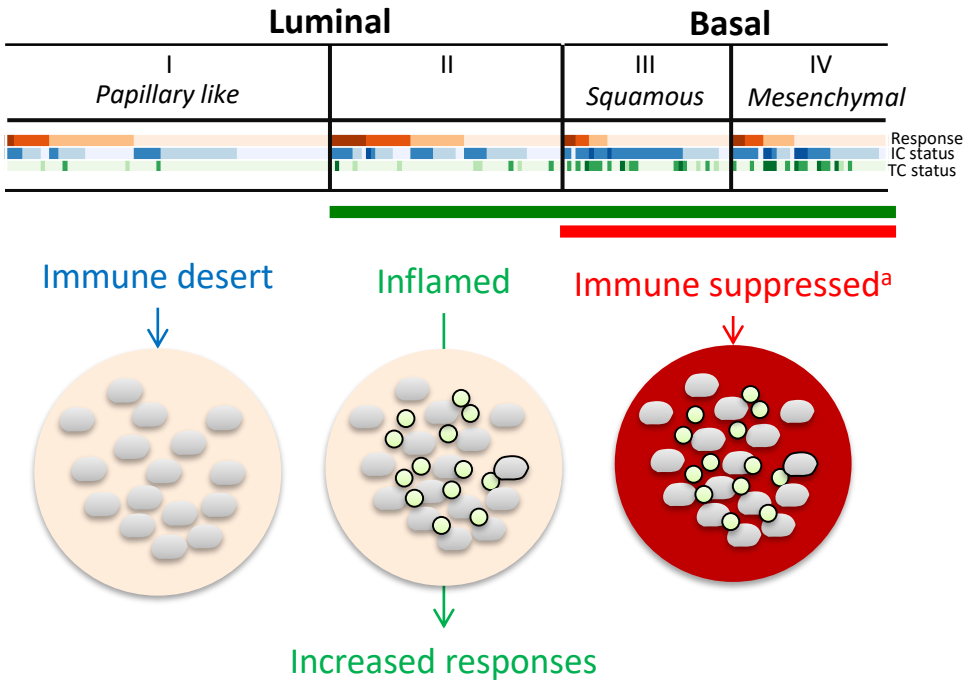
pCR, pathological complete response; Q3W, every 3 weeks; TRAE, treatment-related adverse event.

Powles T, et al. For presentation at: American Society of Clinical Oncology Annual Meeting; *J Clin Oncol*. 2018;36(Suppl). Abstract 4506.

## Additional clinical studies evaluating immune checkpoint inhibitors in the neoadjuvant setting before RC

- Pembrolizumab (PANDORE, France)
- Pembrolizumab + Gemcitabine (Hoosier Oncology Group, US)
- Nivolumab/Urelumab (Jonhs Hopkins University, US)
- Nivolumab/Ipilimumab (Netherlands)
- Durvalumab/Tremelimumab (Spain)

# IMvigor210: TCGA Subtype in mUC




- IMvigor210 subtypes have distinct tumor-immune landscapes that reflect responsiveness to atezolizumab

Tumor stroma
Tumor cells
TIL/immune cells

TIL, tumor-infiltrating lymphocyte. [a] High myeloid, inflammatory, activated stromal/fibroblast markers. Data cutoff: March 14, 2016.

Rosenberg J et al, ASCO 2016

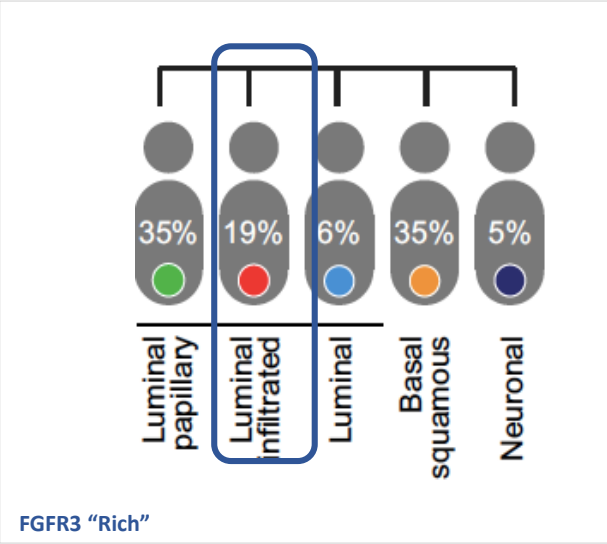
# FGFR alterations are associated with ‘non-T-cell-inflamed’ bladder tumors

