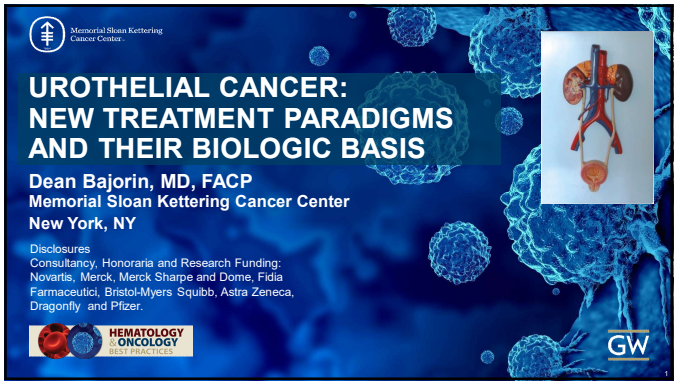


Bladder Cancer Epidemiology and Pathobiology (1)

- Peak incidence 7th decade; Male to Female ratio of 3:1
- Caucasians ~ twice as African Americans, rare in Asians
- Risk factors: smoking (2-4 fold risk over non-smokers), 2-naphthylamine, 4-aminobiphenyl, benzidine and benzene.
- Occupations at risk: aluminum workers, dry cleaners, manufacturers of preservatives and polychlorinated biphenyls, and pesticide applicators.
- Arylamines, also carcinogenic, are metabolically activated to electrophilic compounds by N-hydroxylation in the liver by cytochrome P-450 IA2 and detoxified by N-acetylation.
- Occupations with higher exposure to arylamines include workers in the dye, rubber or leather manufacturing industries, thought to be at higher risk

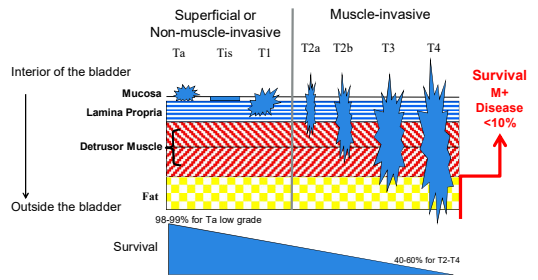
GW 2

Bladder Cancer Epidemiology and Pathobiology (2)

- Histology: 90-95% urothelial (transitional cell) carcinomas; 5% squamous cell cancer, 2% adenocarcinoma, 1% small cell. Mixed histologies are common.
- Schistosoma haematobium infection enhances formation of carcinogenic N nitroso compounds and results in an increased risk of both squamous and transitional cell carcinomas of the bladder.
- Patients with chronic indwelling catheters at higher risk for SCC of bladder
- Cyclophosphamide can increase the risk of bladder cancer nine-fold and phenacetin-containing compounds have been implicated in the development of renal pelvis and ureteral tumors.
- Presentation: Stage I ~ 75%
  Stage II/III ~ 20%
  Stage IV ~ 5%

GW 3

TNM Staging System for Bladder Cancer



Long term (10-20 Year) Outcome of NMIBC "Superficial" Bladder Cancer

Tumor Stage & Grade	% Recurrence (mean/range)	% Progression (mean/range)	% Death (mean/range)
Ta Low grade	64% (40-90%)	7% (2.4-18%)	3.6% (0-14%)
Ta High grade	75% (60-95%)	23% (10-39%)	14% (6-26%)
T1* (90% high grade)	84% (74-90%)	40% (30-52%)	35% (30-38%)

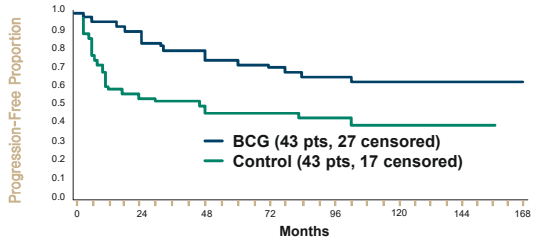
Data compiled from Haukaas S, Daehlin L, Maartmann-Moe H, and Ulvik NM. BJU 1999; 83: 957-963. Holmang S, Hedelin H, Anderstrom C, et al J Urol; 153:1823-1827,1995. Holmang S, Hedelin H, Johansson SL, et al J Urol;162:702-707, 1999. Herr HW. J Urol 2000; 163:60-62. Lebret T, Herve' JM, Botto H et al Eur Urol; 33:170-174, 1998. Leblanc B, Duclos AF, Benard R et al J Urol 1999; 162:1946.

