

SIU **UPDATES**

ASCO GU

ASCO GENITOURINARY CANCER SYMPOSIUM



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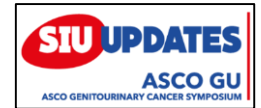
UNA HOTEL via Giovanni Amendola, 57

Team
VESCICA

2018 Genitourinary Cancers Symposium

TRANSLATING EVIDENCE TO MULTIDISCIPLINARY CARE

February 8-10, 2018 | Moscone West Building | San Francisco, CA | #GU18



UROTELIAL CANCER	228
<input type="checkbox"/> MIBC	55
<input type="checkbox"/> NMIBC	28
<input type="checkbox"/> UUT CANCER	13
PROSTATE CANCER	346
BREAST CANCER	192



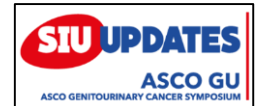
NMIBC

- PATIENT SELECTION (Tumor mutational burden and Immunophenotypes)
- INDIVIDUALIZED EXPERIMENTAL THERAPIES (Immuno-drugs in preclinical and clinical trials)

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Vascular and tumor cell expression of VEGFR2 and molecular subtyping: An innovative biomarker approach in bladder cancer.

Presented Friday, February 9, 2018 by Authors:

Aejaz Nasir, Beverly L Falcon, Dan Wang, Timothy R. Holzer, Elizabeth M Nonte, Mia Yang Chen, Angie D Fulford, Julia H Carter, Larry E Douglass, Bronislaw Pytowski, Katherine M Bell-McGuinn, Richard A. Walgren, Eli Lilly and Company, Indianapolis

Background: Treatment approaches combining anti-angiogenic therapy with chemotherapy have shown promising clinical results in metastatic bladder cancer (BC). In order to interrogate the potential clinico-pathologic and molecular basis of these findings, **we evaluated VEGFR2, vascular density and molecular subtyping in a series of BC patients.**

Methods: A custom-TMA with primary BC tissues from **117 patients** (mean age 71 yrs; range 38-99 yrs; M:F = 83:34) treated at a single institution, was stained and scored (0-3) for **CD34 (vascular density)** and for **VEGFR2 on tumor vessels and cells. CK5/6 and GATA3 IHC was scored by a pathologist to identify main molecular classes of BC.** The association between clinico-pathologic variables, VEGFR2, CD34 and molecular subtypes was analyzed by Fisher's exact test and ANOVA. Univariate and multivariate Cox proportional models were used for survival analysis.

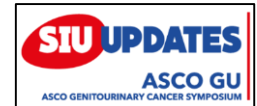
Results: Of 112 analyzable BC tissues, **41% were muscle-invasive (MIBC) vs. 56% non-muscle invasive (NMIBC)** and 3% undetermined. Compared to NMIBC patients those with MIBC had shorter overall survival ($p < 0.001$). The main molecular subtypes included **basal (11%), mixed baso-luminal (28%) and luminal (61%).** Compared to luminal and baso-luminal subtypes, **the majority of basal BCs were muscle invasive** ($p = 0.036$). VEGFR2 expression was higher in tumor vessels but variable in tumor cells. 74% of BCs showed high-medium levels of VEGFR2 (scores 3-2) in tumor vessels and 88% had high-medium levels of tumor vascular density. Within basal, luminal and baso-luminal subtypes, 58%, 78% and 71% had high-medium levels of vascular VEGFR2 ($p = 0.52$), while 83%, 91% and 82% had high-medium levels of tumor vascular density ($p = 0.08$). Survival analyses showed increasing **patient age, higher stage and lower VEGFR2 levels as independent predictors of shorter survival.**

Conclusions: Given the observed complexity of BC regarding VEGFR2 expression and vascular density across molecular subtypes, further investigation is warranted to understand how the frequent expression of VEGFR2 on tumor vasculature and variable expression in tumor cells relates to the efficacy of anti-angiogenic agents across these subtypes in bladder cancer.

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A novel, robust multiplex urine-based immunoassay for bladder cancer detection.

Presented Saturday, June 2, 2018 by Authors:

Hideki Furuya, Yunfeng Dai, Kanani Hokutan, Yair Lotan, Charles Joel Rosser; University of Hawaii Cancer Center, Honolulu, HI; COG Statistics and Data Center and University of Florida, Gainesville, FL; The University of Texas Southwestern Medical Center, Dallas,

Background: The development of non-invasive molecular assays that can accurately detect and monitor BCa would be a major advance, benefiting both patients and healthcare systems. We have previously identified a **urinary protein biomarker panel** that is being developed for application in at-risk patient cohorts. Here, we investigated the potential utility of the multiplex assay in a prospective study.

Methods: The study cohort collected from urology clinics at two institutions was comprised of a total of 145 subjects. The **protein biomarker panel (IL8, MMP9, MMP10, ANG, APOE, SDC1, A1AT, PAI1, CA9, VEGFA)** was **monitored in voided urine samples collected prior to cystoscopy** using a custom multiplex ELISA assay. The diagnostic performance of the biomarker panel was assessed using receiver operator curves (ROC), predictive modeling and descriptive statistics.

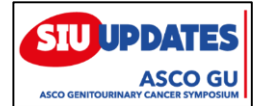
Results: **Urinary biomarker concentrations were significantly elevated in cases versus controls, and in cases with high-grade and muscle-invasive tumors.** The AUC for the 10-biomarker assay was 0.901 (95% confidence interval, 0.850–0.934), with an **overall diagnostic sensitivity and specificity of 0.90 and 0.91, respectively.**

Conclusions: Urinary levels of a 10-biomarker panel enabled discrimination of patients with BCa. The multiplex urinary diagnostic assay will continue in prospective study. Clinical trial information: [NCT03193528](https://clinicaltrials.gov/ct2/show/study/NCT03193528)

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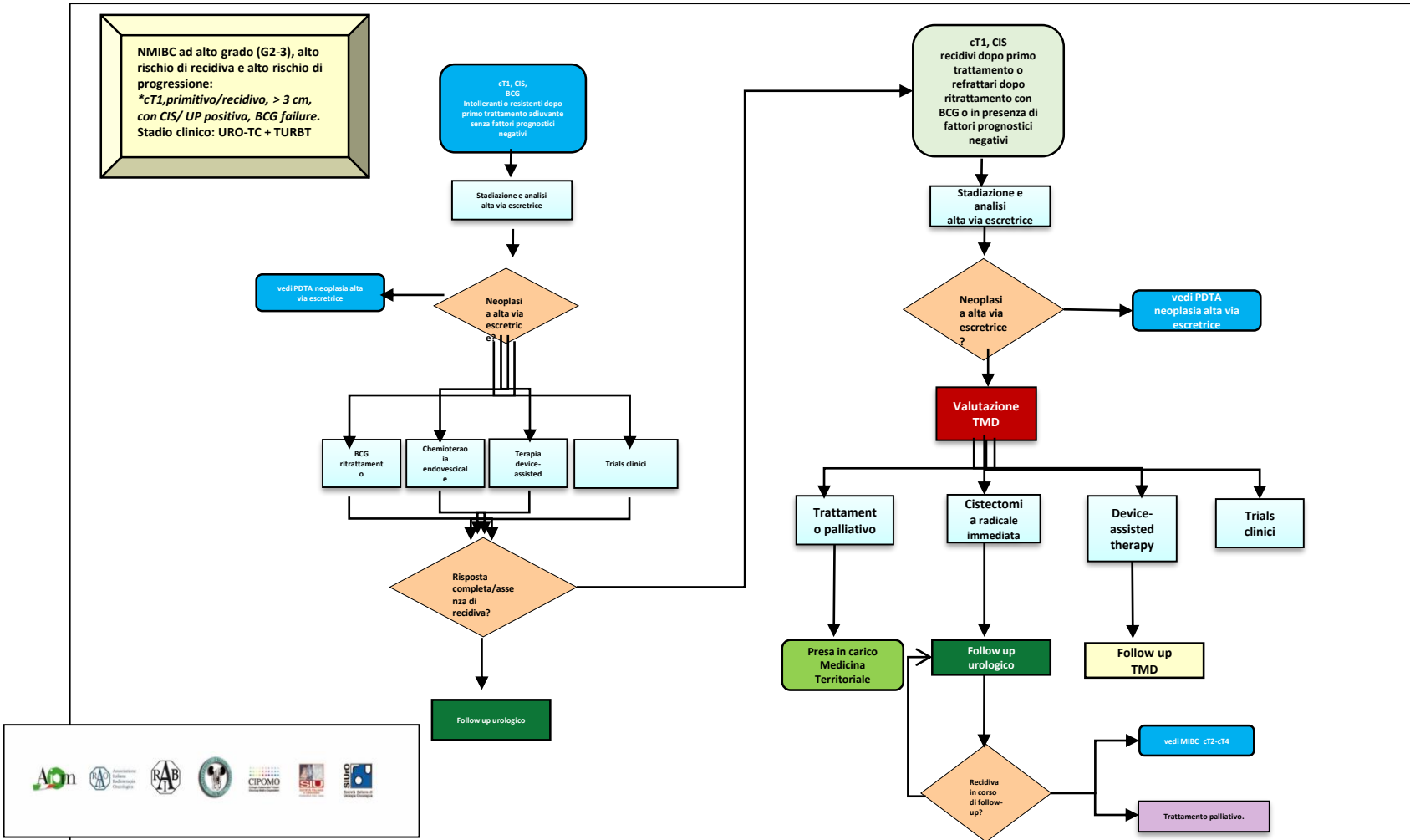
Tumor mutational burden (TMB), intratumoral genetic heterogeneity (ITGH) and BCG responsiveness in high-risk non-muscle invasive bladder cancer (NMIBC).

presented June 2018 by authors: Diogo Assed Bastos et al., São Paulo, Brazil

Methods: We retrospectively identified pts with **high-risk NMIBC treated with TURBT and intravesical BCG** (≥ 6 instillations) from 2009 to 2016. Patients were classified as **BCG-responsive** (BCG-R) and **BCG-unresponsive** (BCG-UR) based on the International Bladder Cancer Group criteria. **Whole-exome sequencing (WES)** was conducted to assess **TMB** and **ITGH**. Immunohistochemistry (IHC) was used to evaluate **PD-L1 expression** and the presence of **tumor infiltrating lymphocytes (TILs - CD8+, CD56, CD68, CD83 and FOXP3)**. Association with BCG responsiveness was evaluated using Mann-Whitney test.

Results: **Thirty-six patients** were identified (BCG-R n = 17, BCG-UR n = 19). Median follow-up was 44 months for BCG-R and 49 months for BCG-UR pts. The majority of pts was male (92.1%), former smoker (68.4%), and presented with high-grade urothelial carcinoma (92.1%) and/or T1 staging (71%). Median time for relapse or progression was 11 months in the BCG-UR group. In this cohort, **TMB was not significantly different in BCG-R and BCG-UR groups**, with a median TMB of 7.63 and 7.89 mutations/Mb, respectively ($P= 0.85$). ITGH assessed by mutant-allele tumor heterogeneity (MATH) score was also similar between the groups, with a median MATH score of 21.6 and 22.8 for BCG-R and BCG-UR, respectively. Exploratory analyses of neoantigen load, DNA damage repair (DDR) gene alterations, PDL-1 expression and TIL subpopulations will be presented at the meeting.

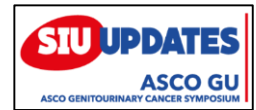
Conclusions: In **this exploratory biomarker study, TMB and ITGH were not able to identify NMIBC pts more likely to benefit from immunotherapy with intravesical BCG**. The identification of predictive biomarkers in this setting is an important unmet need and integrative analysis of TMB, ITGH with other potential predictive biomarkers should be assessed in larger datasets.