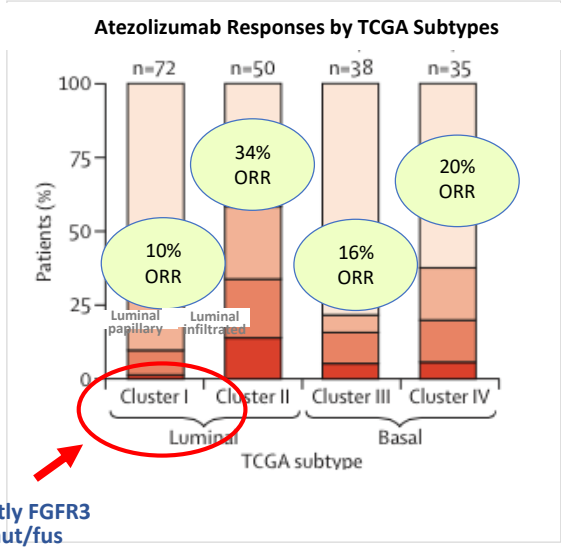
| Gene mutation or fusion | Non T-cell-inflamed (n=76) | | T-cell-inflamed (n=85) | |
|---|---|---|---|---|
| | Samples | Variants | Samples | Variants |
| FGFR3 | 11 | 14 | 0 | 0 |
| FGFR3-TACC3 | 3 | 0 | 0 | 0 |

Sweis RF, et al. Cancer Immunol Res 2016;4:563-568; Choi W, et al. Eur Urol 2017;72:3554-365

# FGFR3 expression associated with poor responses in metastatic UC treated with immune checkpoint inhibitors

- "Luminal" group makes up 60% of metastatic bladder cancer
- FGFR3 is predominately in the luminal papillary ("immune desert")
- "Luminal papillary" cancer has very Poor Response to checkpoint inhibitors
- Treatment with anti-FGFR3 may enhance the effectiveness of checkpoint inhibitors




Robertson et al, Cell 2017,171,1–17

Adapted from Rosenberg et al, ASCO 2016

# Original EAU and ASCO Endorsement Recommendations and Qualifying Statements

| Adjuvant Chemotherapy | |
|---|---|
| Adjuvant cisplatin based combination chemotherapy may be offered to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given. | Adjuvant cisplatin based combination chemotherapy may be offered to patients with pT3/4 and/or or pN+) disease if no neoadjuvant chemotherapy has been given.<br>***While neoadjuvant chemotherapy is recommended, adjuvant chemotherapy may be offered to high-risk patients who did not receive neoadjuvant treatment†*** |