Carcinoma in Situ

- The classical signs and symptoms include dysuria, frequency, and nocturia.
- Up to 25% of patients may be asymptomatic.
- Patients with focal CIS are more likely to be asymptomatic.
- The clinical picture is often confused with other disease processes.
- In association with papillary or nodular tumors
  - Majority (90%)
  - Muscle invasion develops in 42 to 83%
- Isolated finding
  - Minority (10%)
  - Microinvasive carcinoma (20-34%)
  - Focal or diffuse
  - Risk of invasion focal - 8%; diffuse - 78%

Hudson, MA, Herr HW *J Urol* 153:564,1995

Time to Progression Following TURB Resection



muscle invasion and/or metastatic progression

7

TURB Alone in Pts with T1 Tumors

Series	Pts	No Recurrence	Progression
England	192	57(30%)	53(28%)
Heney	63	21(33%)	19(30%)
Malmstrom	28	10(35%)	8(29%)
Torti	51	21(41%)	14(27%)
Wolf	77	20(26%)	32(42%)
Sarkis	43	5(11%)	22(51%)
Holmang	99	13(13%)	39(39%)
Herr	47	2(4%)	25(53%)
Totals	600	149(25%)	212(35%)

BCG in T1 Pts with Tumors

Series	Pts	Recurrence	Progression
Herr	13	N/A	7(54%)
Boccon-Gibod	47	17(36%)	10(21%)
Eure	30	10(34%)	5(17%)
Cookson	86	8(9%)	6(7%)
Pansadoro*	50	14(28%)	6(12%)
Zhang	38	26(68%)	8(21%)
Hurle	51	23(45%)	7(14%)
Jimenez	61	24(39%)	6(10%)
Herr	25	N/A	10(40%)
Total	401		65(16%)

8

Definition of BCG Unresponsive High-Risk NMIBC

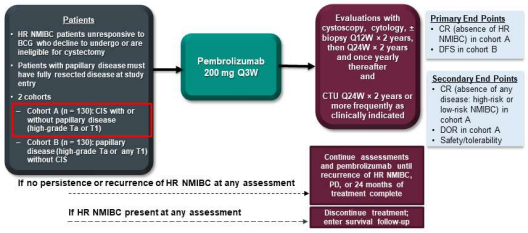
- Adequate BCG therapy: At least 5 of 6 instillations of induction BCG (adequate induction) + at least 2 of 3 doses of maintenance therapy or 2 of 6 doses of a second induction course
- BCG refractory: Stage progression at 3 months after BCG induction (i.e. high grade T1 at 3 mo after initial CIS or HG Ta) or persistent HR NMIBC at 6 months despite adequate BCG
- BCG relapsing: Recurrence of HR NMIBC after achieving a disease-free state within 12 months after adequate BCG

Current Treatment for BCG-Unresponsive HR NMIBC

- In absence of intervention, BCG-unresponsive CIS will persist and progress.
- Radical cystectomy is standard option for patients with BCG-unresponsive NMIBC
  - Significant morbidity and mortality
  - Negative impact on quality of life
  - Many patients refuse or are ineligible for cystectomy
- Urgent need for novel therapies to reduce risk of recurrence and preserve bladder
- Due to lack of suitable comparator, single-arm designs are suitable in BCG-unresponsive population

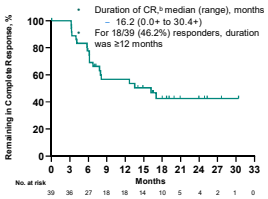
9

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



Complete Response and Duration of Response (update 2020)

Best Response	N = 96 n (%)	95% CI
CR	39 (40.6)	30.7-51.1
Non-CR	56 (58.3)	47.8-68.3
Persistent	40 (41.7)	31.7-52.2
Recurrent	6 (6.3)	2.3-13.1
NMIBC stage progression	9 (9.4)	4.4-17.1
Non-bladder malignancy[a]	1 (1.0)	0.0-5.7
Progression to T2	0	NA-NA
Nonevaluable	1 (1.0)	0.0-5.7

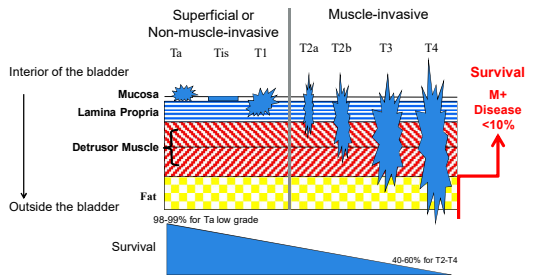


[a]Patient developed new liver lesions (substantiated by imaging) and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline imaging showed subtle findings that, in retrospect, could be attributed to pancreatic cancer. Clinical course and laboratory values further supported the diagnosis of metastatic pancreatic cancer. [b]Month 0 = time point when initial CR was achieved. The onset of response was 3 months for most patients. Data cutoff: May 24, 2019. Duration of follow-up data cutoff date: September 24, 2019.