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Phase II trial of BC-819 intravesical gene therapy in combination with BCG in patients with non-muscle invasive bladder cancer (NMIBC). Authors:

Sarel Halachmi, Ilan Leibovitch, Amnon Zisman, Avi Stein, Shalva Benjamin, Ami Sidi, Ron Knickerbocker, Michal Limor, Yan Moore; Bnai Zion Medical Center, Haifa, Israel; Meir Medical Center, Kfar Saba, Israel; Shamir Medical Center, Tzrifin, Israel

Background: BC-819 is an intravesical gene therapy consisting of a recombinant DNA construct which delivers a lethal cellular toxin, engineered from diphtheria, specifically to malignant cells in the bladder. In this study we tested the feasibility of administering BC-819 in combination with BCG with the goal of improving outcomes for patients with NMIBC. **Methods:** This phase II multi-center trial assessed 3 intravesical combination induction schedules of BC-819 and BCG; alternating (A), sequential (S), and twice weekly (TW) for 6-12 weeks. The population included adult patients for whom BCG was indicated. All patients underwent transurethral resection of the bladder tumor (TURBT) prior to study entry. The **primary endpoint was safety; recurrence was assessed as a secondary endpoint.**

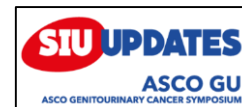
Results: 38 Caucasian patients were included in the intent-to-treat population; 16 in A, 6 in S, and 16 in TW cohorts. The median follow-up is 18-mo. The mean age was 69 years (± 11.3), 92% were males. 29% had prior BCG. 16% of patients had CIS lesions, and 47% had multiple recurrences prior to participation. In 86% the resected tumor size ≥ 1.0 cm. The overall median time to recurrence (mTTR) was not reached. **The 24-months rates of recurrence and progression were 46% and 24%, respectively.** The longest median time to recurrence among the three schedules was in the alternating group, but due to the small numbers of patients in each group the best schedule could not be determined. Therapy was associated with 5 AEs (in 5 patients; 13%) related to BC-819 (2 UTIs – 1 mild/1 moderate, 2 hematurias – both mild, 1 dysuria - mild) and 29 related to BCG. 3 SAEs were reported, none related to BC-819.

Conclusions: These data demonstrate that **administration of BC-819 in combination with BCG is feasible and exhibits clinically meaningful activity in all three induction schedules. The safety profile suggests that BC-819 is well tolerated and does not add substantial toxicity to intravesical therapy.** A phase 3 randomized trial of BC-819 and BCG in patients with NMIBC is planned. NCT01878188. Clinical trial information: [NCT01878188](https://clinicaltrials.gov/ct2/show/study/NCT01878188)

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A multicenter clinical trial of intravesical BCG in combination with ALT-803 in patients with BCG-unresponsive non-muscle invasive bladder cancer.

Presented Friday, February 9, 2018 by authors:

Karim Chamie, Amirali Salmasi, Charles Joel Rosser, Amy Rock, Lydia Ferguson, Hing C. Wong; University of California Los Angeles, Los Angeles, CA; University of Hawaii Cancer Center, Honolulu, HI; Altor BioScience, Miramar, FL

Background: BCG unresponsive NMIBC includes patients with persistent high-grade disease or recurrence within 6 months of receiving at least two courses of BCG; or T1 high-grade disease at the first evaluation following BCG induction alone. The recommendation after failing BCG in patients suitable for surgery is cystectomy or for unwilling/unfit patients, salvage chemotherapy or immunotherapy (administered with limited success). This highlights a critical need for novel preservation therapies to facilitate a better quality of life and reduce health-care costs for patients who are unresponsive to BCG. Altor BioScience has initiated a **phase II clinical study in BCG unresponsive patients** to expand on promising data collected from a compassionate use patient who remains disease free more than 2.5 years after ALT-803 plus BCG treatment for refractory NMIBC (Huang 2017).

Methods: This is a **Phase II, open-label, single-arm, multicenter study of intravesical BCG plus ALT-803 in patients with BCG unresponsive high grade NMIBC**. **Group A** will enroll patients who have histologically confirmed presence of **CIS** [with or without Ta or T1 disease]. **Group B** will enroll patients who have histologically confirmed **high-grade Ta or T1 disease (in the absence of CIS)**. All patients will receive **BCG plus ALT-803 weekly for 6 consecutive weeks**. A cystoscopy will be performed at Week 12. Patients with no disease or low-grade Ta will receive a **maintenance course of therapy (3 weekly instillations of BCG plus ALT-803)**. Patients with residual CIS and/or high-grade Ta will receive a re-induction course of therapy. Presence of Ta will require a TURBT. Patients with greater than or equal to T1 disease or new CIS will be deemed treatment failures. Patients with a Complete Response (CR) or low-risk disease at Months 6, 9 and 12 are eligible for continued BCG plus ALT-803 maintenance. The primary endpoint is to assess complete response (CR; absence of lesions on cystoscopy or negative, for cause, biopsies along with negative urine cytology) of CIS at six months. Enrollment is underway. Clinical trial information: [NCT03022825](https://clinicaltrials.gov/ct2/show/study/NCT03022825)

[The potential and promise of IL-15 in immuno-oncogenic therapies.](#)

Robinson TO, Schluns KS.

Immunol Lett. 2017 Oct;190:159-168. doi: 10.1016/j.imlet.2017.08.010. Epub 2017 Aug 16. Review.

[Lancet Oncol.](#) 2018 May;19(5):694-704. doi: 10.1016/S1470-2045(18)30148-7. Epub 2018 Apr 5.

ALT-803, an IL-15 superagonist, in combination with nivolumab in patients with metastatic non-small cell lung cancer: a non-randomised, open-label, phase 1b trial. [Wrangle JM](#)¹, [Velcheti V](#)², [Patel MR](#)³, [Garrett-Mayer E](#)¹, [Hill EG](#)¹, [Ravenel JG](#)¹, [Miller JS](#)³, [Farhad M](#)⁴, [Anderton K](#)¹, [Lindsey K](#)¹, [Taffaro-Neskey M](#)¹, [Sherman C](#)¹, [Suriano S](#)¹, [Swiderska-Syn M](#)¹, [Sion A](#)¹, [Harris J](#)¹, [Edwards AR](#)¹, [Rytlewski JA](#)⁵, [Sanders CM](#)⁵, [Yusko EC](#)⁵, [Robinson MD](#)⁶, [Krieg C](#)¹, [Redmond WL](#)⁴, [Egan JO](#)⁷, [Rhode PR](#)⁷, [Jeng EK](#)⁷, [Rock AD](#)⁷, [Wong HC](#)⁷, [Rubinstein MP](#)⁸.

[Urol Case Rep.](#) 2017 Jun 8;14:15-17. doi: 10.1016/j.eucr.2017.04.015. eCollection 2017 Sep.

Intravesical ALT-803 for BCG-unresponsive Bladder Cancer - A Case Report. [Huang J](#)¹, [Schisler J](#)², [Wong HC](#)³, [Rosser CJ](#)¹, [Sterbis J](#)².



IL-15 is a cytokine that primarily stimulates the proliferation and cytotoxic functions of CD8T cells and NK cells leading to enhanced anti-tumor responses. While having some efficacy in inducing tumor regression as a monotherapy, IL-15 agents also show great potential in being used in combination with other immuno-oncological therapies.

ALT-803 is a pharmacological grade IL-15/IL-15R α complex fused to an Ig1Fc and agonism of the IL-2 and 15 By receptor.

Although IL-2 and IL-15R $\beta\gamma$ agonist and PD-1 monoclonal antibodies or BCG have shown clinical success as monotherapy in some patients, no published studies have assessed the administration of these two classes of agents concomitantly.

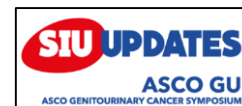
Interesting results were documented with the combination of ALT-803 subcutaneously injected at four dose escalation up to 20 μ g/Kg on weeks 1-5 for 6 weeks cycles and nivolumab every 14 days in NSCLC.

Cytokine treatment with an IL-2 and IL-15R $\beta\gamma$ superagonist at doses capable of inducing anti-tumor immune response is safe and feasible in outpatient setting and that the **cytokine complex might be safely be combined with anti- PD-1 immunotherapy.**

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Phase Ib trial of ALT-803, an IL-15 superagonist, plus BCG for the treatment of BCG-naïve patients with non-muscle-invasive bladder cancer.

Presented Friday, February 9, 2018 by authors:

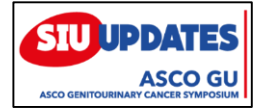
Charles Joel Rosser, Jeffrey Nix, Lydia Ferguson, Liza Hernandez, Hing C. Wong; University of Hawaii Cancer Center, Honolulu, HI; University of Alabama at Birmingham, Birmingham, AL; Altor BioScience, Miramar, FL

Background: This clinical trial evaluates the safety and efficacy of ALT-803, an IL-15 superagonist, plus BCG in BCG-naïve NMIBC patients. **Methods:** Patients with high-risk NMIBC (any **high-grade disease, T1, or CIS who are BCG naïve**) will be **randomized and enrolled into one of two study arms to be treated with either ALT-803 plus BCG or BCG alone.** Patients will receive treatment via a urinary catheter in the bladder, weekly for **6 consecutive weeks during induction.** A response assessment will be performed at Week 12. Patients with no disease or **low-grade Ta** disease will receive a **maintenance course of therapy (3 weekly instillations of either ALT-803 plus BCG or BCG alone).** Presence of Ta will require a TURBT procedure. Patients with presence of **high-grade Ta, CIS or low-grade T1 disease will receive a re-induction course** of therapy (6 weekly instillations of either ALT-803 plus BCG or BCG alone). Presence of Ta/T1 will require a TURBT procedure. Patients with high-grade T1 or greater disease (including disease progression) will be considered a treatment failure. Patients with no disease or low-grade Ta disease at months 6, 12, and 18 are eligible for maintenance treatment according to their assigned randomization. Patients with presence of disease greater than low-grade Ta will be considered a treatment failure. **The primary endpoint of the study is the proportion of patients receiving ALT-803 plus BCG who are responders by month 12 or earlier.** Responders are defined as patients who experience a complete response (CIS patients) or no disease recurrence (defined as reappearance of high-risk disease). Enrollment is underway. Clinical trial information: [NCT02138734](https://clinicaltrials.gov/ct2/show/study/NCT02138734)

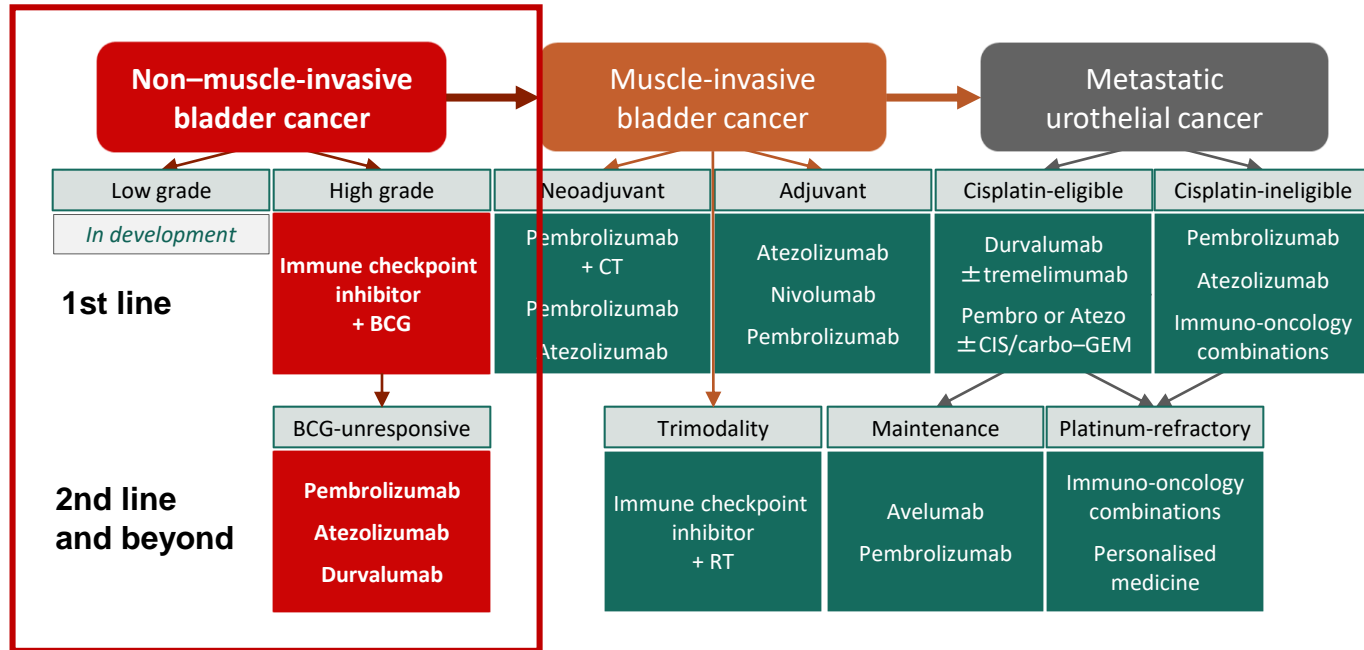
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ONGOING Development of PD-L1/PD-1 Inhibitors in Bladder Cancer



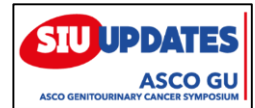
CT: chemotherapy; RT: radiotherapy.

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

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S1605: Phase II trial of atezolizumab in BCG-unresponsive nonmuscle invasive bladder cancer.