Milowsky MI et al, J Clin Oncol 2016

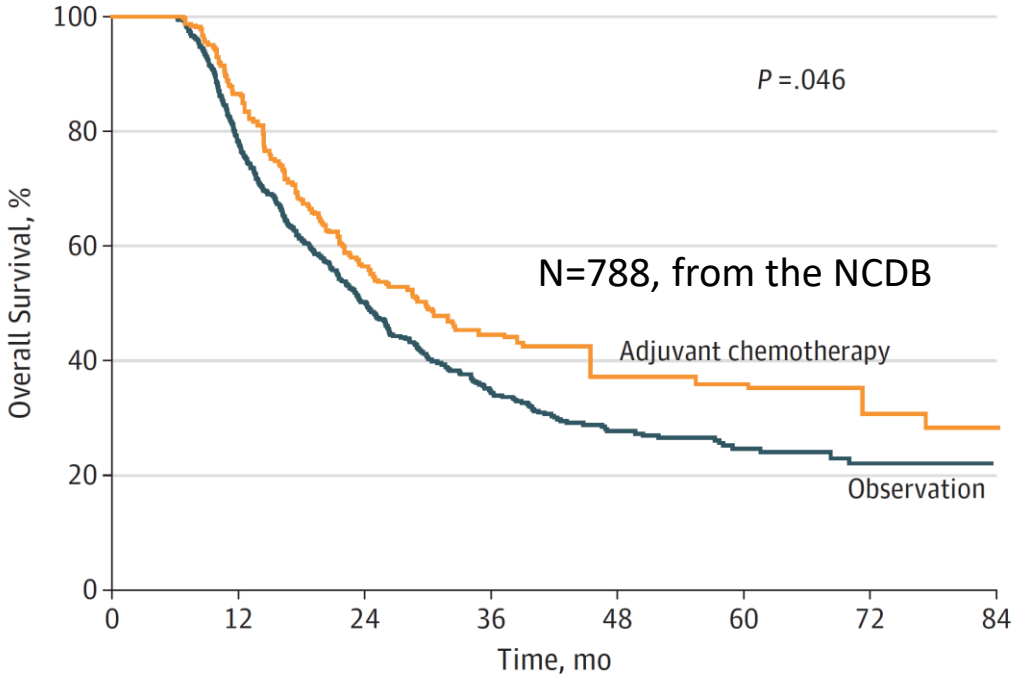
# Ph3 Adjuvant/ Registrational Studies in MIBC

| IO Therapy/Study | Phase/N | Study Arms | Primary Endpoints | **Secondary Endpoints** | Estimated Primary Completion Date |
|---|---|---|---|---|---|
| Nivolumab[1]<br>CheckMate 274<br>(NCT02632409) | Phase 3<br>N=640 | • Nivolumab (adjuvant)<br>• Placebo | • Disease-free survival | • Non-urothelial track recurrence-free survival<br>• Disease-specific survival<br>• OS | April 2020 |
| Pembrolizumab[2]<br>AMBASSADOR<br>(NCT03244384) | Phase 3<br>N=739 | • Pembrolizumab (adjuvant)<br>• Observation | • Disease-free survival<br>• OS (up to 5 years) | • Disease-free survival and OS in PD-L1$^{+}$ and **PD-L1**$^{-}$ patients | February 2019 |
| Atezolizumab[3]<br>IMvigor010<br>(NCT02450331) | Phase 3<br>N=700 | • Atezolizumab (adjuvant)<br>• Observation | • Disease-free survival | • Disease-specific survival<br>• OS<br>• Distant metastasis-free survival<br>• Non-urinary tract recurrence-free survival<br>• Safety, QoL<br>• PK, immunogenicity | October 2019 |

1. Study NCT02632409. ClinicalTrials.gov website. Accessed July 24, 2017. 2. Study NCT03244384. ClinicalTrials.gov website. Accessed July 24, 2017 3. Study NCT02450331. ClinicalTrials.gov website. Accessed July 24, 2017.

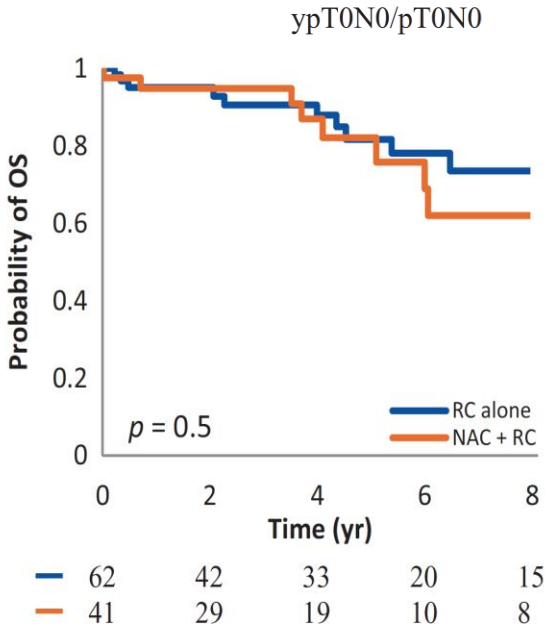
# Adjuvant chemotherapy after Neoadjuvant chemotherapy and RC?