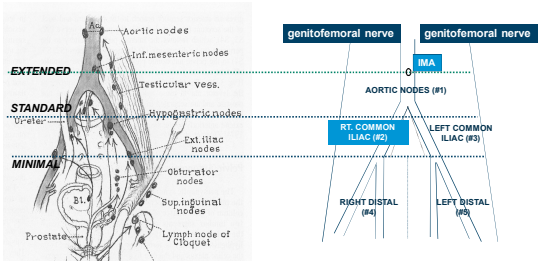
Take-home Points on NMIBC Tumors

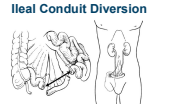
1. Grade plays a major role, high grade does much worse
2. Presence of cis is a poor prognostic variable
3. Tumor multiplicity and size (>3 cm) have a worse prognosis
4. Vascular invasion negatively impacts disease-free survival
5. Intravesical therapy not standard of care for papillary (low-grade) tumors
6. Intravesical chemotherapy reduces short term tumor recurrence but no effect on tumor progression to higher stage or metastases
7. BCG is the standard of care for high-grade NMIBC and is superior to chemotherapy for cis
8. HG NMIBC -standard of care is weekly BCG x 6; maintenance BCG also standard but controversial due to poor tolerance
9. Pembrolizumab is a standard of care for BCG-unresponsive NMIBC (no response or response duration < 12 months)

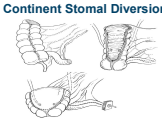
TNM Staging System for Bladder Cancer

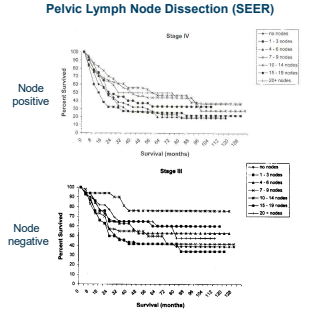


Standard of Care:
Cystectomy and Bilateral Pelvic Lymph Node Dissection









ABC Meta-Analysis: Neoadjuvant Therapy (n=3005)

Endpoint	Chemotherapy type	Number of patients/ events	HR (95% CI)	Effect p-value	Absolute benefit at 5 years (95% CI)	p-value
Overall survival	Single-agent platinum	261/376	1.15 (0.90–1.47)	0.26	−5% (−14% to 4%)	
	Platinum-based combinations	**1430/2433**	**0.86 (0.77–0.95)**	**0.003**	**5% (2% to 9%)**	
	All trials	1691/2890	0.89 (0.81–0.98)	0.022	4% (0% to 7%)	0.029
Disease-free survival	Single-agent platinum	166/217	1.14 (0.83–1.55)	0.42	−5% (−16% to 7%)	
	Platinum-based combinations	**1681/2629**	**0.78 (0.71–0.86)**	**<0.0001**	**9% (5% to 12%)**	
	All trials	1847/2846	0.81 (0.74–0.89)	<0.0001	8% (4% to 11%)	0.024

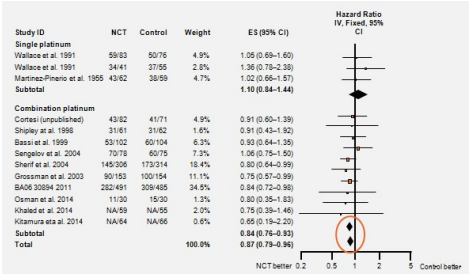
OS benefit (HR=0.86; 95% CI: 0.77–0.95; p=0.003)
5 Yr OS Landmark benefit (OS increased from 45% to 50%)

DFS benefit (HR=0.78; 95% CI: 0.71–0.86; p<0.0001)
5 Yr Landmark benefit is 9%

Advanced Bladder Cancer Meta-analysis Collaboration. Eur Urol 2005 (n=11 trials)

GW 16

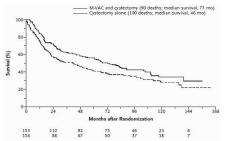
Meta-Analysis: Neoadjuvant Therapy (n=3285)



Yin et al. *The Oncologist* 2016 (n=15 trials)

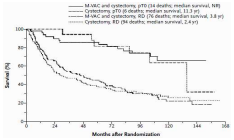
GW 17

Who benefits most from Neoadjuvant Chemotherapy?



SWOG 87-10:
MVAC plus surgery vs Surgery alone

ARM	Median Survival	Alive at 5 yrs	p-value (2-sided)
Surgery	46 mos	43%	.06
MVAC	77 mos	57%	
HR risk of death was 1.33 surgery alone			
HR risk of bladder cancer death 1.66 for surgery alone			



- pCR rates: 38% after MVAC vs 15% Cyst alone
- 5yr OS in patients with pT0N0: 85% (vs 50%)

Complete pathologic response serves as predictive marker for long term survival

Grossman et al. *NEJM*

GW 18

Is Gem/Cis an alternative to MVAC (N=154) ?