Presented Friday, February 9, 2018 Authors:

Peter C. Black, Tangen Catherine, Seth P. Lerner, David James McConkey, M. Scott Lucia, Michael Woods, Trinity Bivalacqua, Wassim Kassouf, Richard Carlton Bangs, Melissa Plets, Ian Murchie Thompson, Parminder Singh; University of British Columbia, Vancouver, BC, Canada; Fred Hutchinson Cancer Research Center, Seattle, WAUT Health Science Center, San Antonio, TX; Mayo Clinic Arizona,

Background: Based on the reported efficacy of **atezolizumab** in metastatic urothelial carcinoma and the **known expression of PD-L1 expression in NMIBC after BCG therapy**, this trial will evaluate the activity of atezolizumab in BCG-unresponsive high risk NMIBC.

Methods: This is a **single arm phase II trial testing systemic atezolizumab (1200 mg IV) every 3 weeks for one year in 135 patients with BCG-unresponsive high risk NMIBC**. The study will enroll **70 patients with CIS** (with or without concomitant Ta/T1) and **65 with Ta/T1 only**. Patients with CIS at baseline will undergo mandatory repeat biopsy at 6 months, and all other patients only for suspected recurrence. Patients with persistent CIS, high grade Ta/T1 recurrence or progression to muscle invasive or metastatic disease will be taken off treatment. The co-primary endpoints are: **(1) complete response (CR) at 6 months in the CIS subgroup, and (2) event-free survival (EFS) at 18 months in the overall population**. Secondary endpoints include duration of CR as well as progression-free, cystectomy-free, bladder cancer-specific, and overall survival in all patients. **Response will be correlated to expression of PD-L1 and CD8 by IHC, and to molecular subtypes and immune signatures by RNA-sequencing**. If ≥ 28 (40%) CIS patients respond, the agent will be considered promising. This design has a significance level of 4.6%, and a power of 96%. If the lower bound of the 90% confidence interval of the 18-month EFS excludes 20%, the investigators will conclude the regimen significantly improves EFS relative to historical data. Successful completion of this trial could lead to a new treatment paradigm for patients with BCG-unresponsive high risk NMIBC.

Clinical trial information: [NCT02844816](https://clinicaltrials.gov/ct2/show/study/NCT02844816)



Anti-Tumour Treatment

Adjuvant and neoadjuvant approaches for urothelial cancer: Updated indications and controversies



Francesco Massari^{a,1}, Matteo Santoni^{b,*,1}, Vincenzo di Nunno^a, Liang Cheng^c,
Antonio Lopez-Beltran^d, Alessia Cimadamore^e, Silvia Gasparrini^e, Marina Scarpelli^e,
Nicola Battelli^b, Rodolfo Montironi^e

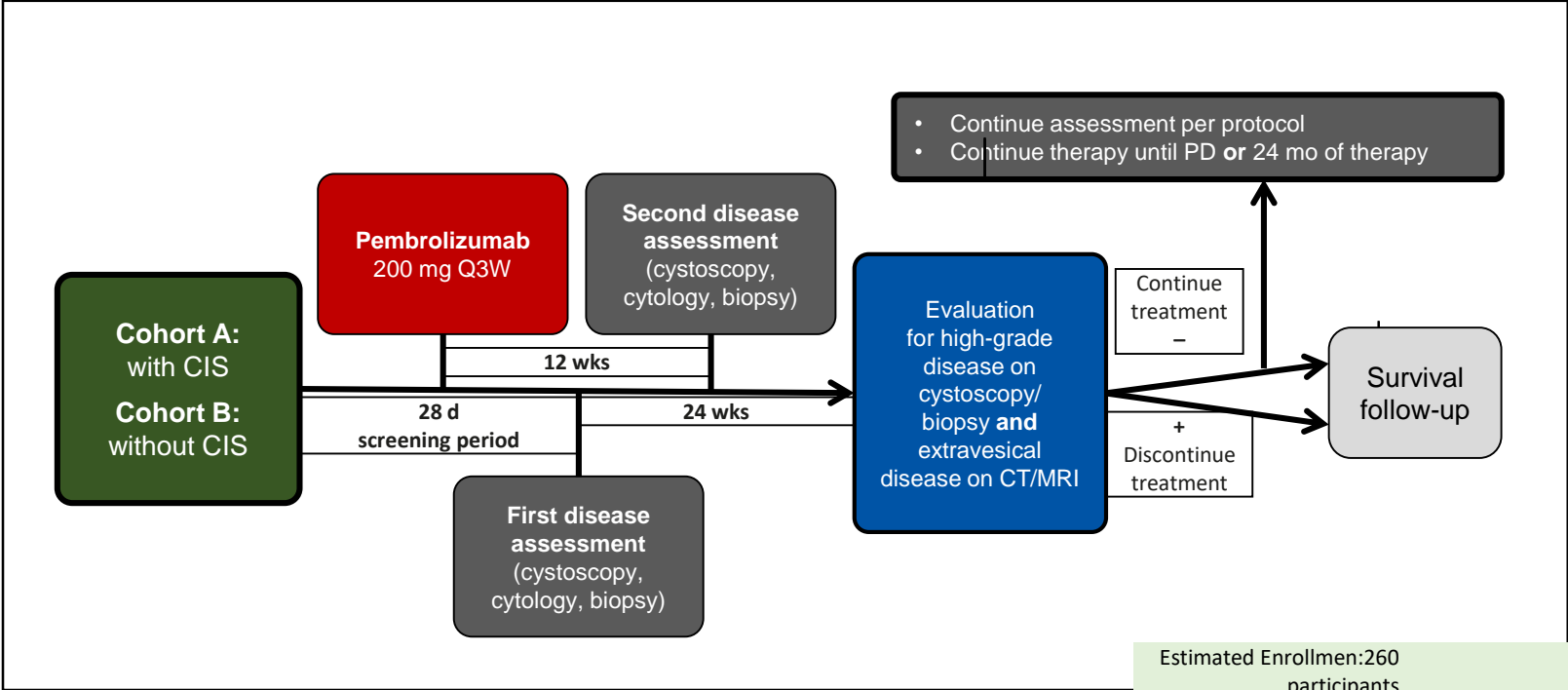
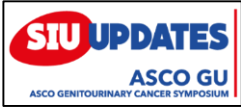
^a Division of Oncology, S. Orsola-Malpighi Hospital, Bologna, Italy

Ongoing clinical adjuvant trials in non-muscle invasive-transitional carcinoma. UC: Urothelial Carcinoma, RR: Recurrence Rate, DFS: Disease Free survival, CRR: Complete Response Rate, RFS: Relapse free survival, EFS: Event Free survival.

Adjuvant trials in non muscle-invasive transitional carcinoma

Study	Experimental arm	Comparator arm	Primary endpoint	Population in study	Phase	N
NCT02901548	DURVALUMAB	NONE	CRR	CIS of the bladder with persistence or progression or recurrence of high-grade CIS after BCG	II	34
NCT02844816	ATEZOLIZUMAB	NONE	EFS, CRR	T1 high-grade, stage CIS, or stage Ta high-grade	II	148
NCT03317158	DURVALUMAB	NONE	6 months EFS	T1 high-grade, stage CIS, or stage Ta high-grade	II	186
NCT03062059	GEMCITABINE	NONE	2 years DFS	Nephroureterectomy due to ureter or renal pelvis UC	II	134
NCT03209206	DOCETAXEL	NONE	RR	Upper urinary tract UC	II	84
NCT03030157	PIRARUBICIN single instillation	PIRARUBICIN Long term instillation	12 months RR	Upper urinary tract UC	II	220
NCT02547350	PIRARUBICIN single instillation	PIRARUBICIN Long term instillation/Observation	RR	Upper urinary tract UC	II	200
NCT02740426	PIRARUBICIN single instillation	OBSERVATION	RFS	Upper urinary tract UC	II	200
NCT02438865	EPIRUBICIN single instillation	EPIRUBICIN Maintenance	RR	Upper urinary tract UC	II	80
NCT03091660	BCG	BCG + Tumour Vaccine	RR	High grade bladder UC	III	969

KEYNOTE-057: Pembrolizumab in Patients With BCG–Unresponsive, High-Risk Non–Muscle-Invasive Bladder Cancer



Estimated Enrollment: 260 participants
 Estimated Study Completion Date: December 27, 2021

CT: computed tomography; MRI: magnetic resonance imaging.
 de Wit R et al. ESMO 2016. Abstract 849TIP.
 ClinicalTrials.gov Identifier: NCT02625961. <https://clinicaltrials.gov/ct2/show/NCT02625961>. Accessed March 8, 2017.

Bladder Trials

Study	Eligibility	Design	Intervention	Institution/Group
NCT02891161 (DUART)	MIBC Cis-ineligible	Phase Ib/II	RT + concurrent/adjuvant durvalumab	Big Ten Consortium
NCT03317158 (ADAPT-Bladder)	NMIBC	Phase I/II	Durvalumab alone, durvalumab + RT, durvalumab + BCG	Hoosier Cancer Research Network
NCT02662062 (PCR-MIB)	MIBC	Phase II	RT + concurrent cisplatin + concurrent/adjuvant pembrolizumab	ANZUP
NCT03171025 (NEXT)	MIBC/urethra/ ureter	Phase II	ChemoRT followed by adjuvant nivolumab	University of Utah
NCT03419130	MIBC No Chemo	Phase IIR	Concurrent pembrolizumab + either conventional RT vs. hypofractionated RT	UCSF
NCT02621151	MIBC	Phase II	RT + concurrent gemcitabine + pembrolizumab	NYU/Multi-institutional
NCT02560636 (PLUMMB)	MIBC, M0-M1	Phase I	RT + concurrent pembrolizumab	Royal Marsden

PRESENTED AT: **2018 Genitourinary Cancers Symposium** | #GU18

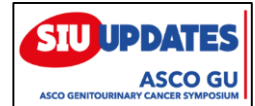
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Presented By Abhishek Solanki at **2018 Genitourinary Cancers Symposium**: Translating Evidence to Multidisciplinary Care

2018 Genitourinary Cancers Symposium

TRANSLATING EVIDENCE TO MULTIDISCIPLINARY CARE

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Long-term results of organ preservation rate and progression risk in high-risk non-muscle-invasive bladder cancer (NMIBC) patients treated with radiofrequency-induced thermochemotherapy effect (RITE) with the Synergo system.

Presented Friday, February 9, 2018 by authors:

Jill-Isabel Kilb, Arne Hauptmann, Florian Wagenlehner, Gerson Luedecke; University Clinic Giessen and Marburg GmbH, Giessen, Germany

Methods: all patients were high-risk NMIBC. Treatment with induction phase: **8 weekly sessions with 2x40 mg MMC. 42°C intravesically induced by RITE.** Followed by a re-resection of the bladder at week 11 to ensure complete remission and **maintenance with treatments every 6 weeks with 2x40 mg MMC for 6 times.** Cystoscopy controls were performed first 2years every 3 months and following in 6 month until now. Study started in 2006 ongoing until now.

Results: we enrolled **67 patients. 65.7% were CIS positive rate. 85% of these patients were treated alternatively to BCG with primary RITE whereas 15% were BCG-failure patients treated alterantively to indicated cystectomy (4/10).** Mean recurrence –free time 3.5 years . In case of recurrence 10.4% progressed to MIBC including 6 metastatic tumors. High-risk NMIBC was observed in **6% resulting in cystectomy** and low risk NMIBC recurrence was 1.5% with organ preservation. **BC death rate was 1 out of 67.** Incomplete treatments induced by SAE of RITE was 9%. **Bladder preservation rate was 80.6% with long-lasting effectiveness (>5 years) of 14/26(53.8%)**

Conclusion. The RITE is in a short and long-term manner a powerful procedure to cure and maintain a recurrence-free BC status in high-risk NMIBC. Bladder preservation rate was achieved in 80.6% lasting for up to 11 year longest.

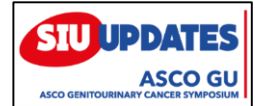
RITE is an alternative to BCG and preferable to early cystectomy in high-risk NMIBC.

It is of note that thermochemotherapy has now been included in the European Guidelines

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Heat targeted drug delivery (COMBAT) in superficial TCC : First midterm results in a cohort of high-risk patients scheduled for cystectomy.

Presented Friday, February 9, 2018 Authors:

Thomas Alexander Voegeli, Eric Frank, Christian Bach, Catejan Nzeh; University of Aachen, Aachen, Germany; Uniclinic RWTH Aachen, 52074 Aachen, Germany; RWTH Aachen University, Aachen, Germany; Barbara Hospital Gladbeck, Gladbeck, Germany

Methods. 58 patients intermediate risk and 37 high-risk NMIBC were treated with COMBAT device which facilitates the irrigation of the bladder with MMC 40 mg at exactly 43°C for 1 hour/6 courses weekly. Side effects were monitored prospectively and success of the treatment was controlled by re-TUR and afterwards by 3 monthly cystoscopy and cytology.