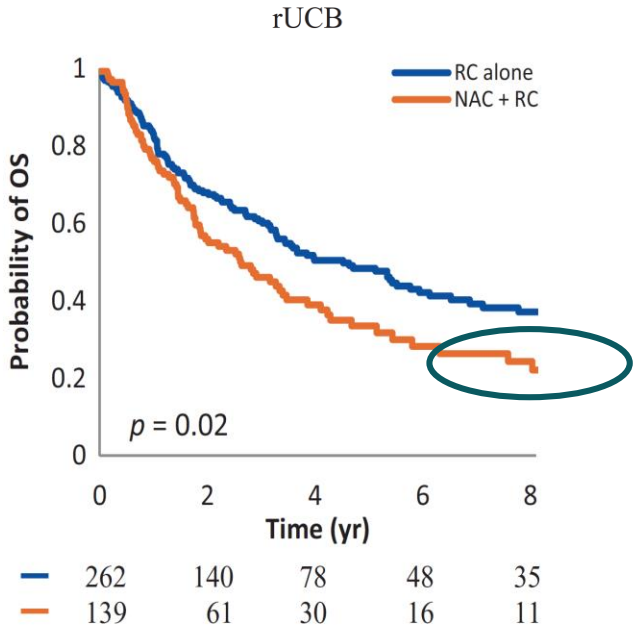
## The case of pT3/T4 and/or pN+ UCB




Seisen T et al. JAMA Oncol. doi:10.1001/jamaoncol.2017.2374 (Epub ahead of print)

# Oncologic Outcomes for Patients with Residual Cancer at Cystectomy Following Neoadjuvant Chemotherapy

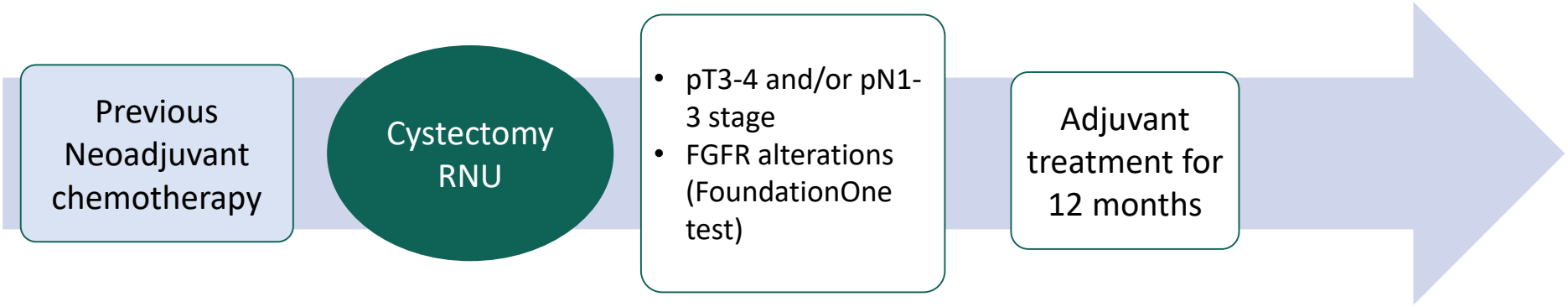



**Unique opportunity for clinical research**

Bhindi B, et al. Eur Urol (2017), http://dx.doi.org/10.1016/j.eur- uro.2017.05.016

Open-label, single-arm, Phase II study, evaluating safety and efficacy of INCB054828 as adjuvant therapy for molecularly-selected, high-risk patients with urothelial carcinoma who have received neoadjuvant chemotherapy and surgery




**Primary Endpoint**: Relapse-free survival; N=56
(100 pts screened)

Study sponsor: EAU-RF

Power: 0.90; Alpha: 0.10; H0: 2-year RFS: 30%; H1: 2-year RFS: 45%
Follow-up duration: 2 years

SIU UPDATES

ASCO GU

ASCO GENITOURINARY CANCER SYMPOSIUM

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