Cycles Delivered	No. Patients (%)
0.5	2 (1.3%)
1	2 (1.3%)
1.5	3 (1.9%)
2	6 (3.9%)
2.5	5 (3.2%)
3	9 (5.8%)
3.5	10 (6.5%)
4	117 (76%)

Chemotherapy logistics:
a) q21 days x 4 cycles (84 days)
b) Goal gem dose: 8000 mg/m^2
c) Goal cisplatin dose: 280 mg/m^2
d) split vs standard dose

88% received at least 3 cycles

Chemo agent	Dose Intensity
Gemcitabine	89%
Cisplatin	90%

Median number of cycles: 4 (0.5-4)
Median start chemo to end: 86 (21-121)

Can cystectomy after GC be performed safely/timely?

Chemotherapy/Surgery Timing	
Median # days start of chemo to cystectomy: 120 (range 21-121)	
Median # days end of chemo to cystectomy: 34 (range 0-106)	
Post chemo cystectomy intervals	
< 30 days	63 patients (40.9%)
< 60 days	134 patients (87.0%)
< 90 days	151 patients (98.1%)

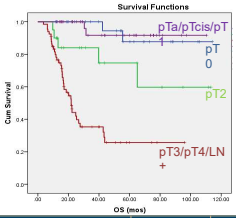
Causes for cystectomy delay (>90 days):
→ bladder sparing 5.4% (9/167)
→ cardiac 1.8% (3/167)

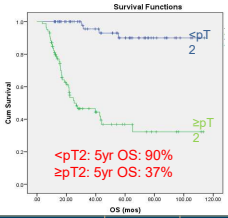
Causes for death (<90 days): 6 deaths
→ POD 2.5% (4/154)
→ post surgical 1.3% (2/154)

What are the pathologic outcomes?

Pathologic Stage	No pts.	%	SWOG 8710	Dash et al.	Yeshchina et al.
pT0N0	30	20%	38%	26%	25%
pTisN0	24	16%			
pTaN0	2	1%			
pT1N0	12	8%			
pT2N0	21	14%			
pT3N0/pT4N0/N+	65	42%			
< pT2N0	68	44%	44%	36%	50%
≥ pT2	86	56%	56%		50%

Is pT0 the appropriate endpoint?





	pT0	pTa/pTcis/pT1	pT2	pT3/pT4/LN+
Median OS (mo)	N/R	N/R	N/R	22 (18-26)
5 yr OS (%)	88%	92%	75%	26%

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Dose Dense Chemotherapy in MIBC

Study	Regimen cycles	Cisplatin Dose Density (mg/m²/week)	N (evaluable)	pT0	< pT2
Blick et al. 2011 GU ASCO	DD MVAC 3-4 cycles	35	80	43%	
*Siefker-Radtke GU ASCO 2012**	DD MVAC + Bevacizumab 4 cycles	35	44	39%	54%
Plimack et al. ASCO 2014	DD GC 3 cycles	35	31	32%	45%
Plimack et al. JCO 32:1895-1901; 2014	DD MVAC 3 cycles	35	40	38%	53%
Choueiri et al J CO 32:1889-1894. 2014	DD MVAC 4 cycles	35	39	26%	49%

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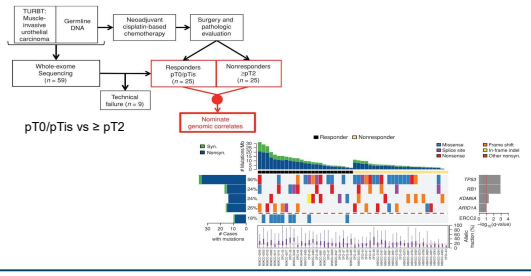
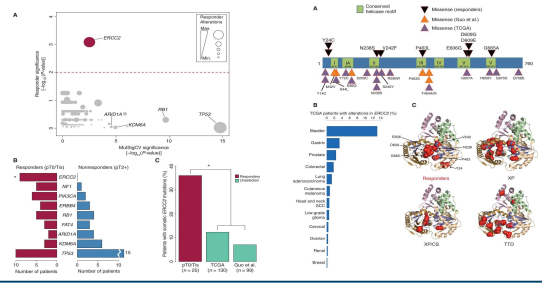
Using the extreme responder approach with Whole Exome Sequencing approach



Van Allen, Mouw, et al. *Cancer Discovery* 2014;4:1140-1153

24

ERCC2 mutations are significantly enriched in responders, and mutations are found in/near conserved sites



Van Allen, Mouw, et al. *Cancer Discovery* 2014;4:1140-1153

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Using Next Generation DNA Sequencing Approach Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based Chemotherapy

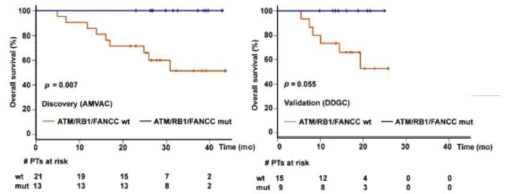

Fig. 2 Progression free survival (PFS) and overall survival (OS) by *ATM/RB1/FANCC* mutation status for the AMVAC discovery and DDGC validation sets. Alteration in any one of *ATM/RB1/FANCC* predicts better PFS ($p = 0.0035$) and OS ($p = 0.007$) in the AMVAC discovery set, with a trend toward significance for OS ($p = 0.0545$) in the DDGC validation set. wt = wild type; mut= mutation; PTs = patients.