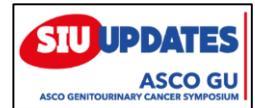
Results. 22 patients referred dysuria, 9 hematuria and 1 required the treatment suspension due to pain and discomfort. The F-U was 14 months (3-29) for the entire cohort, 17 patients had a F-U over 2 years. One patient had recurrence pTa, G3 managed successfully by TUR. **2 patients underwent cystectomy because of invasive recurrence early after intravesical therapy, 1 patient developed bone metastasis** 2 years after therapy without vesical recurrence.

Conclusion. Thermochemotherapy with heated MMC is a well tolerated and new option for patients with NMIBC who are at risk of recurrence and progression. The rate of radical surgery in this heavily pretreated group of patients including 18 BCG-failures was very low. **Thermochemotherapy seems to be a new therapeutic bladder preserving option in high-risk NMIBC tumors.** It is of note that thermochemotherapy has now been included in the European Guidelines

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7.2.1.3.2. Device-assisted intravesical chemotherapy

Microwave-induced hyperthermia

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [199]. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk bladder cancer, a reduced RFS at 24 months in the MMC group was demonstrated [200] (LE: 1b).

Hyperthermic intravesical chemotherapy

Different technologies which increase the temperature of instilled MMC are available, however, data about their efficacy are still lacking.

Electromotive drug administration (EMDA)

The efficacy of MMC using EMDA sequentially combined with BCG in patients with high-risk tumours has been demonstrated in one small RCT [201]. The definitive conclusion however, needs further confirmation.

Non-muscle-invasive Bladder Cancer (Ta, T1 and CIS)

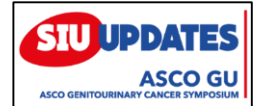
M. Babjuk (Chair), A. Böhle, M. Burger, E. Compérat,
E. Kaasinen, J. Palou, M. Rouprêt, B.W.G. van Rhijn, S. Shariat,
R. Sylvester, R. Zigeuner

2017

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Oncological outcomes of neoadjuvant chemotherapy in patients with locally advanced upper tract urothelial carcinoma: A multicenter study.

Presented Friday, February 9, 2018 Shingo Hatakeyama, Yuka Kubota, Hayato Yamamoto, Takahiro Yoneyama, Yasuhiro Hashimoto, Takuya Koie, Chikara Ohyama; Hirotsaki University Graduate School of Medicine, Hirotsaki, Japan;

Background: The clinical impact of neoadjuvant chemotherapy (NAC) on oncological outcomes in patients with locally advanced upper tract urothelial carcinoma (UTUC) remains unclear. We investigated the oncological outcomes of platinum-based NAC for locally advanced UTUC.

Methods: A total of **426** patients who underwent radical nephroureterectomy at five medical centers between January 1995 and April 2017 were examined retrospectively. Of the 426 patients, **234 were treated for a high-risk disease (stages cT3–4 or locally advanced [cN+] disease) with or without NAC.** NAC regimens were selected based on eligibility of cisplatin. We retrospectively evaluated **post-therapy pathological downstaging, lymphovascular invasion, and prognosis stratified by NAC use.** Multivariate Cox regression analysis was performed for independent factors for prognosis.

Results: Of 234 patients, **101 received NAC (NAC group) and 133 did not (Control [Ctrl] group).** **The regimens in the NAC group included gemcitabine and carboplatin (75%), and gemcitabine and cisplatin (21%).** **Pathological downstagings of the primary tumor and lymphovascular invasion were significantly improved in the NAC than in the Ctrl groups. NAC for locally advanced UTUC significantly prolonged recurrence-free and cancer-specific survival.** Multivariate Cox regression analysis using an inverse probability of treatment weighted (IPTW) method showed that NAC was selected as an independent predictor for prolonged recurrence-free and cancer-specific survival. However, the influence of NAC on overall survival was not statistically significant. **Conclusions: Platinum-based NAC for locally advanced UTUC potentially improves oncological outcomes.** Further prospective studies are needed to clarify the clinical benefit of NAC for locally advanced UTUC.

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Impact of neoadjuvant chemotherapy on pathologic outcomes in patients with upper tract urothelial carcinoma undergoing extirpative surgery.

Presented Friday, February 9, 2018 Authors:

Nima Almassi, Tianming Gao, Byron Lee, Robert Stein, Georges-Pascal Haber, Moshe Chaim Ornstein, Brian I. Rini, Timothy D. Gilligan, Jorge A. Garcia, Andrew J. Stephenson, Petros Grivas; Cleveland Clinic,

Methods: Patients who underwent extirpative surgery for UTUC from 2006-2014 were identified from the National Cancer Database. Among patients with available clinicopathologic data, the incidence of pathologic down-staging, defined as a lesser pathologic compared to clinical stage, was **compared between patients who did and did not receive NAC**. A multivariable model was developed to identify predictors of pathologic down-staging.

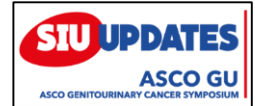
Results: 7,244 patients were identified with non-metastatic UTUC who underwent extirpative surgery in the study period. 260 patients (3.6%) received NAC, with the use of NAC increasing over time from 2.0% patients in 2006 to 7.1% of patients in 2014 (linear trend $p < 0.001$). Clinical and pathologic staging data were available for 119 and 2904 patients who did and did not receive NAC, respectively. **Thirty patients (25.2%) who received NAC experienced pathologic down-staging, compared to 52 patients (1.8%) who did not receive NAC ($p < 0.0001$).** On multivariable analysis, NAC was associated with a higher likelihood of pathologic down-staging (OR 10.2, 95% CI 5.4-19.3). Additional predictors of pathologic down-staging include a higher clinical T stage ($p = 0.001$) and African-American race (OR 2.7, 95% CI 1.1-6.6). **Compared to renal pelvis UTUC, ureteral UTUC was associated with a similar likelihood of pathologic down-staging.**

Conclusions: NAC is infrequently used among patients with UTUC undergoing extirpative surgery. **A higher incidence of pathologic down-staging was observed among patients receiving NAC.** These findings suggest clinical benefit of NAC with respect to pathologic outcomes in patients with UTUC and may help guide selection of patients for NAC prior to radical surgery until data from prospective studies becomes available.

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Evaluation of the timing of adjuvant mitomycin C following nephroureterectomy for urothelial carcinoma of the upper urinary tract.

Presented Friday, February 9, 2018

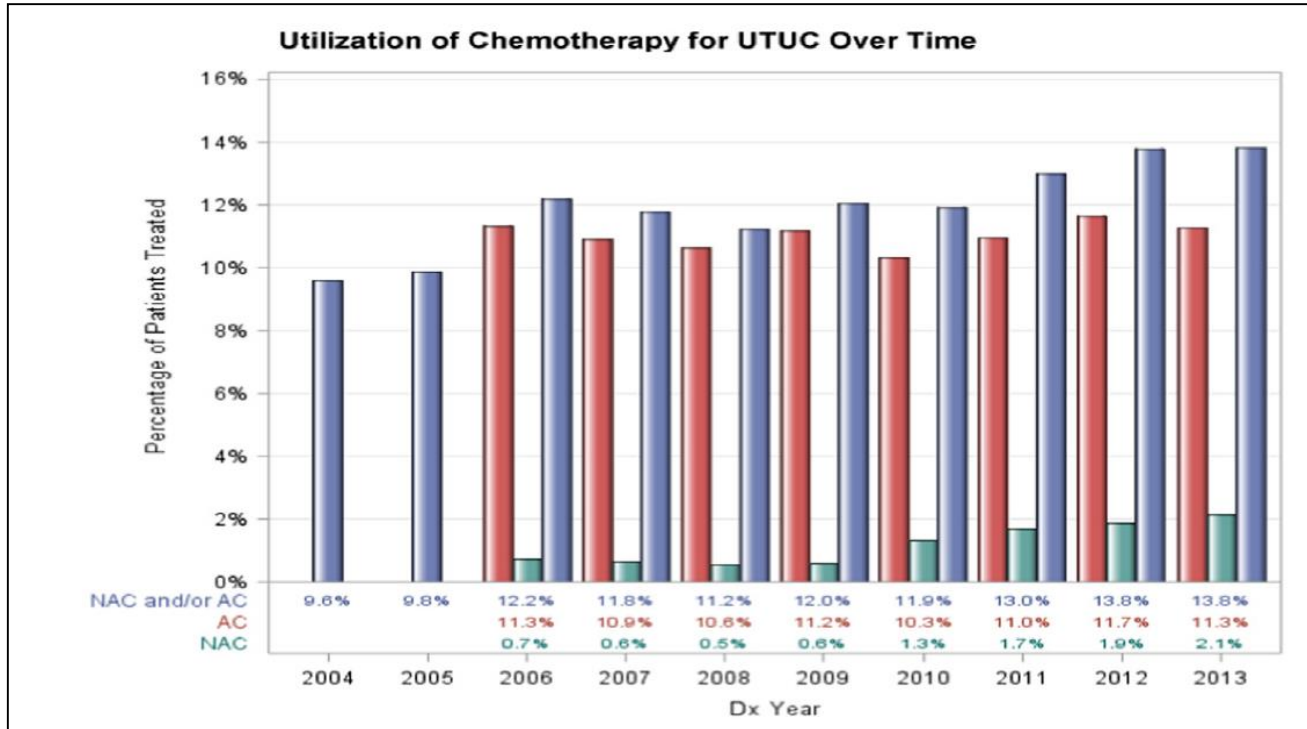
Blake Noennig, Shahab Bozorgmehri, Russell Terry, Brandon Otto, Mike Blute, Li-Ming Su, Paul Crispen; University of Florida, Gainesville, FL

Background: Results of randomized trials support a single dose of intravesical chemotherapy (IVC) following radical nephroureterectomy (RNU) for urothelial carcinoma. Our goal was to evaluate the impact of the timing of intravesical mitomycin C (MMC) administration on the rate of bladder tumor recurrence (BTR) following RNU.

Methods: After obtaining IRB approval, we performed a retrospective review of patients who underwent RNU for upper tract urothelial carcinoma (UTUC) and received intravesical MMC between 2008 and 2016 at our institution. Patients were categorized into two separate groups based on the timing of MMC administration: **(1) patients who received MMC on the day of surgery (POD0) and (2) patients who received MMC on post-operative day 1 or later (POD1).** Our primary endpoint was **BTR rate within the first year after surgery.** Our secondary endpoint was overall BTR rate.

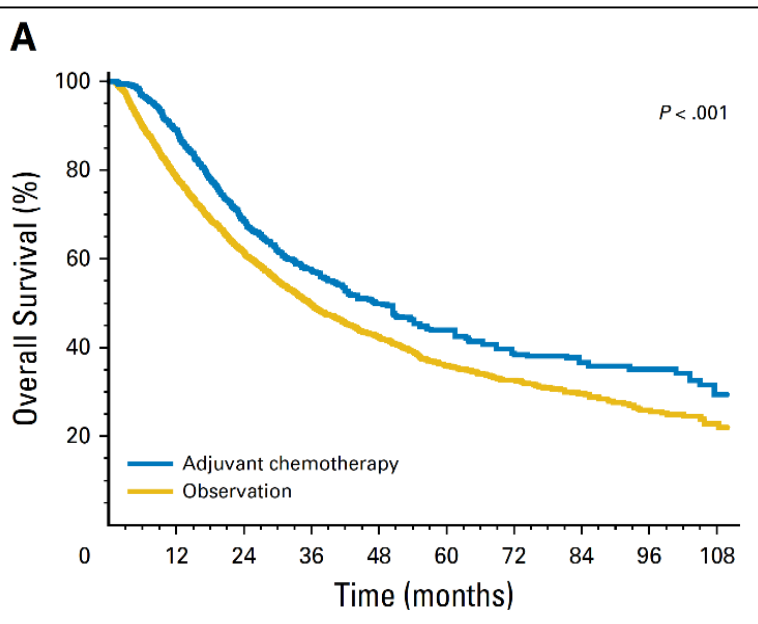
Results: **Fifty-one patients** met our inclusion criteria: (POD0: **n = 30**; POD1: **n = 21**). Mean length of follow-up for each group was 22.1 and 12.5 months, respectively ($p = 0.02$). There were no statistically significant differences in baseline characteristics of age, gender, race, surgical approach, tumor grade, tumor stage, surgical margins, nodal status, concomitant CIS, or history of bladder cancer. BTR rates at 1 year for the POD0 and POD1 groups were 16% and 33%, respectively ($p = 0.17$). **Overall BTR rates were 23% and 33%, respectively** ($p = 0.43$). Multivariate analysis noted that **the POD0 patients had a significantly lower rate of BTR in the first year postoperatively** (HR = 0.082, 95% CI = 0.01-0.56, $p = 0.01$). Other factors that were associated with a higher rate of BTR within the first year were open surgery (HR = 7.9, 95% CI = 1.18-53.88, $p = 0.03$), positive surgical margins (HR = 37.9, 95% CI = 1.74-825.35, $p = 0.02$), and concomitant CIS (HR = 10.8, 95% CI = 1.08-108.72). **Conclusions:** Our results suggest that the **timing of intravesical MMC administration may impact the rate of BTR following RNU for urothelial carcinoma.**