Plimack et al, European Urology 2015

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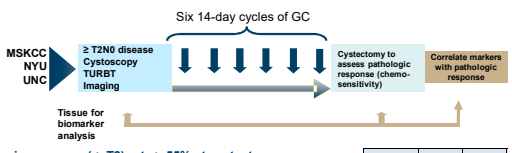
Dose Dense GC: A Multicenter Phase II Study



Pathologic response (<pT2) rate > 55% at cystectomy

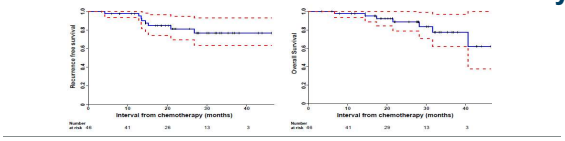
Primary endpoint was met with 57% downstaged to <pT2N0. For those with RC (41), 63% were down-staged to <pT2N0.

19 patients (41%) required toxicity-related dose modifications. Seventy percent of patients completed all 6 planned cycles.

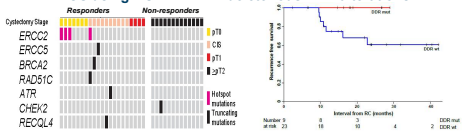
<pT2N0 (26)	T0	7
	Ta	1
	CIS	13
	T1	5
≥pT2N0 (13)	T2	7
	T3	6
Node +	T2bN1	2

27

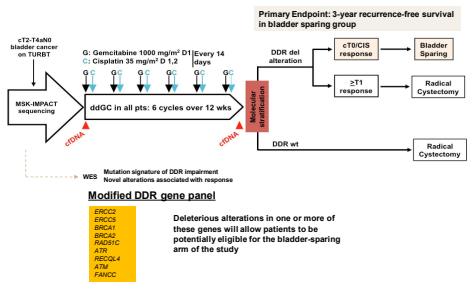
Dose Dense GC: A Multicenter Phase II Study



NGS using MSK IMPACT: deleterious DDR alterations



Study Design: A031701



Modified DDR gene panel

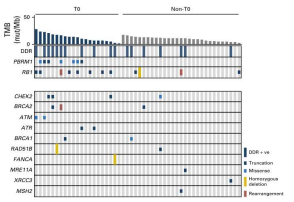
ERCC2
ERCC5
BRCA1
BRCA2
RAD51C
ATR
RECQL4
ATM
FANCC

Deleterious alterations in one or more of these genes will allow patients to be potentially eligible for the bladder-sparing arm of the study

271 patients

PURE Trial: Pembrolizumab as Neoadjuvant Therapy prior to Cystectomy

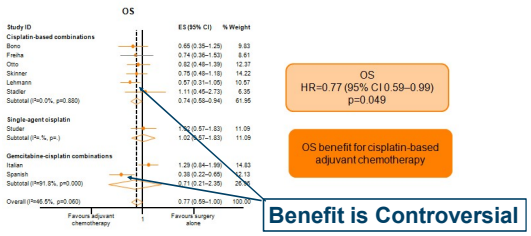
Necchi et al JCO 2018



Characteristic	No. (%)
Time frame of accrual	Feb 2017 to Mar 2018
Median age, years (IQR)	66 (60-72)
Gender	
Male	41 (82)
Female	9 (18)
Smoking status	
Nonsmoker	19 (38)
Former smoker	22 (44)
Current smoker	9 (18)
Clinical T stage	
T2N0	21 (42)
T3N0	27 (54)
T2-3N1	2 (4)
Hydronephrosis	9 (18)

Response	All Treated Patients (N = 50)	PD-L1 CPS ≥ 10% (n = 35)	PD-L1 CPS < 10% (n = 15)
Primary end point			
Pathologic complete response, No. (%)	21 (42)	19 (54.3)	2 (13.3)
95% CI	28.2 to 56.8		
Secondary end point			
Pathologic downstaging to pT<2, No. (%)	27 (54)	23 (65.7)	4 (26.7)
95% CI*	39.3 to 68.2		
Treatment failure, No. (%)			
pT2N0	2 (3.8)		
pT3-4N0	6 (12)		
pTanyN+	10 (20)		
Additional MVAC chemotherapy†	5 (10)		
RECIST v1.1 PD	0		

Adjuvant Therapy for High Risk Pts (≥ pT3, N0)?



OS
HR=0.77 (95% CI 0.59–0.99)
p=0.049

OS benefit for cisplatin-based adjuvant chemotherapy

Benefit is Controversial

1. Leow et al. *Eur Urol* 2014; 945 patients from 9 randomized controlled trials

31

Adjuvant Chemotherapy Trials for High Risk Pts (≥ pT3, N0)

Trial	Number of patients	Regimen	Survival benefit	Completed accrual
US Intergroup[1]	114	MVAC	No	No
Italian multicentre[2]	194	Gemcitabine/cisplatin	No	No
SOGUG[3]	142	Paclitaxel/gemcitabine/ cisplatin (PGC)	Yes PGC: median OS not reported; 5-year OS: 60% Observation: median OS: 26 months; 5-year OS: 31% p<0.0004	No
EORTC 30994[4]	284	Gemcitabine/cisplatin MVAC DD-MVAC	No	No

All four trials failed to meet their original accrual goals (40–60% of target) and closed early

1. Stadler et al. *J Clin Oncol* 2011; 2. Cognetti et al. *Ann Oncol* 2012; 3. Paz-Ares et al. ASCO 2010; 4. Sternberg et al. *Lancet Oncol* 2015

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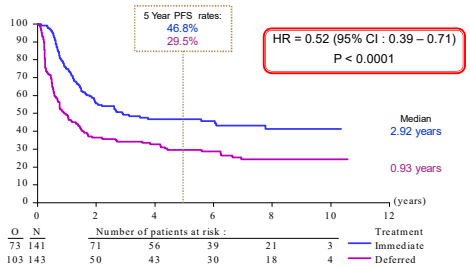
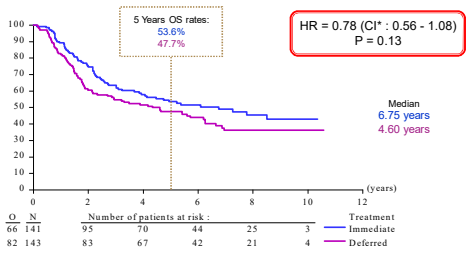
A Significant Improvement in PFS (ITT)



33

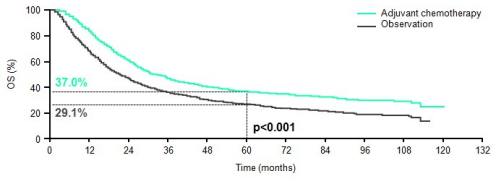
Overall Survival (ITT)
A non-significant reduction of 22% in the risk of death



*95.09%, adjusted for interim analysis

34

Population-based data analysis– Benefit observed
5,653 patients from the National Cancer Data Base



Stratified analyses adjusted for propensity score demonstrated an improvement in OS with adjuvant chemotherapy (HR=0.70; 95% CI 0.64–0.76)

Galsky et al. *J Clin Oncol* 2016

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ICR The Institute of Cancer Research

POUT

CANCER RESEARCH UK

Results of POUT - A phase III randomised trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC)

Alison Jane Birtle*, John David Chester, Robert Jones, Mark Johnson, Michaela Hill, Richard T Bryan, James Catto, Jenny Donovan, Ann French, Chris Harris, Francis Keeley, Roger Kockelbergh, Thomas Powles, Rachel Todd, Lucy Tregellas, Caroline Wilson, Andrew Winterbottom, Rebecca Lewis, Emma Hall, on behalf of the POUT Investigators
*Chief Investigator

PRESENTED AT: **2018 Genitourinary Cancers Symposium**

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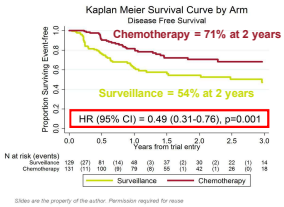
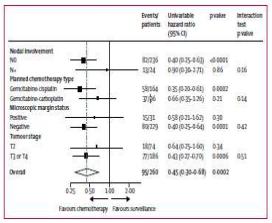
Primary endpoint: DFS





ASCO GU Symposium 2018
Birtle et al. Lancet 2020

37

Cisplatin-based adjuvant chemotherapy is 'recommended' in clinical practice guidelines

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Guideline on Muscle-Invasive and Metastatic Bladder Cancer (European Association of Urology Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement

"Adjuvant chemotherapy may be offered to high-risk patients who have not received neoadjuvant therapy*

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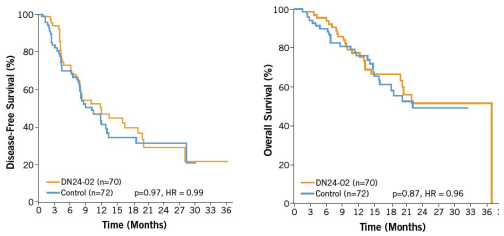
Prognosis of High Risk MIBC patients status post cystectomy Phase 2 randomized trial of DN24-02 Rx vs observation