UTILIZATION OF PERIOPERATIVE SYSTEMIC CHEMOTHERAPY IN UPPER TRACT UROTHELIAL CARCINOMA

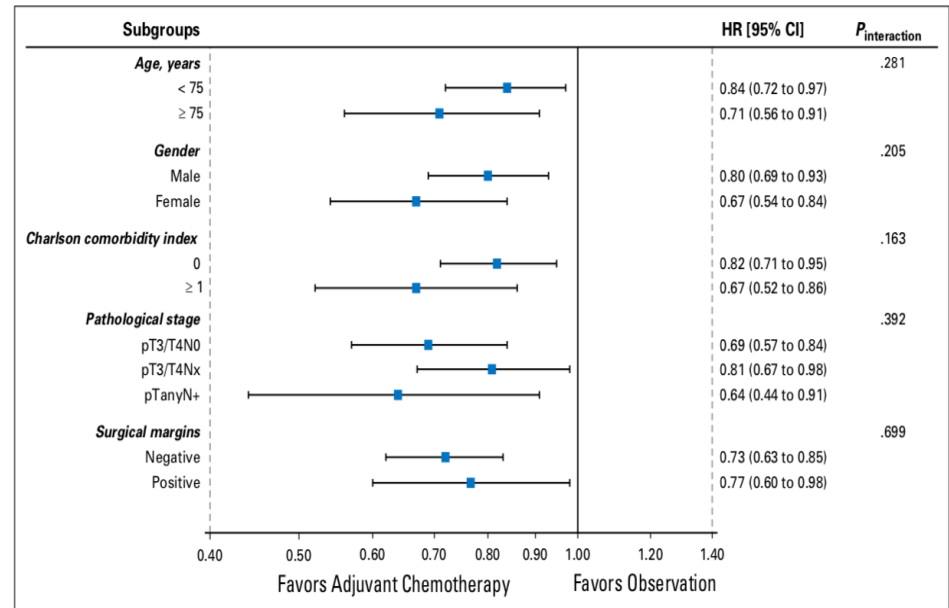


Effectiveness of Adjuvant Chemotherapy After Radical Nephroureterectomy for Locally Advanced and/or Positive Regional Lymph Node Upper Tract Urothelial Carcinoma

Thomas Seisen, Ross E. Krasnow, Joaquim Bellmunt, Morgan Rouprêt, Jeffrey J. Leow, Stuart R. Lipsitz, Malte W. Vetterlein, Mark A. Preston, Nawar Hanna, Adam S. Kibel, Maxine Sun, Toni K. Choueiri, Quoc-Dien Trinh, and Steven L. Chang



Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	Nei pazienti con carcinoma uroteliale della vescica e stadio patologico pT3-4 pN- o qualsiasi pT pN+ (se non precedentemente trattati con chemioterapia neoadiuvante e se candidabili a cisplatino) può essere presa in considerazione una polichemioterapia adiuvante comprendente cisplatino	Positiva debole





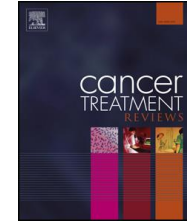
Anti-Tumour Treatment

Adjuvant and neoadjuvant approaches for urothelial cancer: Updated indications and controversies



Francesco Massari^{a,1}, Matteo Santoni^{b,*,1}, Vincenzo di Nunno^a, Liang Cheng^c, Antonio Lopez-Beltran^d, Alessia Cimadamore^e, Silvia Gasparrini^e, Marina Scarpelli^e, Nicola Battelli^b, Rodolfo Montironi^e

^aDivision of Oncology, S. Orsola-Malpighi Hospital, Bologna, Italy



Ongoing clinical adjuvant trials in non-muscle invasive-transitional carcinoma. UC: Urothelial Carcinoma, RR: Recurrence Rate, DFS: Disease Free survival, CRR: Complete Response Rate, RFS: Relapse free survival, EFS: Event Free survival.

Adjuvant trials in non muscle-invasive transitional carcinoma

Study	Experimental arm	Comparator arm	Primary endpoint	Population in study	Phase	N
NCT02901548	DURVALUMAB	NONE	CRR	CIS of the bladder with persistence or progression or recurrence of high-grade CIS after BCG	II	34
NCT02844816	ATEZOLIZUMAB	NONE	EFS, CRR	T1 high-grade, stage CIS, or stage Ta high-grade	II	148
NCT03317158	DURVALUMAB	NONE	6 months EFS	T1 high-grade, stage CIS, or stage Ta high-grade	II	186
NCT03062059	GEMCITABINE	NONE	2 years DFS	Nephroureterectomy due to ureter or renal pelvis UC	II	134
NCT03209206	DOCETAXEL	NONE	RR	Upper urinary tract UC	II	84
NCT03030157	PIRARUBICIN single instillation	PIRARUBICIN Long term instillation	12 months RR	Upper urinary tract UC	II	220
NCT02547350	PIRARUBICIN single instillation	PIRARUBICIN Long term instillation/Observation	RR	Upper urinary tract UC	II	200
NCT02740426	PIRARUBICIN single instillation	OBSERVATION	RFS	Upper urinary tract UC	II	200
NCT02438865	EPIRUBICIN single instillation	EPIRUBICIN Maintenance	RR	Upper urinary tract UC	II	80
NCT03091660	BCG	BCG + Tumour Vaccine	RR	High grade bladder UC	III	969

NEOADJUVANT PHASE 2 TRIALS FOR UPPER TRACT UROTHELIAL CARCINOMA

Agents	Sponsor	ClinicalTrials.gov Identifier	Patient Selection	Design	Primary Endpoint	Sample Size
Gem-Cis	Xiangya Hospital of Central South University	NCT02876861	High grade UTUC	Single arm Phase 2	OS	50
Durvalumab + Tremelimumab	MDACC, MedImmune	NCT02812420	High risk UTUC, CDDP-ineligible	Single arm Phase 2	Safety	15
Gem-Cis	MSKCC	NCT01261728	High grade UTUC	Single arm Phase 2	Path Response	54
Gem-Carbo; DD-MVAC	ECOG-ACRIN	NCT02412670	High grade UTUC	Non-randomized Phase 2	pCR	60

- No neoadjuvant trials for high-risk UTUC are running in EU

ONGOING **PHASE 3 TRIALS**: POSTOPERATIVE SETTING FOR HIGH-RISK PATIENTS WITH BLADDER OR UPPER TRACT UROTHELIAL CANCER

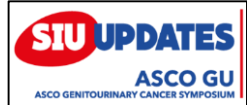
Study	Agent	ClinicalTrials.gov Identifier	PD-L1 Selection	Standard Arm	Primary Endpoint	Sample Size
IMvigor010	Atezolizumab	NCT02450331	Yes ^a	Observation	DFS	440
CheckMate 274	Nivolumab	NCT02632409	No	PBO	DFS	600
Ambassador	Pembrolizumab	TBD	No	PBO	TBD	TBD

^a No PD-L1 selection in the amended trial design.
 DFS: disease-free survival; PBO: placebo; TBD: to be determined.

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Interim results from PURE-01: A phase 2, open-label study of neoadjuvant pembrolizumab (pembro) before radical cystectomy for muscle-invasive urothelial bladder carcinoma (MIUC).

Presented Friday, February 9, 2018 Authors:

Andrea Necchi, Alberto Briganti, Daniele Raggi, Patrizia Giannatempo, Luigi Mariani, Antonella Messina, Andrea Anichini, Giuseppina Calareso, Flavio Crippa, Mario Catanzaro, Nicola Fossati, Giorgio Gandaglia, Andrea Salonia, Roberto Salvioni, Francesco Montorsi; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Vita-Salute San Raffaele University, Urological Research Institute

Background: MIUC is an aggressive disease and > 40% of patients (pts) will develop recurrence after radical cystectomy (RC). Despite cisplatin-based neoadjuvant chemotherapy yields Level 1 evidence, it is administered in a minority of pts worldwide. Pembro is an EMA and FDA-approved standard therapy for metastatic UC after platinum failure or for cisplatin-ineligible pts. Our hypothesis was that pembro, given neoadjuvantly, could downstage MIUC and reduce recurrence.

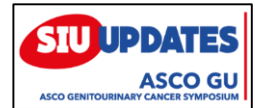
Methods: **PURE-01 (NCT02736266) is an open-label, single-arm, phase 2 study to evaluate the activity, medical and surgical safety, and immune modulatory effects of pembro administered as a short window-of-opportunity course of therapy preceding RC.** Eligibility criteria included: **T2-T4aNO stage, and residual disease after transurethral resection of the bladder** (TURB, surgical opinion, cystoscopy or radiological presence). The study includes cisplatin eligible- and ineligible pts. Pts receive 3 cycles of pembro 200mg 3 weekly before RC (planned < 3 weeks of the last dose). Computed tomography (CT) scan, FDG-PET/CT scan, and bladder multiparametric magnetic resonance imaging (mpMRI) are done during screening and before RC. Radiologically non responders to pembro (per investigator decision; i.e., study failures) are given 3 additional courses of dose-dense MVAC chemotherapy. After RC, pts are managed according to local guidelines (adjuvant chemotherapy vs observation). Further anti PD-1/PD-L1 therapy will not be given post-operatively. **Pathologic complete response (pT0) is the primary endpoint.** All pts enrolled who receive at least 1 cycle of study drug will be included in the ITT analysis. The H_1 is $pT0 \geq 20\%$ and $H_0 pT0 \leq 10\%$. In a 2-stage design, 90 pts overall will be accrued (80% power and a 2-sided test of significance at the 10% level). A first interim analysis for safety is planned after 18 patients enrolled and treated (by December 1st, 2017). Activity results and early translational findings (immune-cell profiling) will be added, and may be regarded to as first data of preoperative immunotherapy before major surgery. Clinical trial information: [NCT02736266](https://clinicaltrials.gov/ct2/show/study/NCT02736266)

OSR overall
enrolled patients:
36
June 18th 2018

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Comparative effectiveness of bladder-preserving tri-modality therapy versus radical cystectomy for muscle-invasive bladder cancer.

Presented Friday, February 9, 2018 Authors:

Trevor Joseph Royce, Adam S. Feldman, Matthew Mossanen, Joanna C. Yang, William U. Shipley, Pari Pandharipande, Jason A. Efstathiou; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital/ Harvard Medical School, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Institute for Technology Assessment, Massachusetts General Hospital, Boston, MA

Background: This study compared the effectiveness of TMT and RC using decision-analytic modeling with the primary endpoint of quality-adjusted life years (QALYs).

Methods: We developed a Markov model simulating the lifetime outcomes for 67-year-old patients after definitive treatment for American Joint Committee on Cancer clinical Stage T2-T4aN0M0 MIBC using two strategies: TMT or RC +/- neoadjuvant chemotherapy (NAC). Probabilities and utilities were extracted from the literature to determine the incremental effectiveness in QALYs. Sensitivity analyses were performed.

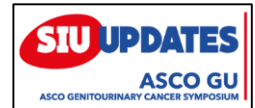
Results: TMT was the most effective strategy with an incremental gain of 1.13 QALYs over RC (8.37 versus 7.24 QALYs, respectively). One-way sensitivity analyses demonstrated the model was most sensitive to the quality of life (QoL) parameters (i.e. the utilities) for RC and TMT; TMT was more effective than RC irrespective of the RC utility (the 95% confidence interval of the RC parameter demonstrated an incremental gain with TMT of 0.01 to 4.77 QALYs). The model was relatively less sensitive to the probability of death for either strategy. Probabilistic sensitivity analysis demonstrated that TMT was more effective than RC for 75% of model iterations.

Conclusions: Treatment of MIBC with organ-sparing TMT in appropriately-selected patients may result in a gain of over 1 QALY relative to RC.

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Survival outcomes and costs of trimodal therapy compared with radical cystectomy among patients diagnosed with localized muscle-invasive bladder cancer.

Presented Friday, February 9, 2018 Authors:

Stephen Bentley Williams, Yong Shan, Usama Jazzar, Hemalkumar B Mehta, Jacques G. Baillargeon, Jinhai (Stephen) Huo, Eduardo Orihuela, Douglas S. Tyler, Todd A. Swanson, Ashish M. Kamat; UT MD Anderson Cancer Center, Pearland, TX; UT Medical Branch at Galveston, Galveston, TX; UT MD Anderson Cancer Center, Houston, TX; Duke University Medical Center, Hillsborough, NC

Methods: A total of 3,200 patients aged 66 years or older diagnosed with **clinical stage T2-4a bladder** cancer from January 1, 2002- December 31, 2011 from the Surveillance, Epidemiology, and End Results (**SEER**)-**Medicare** data were analyzed. Cox regression analysis and propensity score matching methods were used to determine predictors for overall and cancer-specific survival.

Results: A total of **3,200 patients** met inclusion criteria. After **propensity score matching, 687 patients underwent trimodal therapy and 687 patients underwent radical cystectomy. Patients who underwent trimodal therapy had significantly decreased overall** (Hazard Ratio (HR) 1.49, 95% Confidence Interval (CI), 1.31-1.69, $p < 0.001$) **and cancer-specific** (HR 1.55, 95% CI 1.32-1.83, $p < 0.001$) **survival**, respectively. While there was no difference in costs at 30 days, **median total costs were significantly higher with trimodal therapy than radical cystectomy at 90-d** (\$63,355 vs. \$73,420, $p < 0.001$) and 180-d (\$98,005 vs. \$164,720, $p < 0.001$), respectively. Extrapolating these figures to the total US population results in excess spending of \$179 million for trimodal therapy compared to less costly radical cystectomy for patients diagnosed in 2011.

Conclusions: Trimodal therapy was associated with significantly decreased overall and cancer-specific survival resulting in excess national spending of \$179 million in 2011 compared with radical cystectomy.

Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder Cancer Clinic

Girish S. Kulkarni, Thomas Hermanns, Yanliang Wei, Bimal Bhindi, Raj Satkunasivam, Paul Athanasopoulos, Peter J. Bostrom, Cynthia Kuk, Kathy Li, Arnold J. Templeton, Srikala S. Sridhar, Theodoros H. van der Kwast, Peter Chung, Robert G. Bristow, Michael Milosevic, Padraig Warde, Neil E. Fleshner, Michael A.S. Jewett, Shaheena Bashir, and Alexandre R. Zlotta

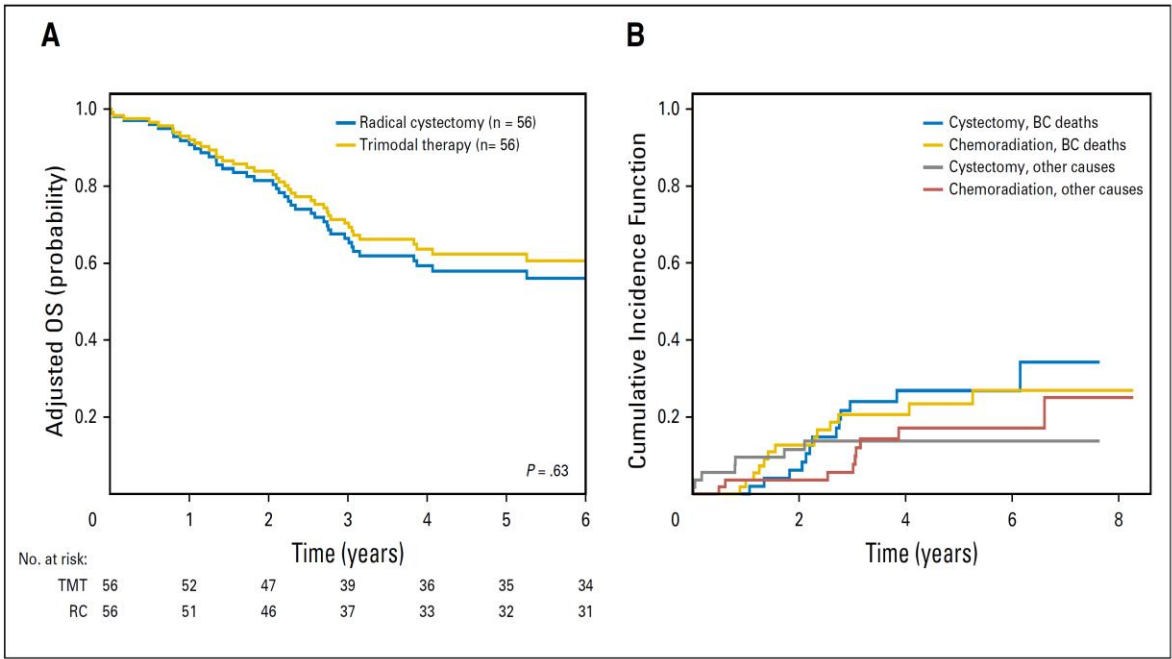


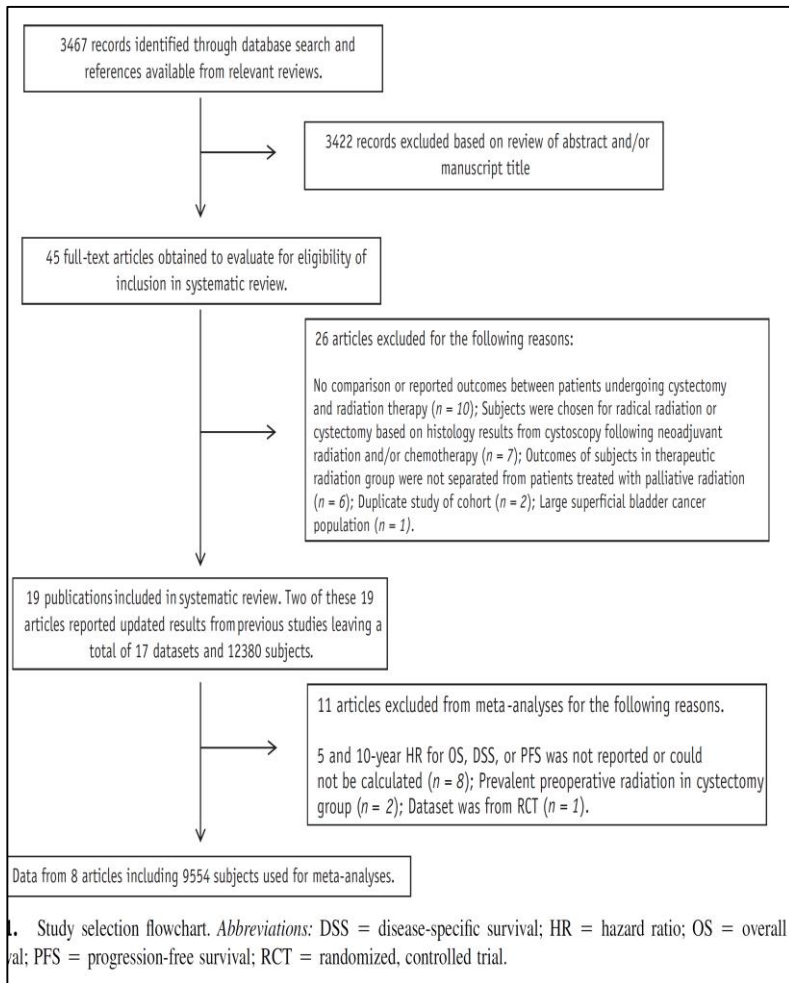
Fig 2. Propensity score matched survival outcomes of patients after radical cystectomy versus trimodality therapy chemoradiation. (A) Kaplan-Meier curve of overall survival (adjusted for treatment, TMT v RC); and (B) cumulative incidence function for disease-specific survival. BC, bladder cancer; OS, overall survival; RC, radical cystectomy; TMT, trimodal therapy.

Results

A total of 112 patients with MIBC were included after matching (56 who had been and 56 who underwent RC). The median age was 68.0 years, and 29.5% had stage At a median follow-up of 4.51 years, there were 20 deaths (35.7%) in the RC group (BC) and 22 deaths (39.3%) in the TMT group (13 as a result of BC). The 5-year D and 76.6% in the RC and TMT groups, respectively ($P = .49$). Salvage cystectomy 6 (10.7%) of 56 patients who received TMT.

Conclusion


In the setting of a MDBCC, TMT yielded survival outcomes similar to those of men who underwent RC. Appropriately selected patients with MIBC should be offered to discuss various treatment options, including organ-sparing TMT.



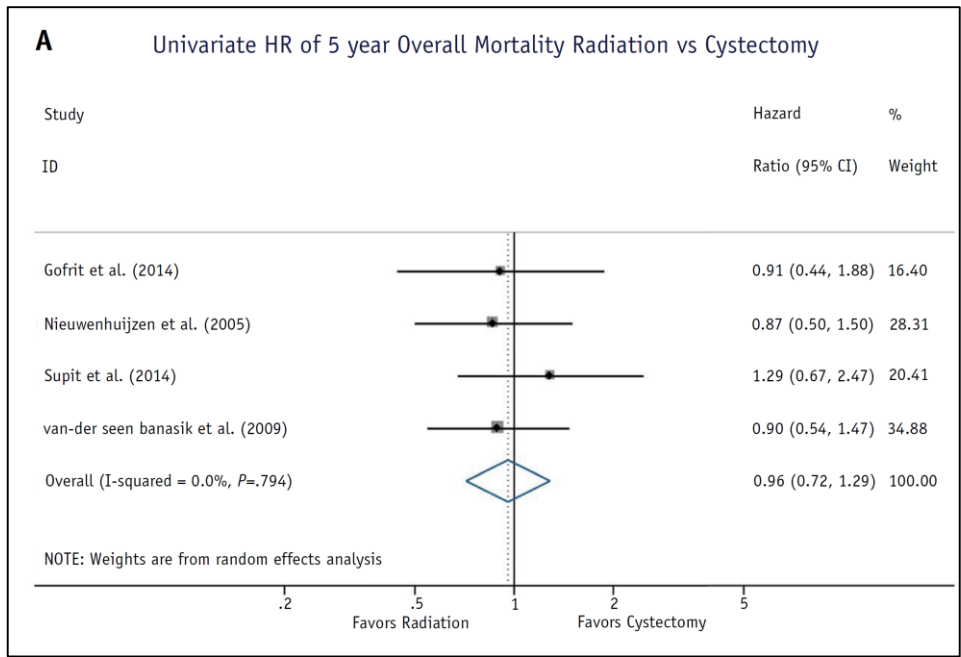
Clinical Investigation

Radical Cystectomy Compared to Combined Modality Treatment for Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-Analysis

Vishal Vashistha, MD,* Hanzhang Wang, MS,† Andrew Mazzone, BS,† Michael A. Liss, MD,† Robert S. Svatek, MD,† Mary Schleicher, RN, BSN, MLIS,* and Dharam Kaushik, MD†



2018



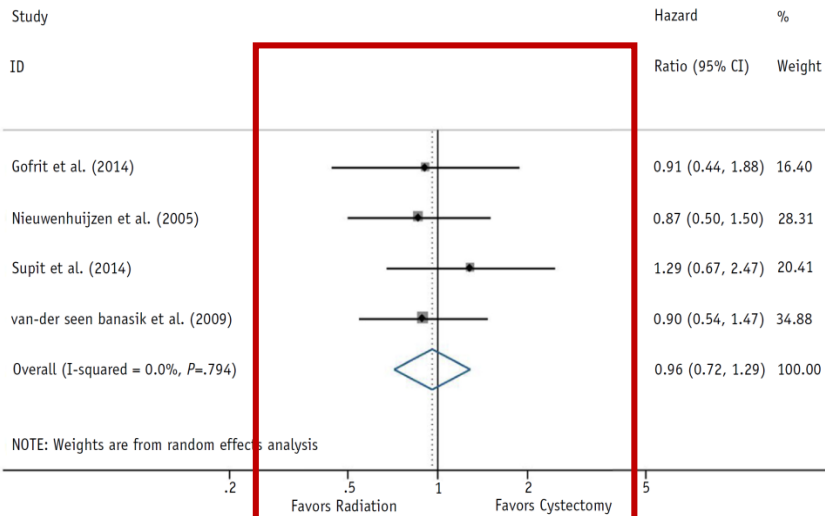
Clinical Investigation

Radical Cystectomy Compared to Combined Modality Treatment for Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-Analysis