High Risk defined as ≥ pT2 post neoadjuvant ChemoRx or pT3 without prior ChemoRx



Bajorin et al. ASCO 2016

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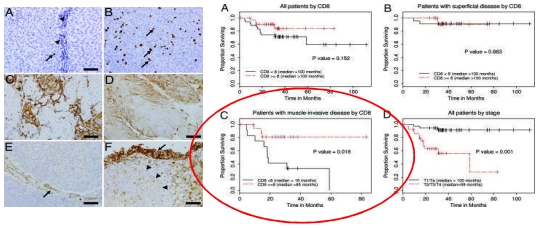
Muscle-Invasive Bladder Cancer: CD8 tumor-infiltrating lymphocytes in primary tumor predictive of survival



Sharma et al, PNAS, 2007

Trials for High Risk Pts s/p surgery defined as ≥ pT2 post neoadjuvant ChemoRx or pT3 without prior neoadjuvant ChemoRx

AMBASSADOR (NCT03244384)

- High risk of recurrence originating in the bladder, ureter or renal pelvis
- Surgical resection (e.g. radical cystectomy or nephroureterectomy)

Co-primary endpoints: DFS and OS; N=739

R → Pembrolizumab / Observation

CheckMate 274 (NCT02632409)

- High risk of recurrence originating in the bladder, ureter or renal pelvis
- Surgical resection (e.g. radical cystectomy or nephroureterectomy)

Co-primary endpoints: DFS in pts with ≥1% PD-L1 and all patients; N=640

R → Nivolumab / Placebo

IMvigor010 (NCT02450331)

- High risk of recurrence originating in the bladder, ureter or renal pelvis
- Surgical resection (e.g. radical cystectomy or nephroureterectomy)

Primary endpoint: DFS; N=700

R → Atezolizumab / Observation

IMvigor010 Study Design

Key eligibility[a]

- **High-risk MIUC (bladder, renal pelvis, ureter)**
- **Radical cystectomy/nephroureterectomy with LN dissection** within ≤ 14 weeks
  - **ypT2-T4a or ypN+** for patients treated with **NAC[b]**
  - **pT3-T4a or pN+** for patients **not treated with NAC[c]**
- No postsurgical radiation or AC
- If no prior NAC given, patient had to be ineligible for, or declined, cisplatin-based AC
- ECOG PS 0-2
- **Tissue sample for PD-L1 testing**

R 1:1

Atezolizumab 1200 mg q3w *(16 cycles or 1 year)*

No crossover allowed

Observation[c] q3w

Disease recurrence/ survival follow-up

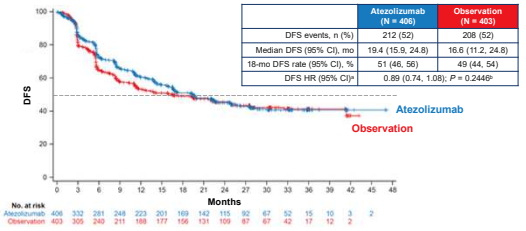
Tumor assessments: q12w for years 1-3, (q24w for years 4-5 and at year 6)

Stratification factors	
• Number of LNs resected (< 10 vs ≥ 10)	• Tumor stage (≤ pT2 vs pT3/pT4)
• Prior NAC (Yes vs No)	• PD-L1 status[a] (IC0/1 vs IC2/3)
• LN status (+ vs –)	

- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

Hussain M. IMvigor010 primary analysis [abs 5000]. https://bit.ly/2SKSAD3

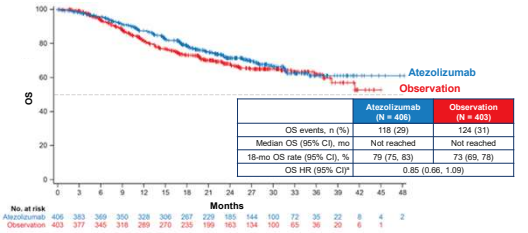
DFS in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); $P = 0.2446$[b]	

Hussain M. IMvigor010 primary analysis [abs 5000].
https://bit.ly/2SKSAD3

Interim OS Analysis in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

Hussain M. IMvigor010 primary analysis [abs 5000].
https://bit.ly/2SKSAD3

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CheckMate 274: Study Design

- CheckMate 274 is a phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

N = 709

Key inclusion criteria
- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Minimum follow-up, 5.9 months
Median follow-up inITT population, 20.9 months (NIVO) and 19.5 months (PBO)

Stratification factors
- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status

R 1:1 → NIVO IV 240 mg Q2W / PBO IV Q2W

Treat for up to 1 year of adjuvant therapy

Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IHC, immunohistochemistry; ITT, intent-to-treat; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; R, randomized.