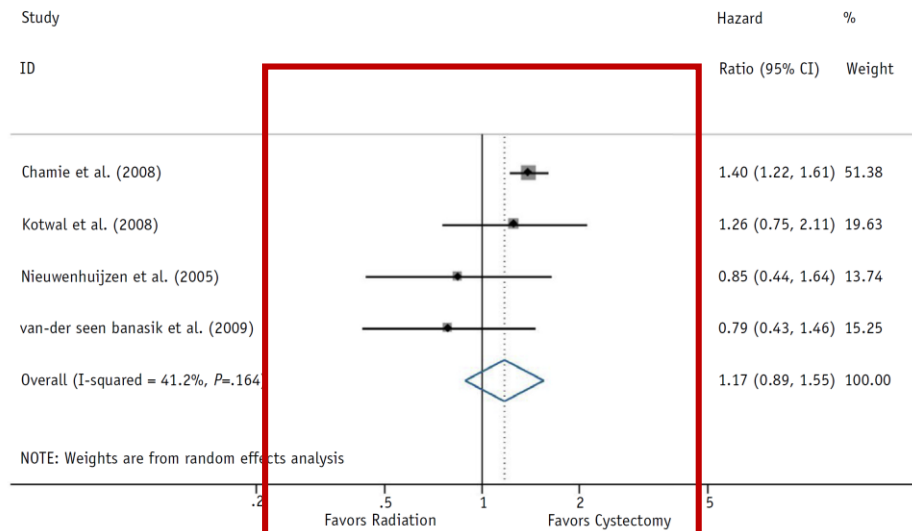


Vishal Vashistha, MD,* Hanzhang Wang, MS,† Andrew Mazzone, BS,‡
Michael A. Liss, MD,† Robert S. Svatek, MD,† Mary Schleicher, RN, BSN, MLIS,*
and Dharam Kaushik, MD†

A Univariate HR of 5 year Overall Mortality Radiation vs Cystectomy



D Univariate HR of 10 year Disease Specific Mortality Radiation vs Cystectomy





Review article

A systematic review and meta-analysis on the oncological long-term outcomes after trimodality therapy and radical cystectomy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer

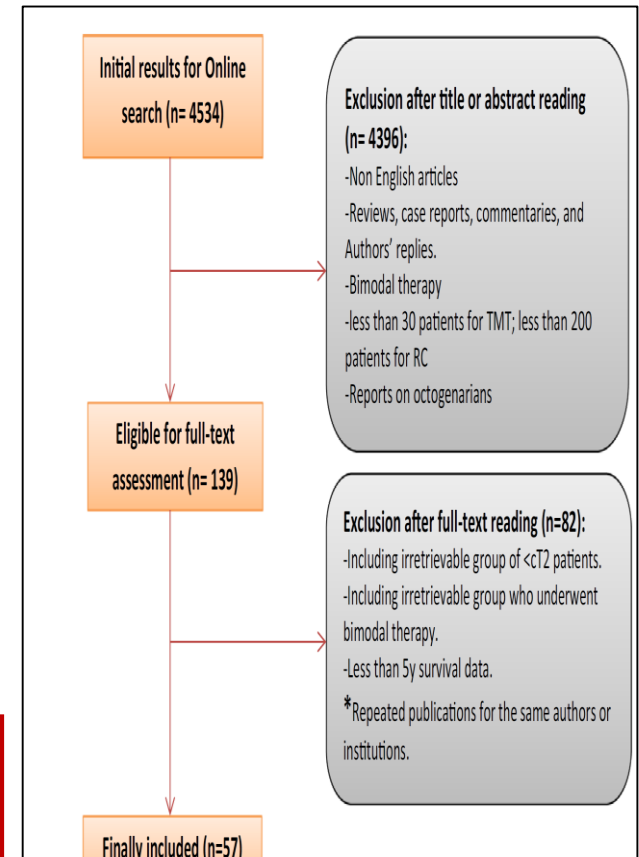
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Objective: This study aimed to comprehensively analyze the oncological long-term outcomes of trimodal therapy (TMT) and radical cystectomy (RC) for the treatment of muscle-invasive bladder cancer (BC) with or without neoadjuvant chemotherapy (NAC).

Patients and methods: A systematic search was conducted according to the PRISMA guidelines for studies reporting on outcomes after TMT and RC. A total of 57 studies including 30,293 patients were included. The 10-year overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) rates for TMT and RC were assessed.

Results: The mean 10-year OS was 30.9% for TMT and 35.1% for RC ($P = 0.32$). The mean 10-year DSS was 50.9% for TMT and 57.8% for RC ($P = 0.26$). NAC was administered before therapy to 453 (13.3%) of 3,402 patients treated with TMT and 812 (3.0%) of 27,867 patients treated with RC ($P < 0.001$). Complete response (CR) was achieved in 1,545 (75.3%) of 2,051 evaluable patients treated with TMT. A 5-year OS, DSS, and RFS after CR were 66.9%, 78.3%, and 52.5%, respectively. Downstaging after transurethral bladder tumor resection or NAC to stage $\leq pT1$ at RC was reported in 2,416 (29.1%) of 8,311 patients. NAC significantly increased the rate of pT0 from 20.2% to 34.3% ($P = 0.007$) in cT2 and from 3.8% to 23.9% ($P < 0.001$) in cT3–4. A 5-year OS, DSS, and RFS in downstaged patients ($\leq pT1$) at RC were 75.7%, 88.3%, and 75.8%, respectively.

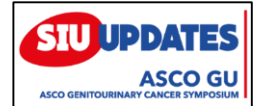
Conclusion: In this analysis, the survival outcomes of patients after TMT and RC for MIBC were comparable. Patients who experienced downstaging after NAC and RC exhibited improved survival compared to patients treated with RC only. Best survival outcomes after TMT are associated with CR to this approach. © 2018 Elsevier Inc. All rights reserved.



2018 Genitourinary Cancers Symposium

TRANSLATING EVIDENCE TO MULTIDISCIPLINARY CARE

February 8-10, 2018 | Moscone West Building | San Francisco, CA | #GU18



Genomic profiling of muscle invasive bladder cancer to predict response to bladder-sparing trimodality therapy.

Presented Friday, February 9, 2018 Authors:

David Tomoaki Miyamoto, Ewan Gibb, Kent William Mouw, Yang Liu, Chin-Lee Wu, Michael Drumm, Jonathan Lehrer, Hussam Al-Deen Ashab, Nicholas Erho, Marguerite Du Plessis, Kaye Ong, William U. Shipley, Elai Davicioni, Jason A. Efstathiou; Massachusetts General Hospital/ Harvard Medical School, Boston, MA; GenomeDx Biosciences Inc., Vancouver, BC, Canada; Dana-Farber Cancer Institute

Background: Genomic profiling has demonstrated MIBC can be divided into molecular subtypes with differing responses to chemotherapy. We **explored the utility of genomic data to select patients for bladder-sparing trimodality therapy.**

Methods: Transcriptome wide gene expression profiles were generated for 189 MIBC TURBT samples from patients treated with trimodality therapy at a single institution. Of these, 103 passed microarray QC. **Molecular subtype and expression of bladder cancer genes were assessed for association with overall and disease-specific survival.**

Results: The chemoradiation cohort (n = 103) had a median followup of 6.9 years for alive patients, and was classified into **four subtypes: basal (n = 44), basal claudin-low (n = 12), infiltrated luminal (n = 17) and luminal tumors (n = 30).** **There was no significant difference in overall or disease-specific survival by subtype.** However, higher expression of the **luminal-associated PPARG** was correlated with increased survival after adjusting for subtype and clinical factors (HR = 0.52, p = 0.002). In contrast, a **p53** signature predicted worse survival after adjusting for clinical factors (HR = 1.92, p = 0.022). Elevated mRNA expression of the DNA damage repair **gene MRE11** was associated with improved survival in the trimodality cohort (HR = 0.69, P = 0.031), consistent with its potential role as a predictive biomarker for radiation response.

Conclusions: Transcriptional profiling of MIBC revealed gene signatures correlated with response to chemoradiation, suggesting the potential of genomics to guide use of trimodality therapy.



**“TRATTAMENTO CONSERVATIVO TRIMODALE DI
ELEZIONE IN PAZIENTI SELEZIONATI AFFETTI DA
NEOPLASIA VESCICALE MUSCOLO INVASIVA
ORGANO CONFINATA”**

Coordinatori Task Force Vescica Urinaria:

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Task Force:

Gruppo degli Urologi – Luca Cristinelli
Gruppo dei Radioterapisti – Barbara Jereczek Fossa
Gruppo degli Oncologi Medici – Claudio Verusio



**STUDIO OSSERVAZIONALE TMT
(STANDARD MINIMI)**

CRITERI DI INCLUSIONE

CRITERI D'INCLUSIONE CORRELATI AL PAZIENTE

(necessaria la soddisfazione contemporanea di tutti i requisiti):

- Karnofsky 80-100%, ECOG ≤ 2
- Charlson Index < 5
- Clearance creatinine calcolata ≥ 60 ml/min
- Volume vescicale (valutazione ecografica e/o flussometrica) ≥ 150 ml
- Residuo vescicale post minzionale (valutazione ecografica e/o flussometrica) < 100 cc
- Disponibilità a procedere a cistectomia di salvataggio (definita dopo colloquio multidisciplinare)
- Firma di un Consenso Informato **[Allegato n.1]** che includa anche il punto precedente

CRITERI DI INCLUSIONE

- **CRITERI DI INCLUSIONE CORRELATI ALLA MALATTIA:**
- Neoplasia vescicale transizionale organo confinata (cT2 - cT3a)
- Lesione unica di diametro massimo ≤ 5 cm (documentata endoscopicamente)
- Numero di neoplasie ≤ 3 per un diametro complessivo ≤ 5 cm (documentate endoscopicamente)
- Stadio clinico N0, M0 (documentate da TC torace e addome con mdc e scintigrafia ossea/PET negative per secondarismi)

CRITERI DI ESCLUSIONE

CRITERI DI ESCLUSIONE CORRELATI AL PAZIENTE

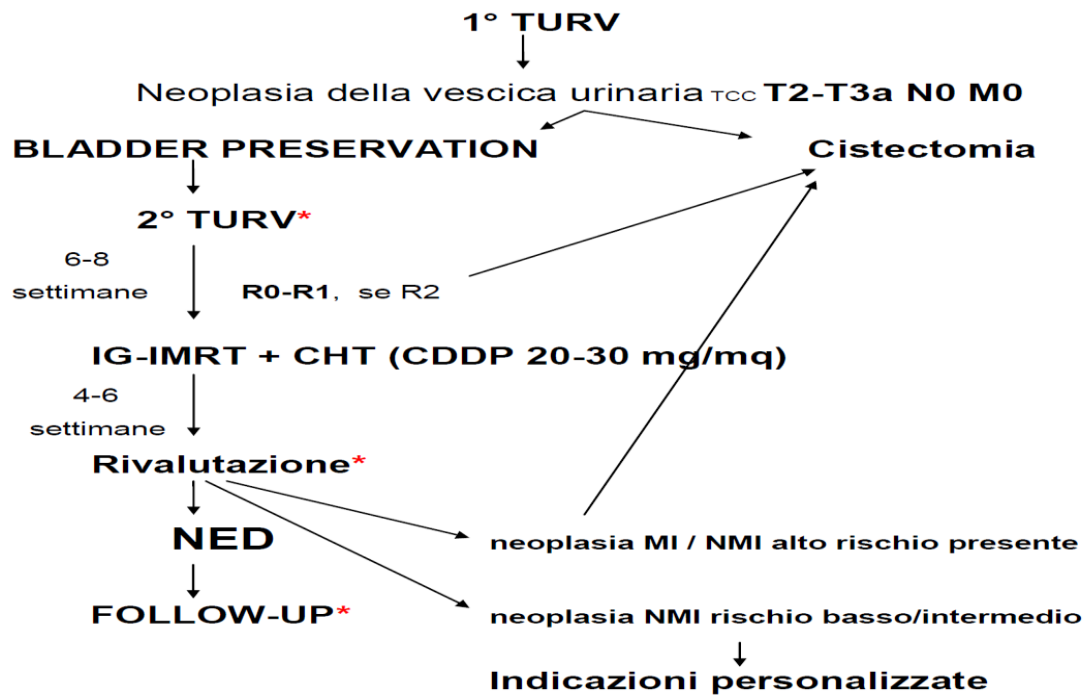
- Progresa RT pelvica indipendentemente dalla patologia primitiva trattata
- Seconda neoplasia (escluso basalioma)
- Assoluta indisponibilità a procedere ad intervento chirurgico di salvataggio

CRITERI DI ESCLUSIONE CORRELATI ALLA MALATTIA:

- Neoplasia vescicale clinicamente non muscolo invasiva stadio Ta/T1
- Malattia multifocale (>3 lesioni)
- Presenza di CIS associato in oltre il 30% delle biopsie ottenute mediante mapping vescicale (includente almeno 1 biopsia per settore: parete laterale destra, sinistra, posteriore, cupola, anteriore, trigono)
- Presenza di neoplasia transizionale documentata all'uretra prostatica
- Presenza di neoplasia transizionale o di patologia ostruttiva documentata a carico delle alte vie escretrici
- Stadio clinico N+/M+
- Localizzazione endodiverticolare della neoplasia vescicale
- Idro-ureteronefrosi correlata alla neoplasia vescicale
- Coinvolgimento neoplastico diffuso del collo vescicale

BLADDER PRESERVATION

FLOW-CHART



*Sec. Protocollo Standard minimi ROL

RADIOTERAPIA

- PTV Vescica urinaria in toto: non oltre 60.8 Gy in 32 frazioni (1,9 Gy/fr)
- PTC Boost (SIB) su sede di pregressa neoplasia: 64 Gy in 32 frazioni (2 Gy/fr)
- PTV Linfonodi pelvici: 51,2 Gy in 32 frazioni (1,6 Gy/fr): iliaci interni, esterni ed otturatori e presacrali
- La dose PTV linfonodale può essere aumentata fino a 1,7 Gy x 32 frazioni → 54,4 Gy (in relazione al volume, vicinanza anse ecc.)

Quindi:

SIB: PTVI (ex sede di T vescicale): 64 Gy in 32 frazioni (2 Gy/fr)

PTVII (vescica): 57,6 Gy in 32 fr (1,8 Gy/fr) - 60,8 Gy in 32 frazioni (1,9 Gy/fr)

PTVII (pelvi): 51,2 Gy in 32 frazioni (1,6 Gy/fr) - 54,4 Gy in 32 frazioni (1,7 Gy/fr)

IG-IMRT


SIB

FOLLOW-UP

	Fine trattamento	6 m	12 m	15 m	18 m	21 m	24 m	Poi ogni 6 m	Poi ogni 12m
UCS* in anestesia	√	√	√						
Biopsie a caldo di cicatrice	√	√	√						
Biopsie caldo/freddo di aree sospette	√	√	√						
UCS* live				√	√	√	√	√	
<u>Tc</u> TAP		√	√		√		√		√
PAP** trimestrali				√	√	√	√		
PAP** semestrali								√	
Questionari (QOL, IPSS, IIEF-5)	√	√	√				√		√

*UCS: Uretrocistoscopia

Emerging critical issues

- 1. PRECISION SELECTION:** It is currently not possible to select patients for therapy based on IHC, clinical parameters, TCGA subgroups or second generation biomarkers such as mutational load, gene signatures or the presence of microsatellite instability. *What is meant with this?*
 - 2. QUALITY OF THE STUDIES AND RESULTS:** there are many trials ongoing but we actually do not know what is the elective clinical setting and the most adequate schedule for CPI administration. *Where we are now?*
 - 3. TREATMENT-RELATED AEs:** the toxicity of CPI therapy is consistently different than that after conventional CT. *Are we ready to identify and face novel AEs?*
 - 4. COST/EFFECTIVENESS:** CPI therapy is expected to be not bearable in the next future. *What shall we do to make it available in individualized patients in different countries?*
- 

Emerging critical issues

1. PATIENTS SELECTION

The expression of PD-1/PD-L1 by IHC assays in UC is extremely variable according to the different drugs and the different clinical setting.

How this expression me be assumed as a predictive biomarker of clinical benefit?

Role and limits of different assays:

- variability
- reproducibility
- equivalence
- significance

Programmed Cell Death 1 (PD-1) Ligand (PD-L1) Expression in Solid Tumors As a Predictive Biomarker of Benefit From PD-1/PD-L1 Axis Inhibitors: A Systematic Review and Meta-Analysis

Monica Khunger
 Adrian V. Hernandez
 Vinay Pasupuleti
 Sagar Rakshit
 Nathan A. Pennell
 James Stevenson
 Sanjay Mukhopadhyay
 Kurt Schalper
 Vamsidhar Velcheti

2017 by American Society of Clinical Oncology

Significantly higher ORRs were observed for PD-L1 positive tumors VS PD-L1-negative tumors in

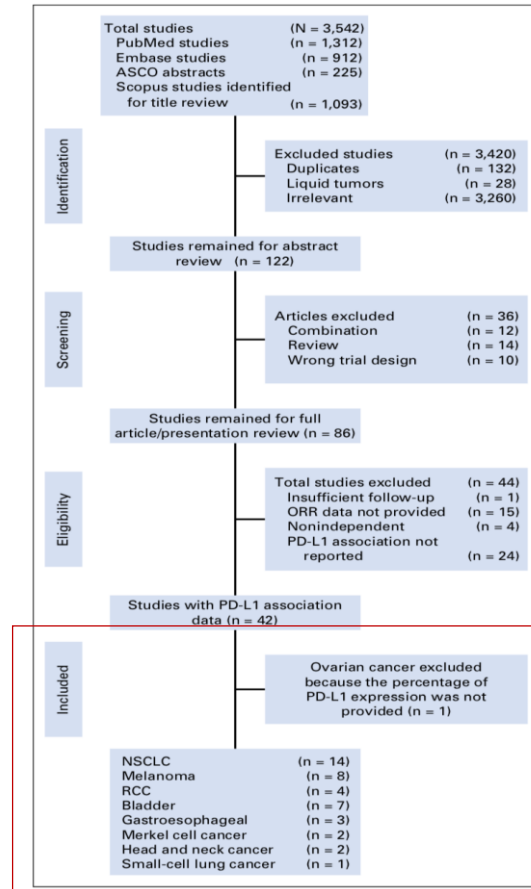
- NSCLC (14 trials ; OR, 2.51)
- Melanoma (8 trials OR 2.04) and
- **Bladder cancer (7 trials, OR 2.20)**

Pembro was approved by FDA for patients with NSCLC in the front-line setting with TC PD-L1 expression > 50% and for mUC with TC PD-L1 expression cut-off > 1%

In some studies patients respond to PD-1/PD-L1 axis inhibitors despite negative tumor PD-L1 expression

1° critical point: *Currently, different methods of measuring PD-L1 status exists for each drug and the results are not interchangeable. There is no evidence supporting the PD-L1 biomarker for selecting patients for ICI therapy in chemotherapy-naive patients.*

What is the current role of IHC assays in patient selection?



Emerging critical issues

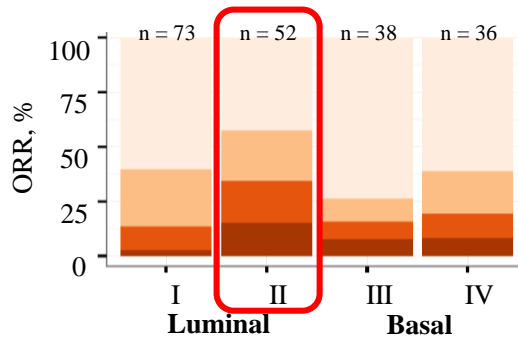
1. PATIENTS SELECTION

Different molecular Subtypes TCGA were found to correlate with different clinical stage of BC (NMIBC/MIBC/mMIBC) and different clinical response and OS after ICI therapy.

What is (should be) the role of individual immunophenotype in the design of clinical studies and in patient selection?

- **luminal-papillary**
- **luminal–infiltrating**
- **basal/squamous**
- **neuronal**

TCGA Subtype II Is Associated With Higher ORR to Atezolizumab therapy



Luminal II tumors have high T_{eff} and low stromal gene expression

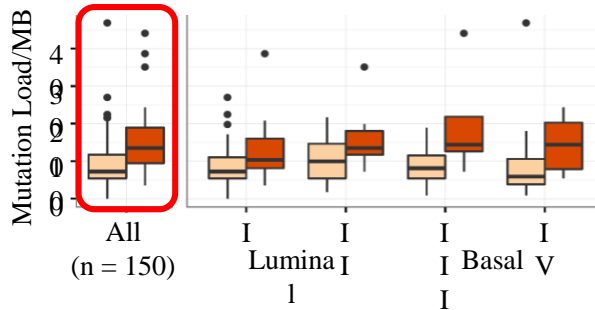
PD-L1 IC

TCGA Subtype

PD-L1 IC + TCGA Subtype + Mutation Load

Rosenberg JE et al, Lancet 2016

Mutation Load by FoundationOne and Response/Survival to Atezolizumab therapy



Mutation Load

Microsatellite instability (MSI)?

2° critical point:
IHC alone or in combination with TCGA subtype and mutation load?
MSI high or mutational load predictive?

Balar AV, Lancet 2017

Emerging critical issues

2. QUALITY OF THE STUDIES AND RESULTS

There are currently many clinical trials ongoing in different settings:

- neo-adjuvant
- adjuvant
- for metastatic and non metastatic
- for eligible and non eligible CDDP
- for exposed and never treated CDDP
- for MIBC and NMIBC
- ICI vs CT
- ICI and CT in combination or sequence
- Single agent and multidrugs in different settings

Too many?

Why not only PRTs?

Strategies based on ICI and new drugs require the collaboration of

- urologists
- medical oncologists
- pathologists
- biologists and gene codification and
- therapy experts

Are we ready?

Emerging critical issues

SYSTEMIC IMMUNOTHERAPY IN GU CANCER HOW TO EVALUATE THE CLINICAL BENEFIT?

Since there are no reliable clinical or biological markers of ICI therapy activity, radiologic evaluation plays a leading role in decision-making care.

How much the definition of clinical response could be influenced by the quality of radiology?

Poor correlation between OR or PFS with OS.

How this may limit the evaluation of the real efficacy of ICI?

Response rate correlates poorly with OS, but 6-month PFS is a better predictor of 12-month OS.

Ritchie et al. JAMA Oncol; 2018

6-month PFS as a primary end point?

Emerging critical issues

SYSTEMIC IMMUNOTHERAPY IN GU CANCER HOW TO EVALUATE THE CLINICAL BENEFIT?

THE PROBLEM OF PSEUDOPROGRESSIONS

Some patients with apparent progressive disease on the basis of traditional response criteria (RECIST) had delayed deep and durable response when they continued with CPI therapy. Pseudoprogression may reflect immune infiltration and not tumor cell infiltration

Escudier et al. Eur Urol 2017

- 1. Should treatment beyond progression be considered due to potential pseudoprogression?*
- 2. Are there now immuno-response criteria on imaging we have to follow (at least in clinical trials?)*
- 3. Where we are with radiomics?* (analyze data extracted from standard medical imaging to generate imaging biomarkers)
Sun et al. NCI-EORTC-AARC 2017
- 4. cfDNA (liquid biopsy)?* Is this the way of the near future?

Emerging critical issues

TREATMENT-RELATED AEs:

The ICI therapy-related toxicity is consistently different in grade and quality than that known after conventional CT

- hypertension
- fatigue
- nausea
- mucosal inflammation
- proteinuria
- stomatitis
- asthenia
- decreased appetite
- vomiting
- constipation

Any organ system may be affected by immuno-related AEs

- hypothyroidism
- hyperthyroidism
- pneumonitis
- hypophysitis
- hepatitis
- type-1 DM
- severe skin reaction
- colitis

Are we ready to recognize and treat them adequately?

Emerging critical issues

COST/EFFECTIVENESS

[Eur Urol](#). 2018 Mar 22.

Cost-effectiveness of Pembrolizumab in Second-line Advanced Bladder Cancer.

[Sarfaty M](#)¹, [Hall PS](#)², [Chan KKW](#)³, [Virik K](#)⁴, [Leshno M](#)⁵, [Gordon N](#)⁶, [Moore A](#)⁶, [Neiman V](#)⁷, [Rosenbaum E](#)⁷, [Goldstein DA](#)⁶.

Cost-effectiveness and WTP thresholds vary between countries. The cost-effectiveness of Pembrolizumab for the treatment of patients with metastatic bladder cancer who had previously failed one treatment regimen. ***It would cost***

- **\$122 557 in the United States**

- **\$91 995 in the United Kingdom**

- **\$90 099 in Canada**

- **\$99 966 in Australia** to gain one quality-adjusted life-year with pembrolizumab versus chemotherapy in these patients, which may be considered **cost-effective only in the United States because of the differences in willingness-to-pay thresholds.**

In Italia mediamente il costo del trattamento con Pembrolizumab/mese/paziente è tra **3.500 e 5.000 euro** e il trattamento deve essere inteso per il paziente tollerante mediamente per 3 anni.

Nel 2014 la spesa globale degli antitumorali è stata di 100 miliardi di dollari e solo in Europa questi rappresentano il 14% dei costi della Sanità. Ora le proiezioni prevedono un incremento, entro il 2018, pari al 18% giudicato difficilmente sostenibile.

Abbiamo evidenze che nella II e III linea la terapia con ICI sia più efficace della BSC, se non in tutti almeno nella maggioranza dei casi?