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Select baseline demographic and disease characteristics in all randomized patients

CheckMate 274

	NIVO (N = 353)	PBO (N = 356)
Mean age (range), years	65.3 (30–92)	65.9 (42–88)
Male, %	75.1	77.2
Region, %		
United States	13.9	14.9
Europe	48.2	48.0
Asia	22.7	20.8
Rest of the world	15.3	16.3
ECOG PS,[a] %		
0	63.5	62.1
1	34.6	35.1
2[b]	2.0	2.5
Tumor origin at initial diagnosis, %		
Urinary bladder	79.0	78.9
Upper tract disease	21.0	21.1
Minor histological variants present, %	41.1	39.6
PD-L1 ≥ 1% by IVRS, %	39.7	39.9
Prior neoadjuvant cisplatin, %	43.3	43.5
Pathologic T stage at resection,[c,d] %		
pT0–2	22.7	24.2
pT3	58.4	57.3
pT4a	16.1	17.4
Other	2.5	0.8
Nodal status at resection,[d] %		
N+	47.3	47.2
N0/x with < 10 nodes removed	26.6	27.8
N0 with ≥ 10 nodes removed	25.8	24.7

[a]Not reported for 1 patient in the PBO arm. [b]ECOG PS of 2 was permitted only for patients who did not receive cisplatin-based neoadjuvant chemotherapy and are ineligible for adjuvant cisplatin-based chemotherapy. [c]The T staging included patients with N+, NE, or NX. [d]Not reported for 1 patient in each arm.
ECOG PS, Eastern Cooperative Oncology Group performance status; IVRS, interactive voice-response system.

GW 46

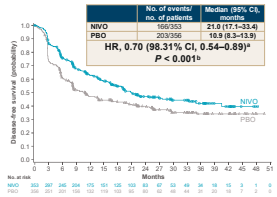
Disease-free survival

CheckMate 274

ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	166/353	21.0 (17.1–33.4)
PBO	203/356	10.9 (8.3–13.9)

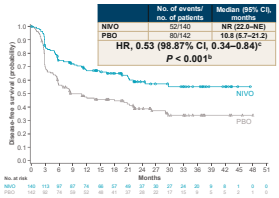
HR, 0.70 (98.31% CI, 0.54–0.89)[a]
P < 0.001[b]



PD-L1 ≥1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	52/140	NR (22.0–NE)
PBO	80/142	10.8 (5.7–21.2)

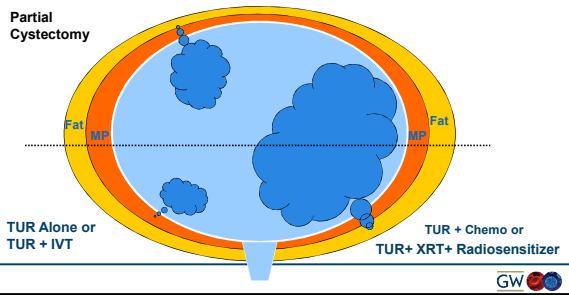
HR, 0.53 (98.87% CI, 0.34–0.84)[a]
P < 0.001[b]



Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541–0.894). [b]Based on a 2-sided stratified logrank test. [a]HR, 0.535 (98.87% CI, 0.340–0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

GW 47

Bladder Preservation for Muscle Invasive Disease "Treatment Selection"



GW 48

Stage T2-T4a TCC: Neoadjuvant Chemotherapy followed by Partial Cystectomy/TUR

Series	Yr	No. Pts.	Chemo	Survival%/Yrs	AWB*
Hall et al	1984	54 TUR	M	31/54 (57%)/ 3 yrs	75% (3)
Simon et al	1990	9/30 PC	M-VAC	7/9 (78%)/ 3 yrs	43% (5)
Herr, Bajorin, Scher	1992	60/111 (15 PC/28 TUR)	M-VAC	32/43 (74%)/10 yrs	58% (10)
Thomas et al	1999 1984	44 TUR/6 PC 61 TUR	CM M	57-72% /5 yr 58%/ 2yr, 39%/ 5 yr	48% (2)
Flores et al	1996	71 TUR	CMV	47%/ 5 yr	55%(3)
Sternberg et al	1999 1993	TUR/ PC/ RC 28 PC	M-VAC M-VAC	59%/ 5 yrs 75% / 3 yrs	57% (5)
Rosa et al	2002	40 TUR	CMV	52%/ 5 yrs	52% (7)

Tri-Modality Therapy for Bladder Preservation Selected Series with > 100 patients

Series (# pts)	Stages/ Chemo-sens	RT/ (fraction) then Consolidation (fract)	CR	5 yrs OS	5 yr Surv w/ bladder
MGH (106)	T2-4a Cisplatin	39.6 (1.8) then 25.2 (1.8)	66%	52%	43%
RTOG (123)	T2-4a (Neo MCV) Cisplatin	39.6 (1.8) then 25.2 (1.8)	61% vs 55%	49% vs 48%	36% vs 40%
Paris (120)	T2-4 Cis & 5-FU	24 (3) then 20 (2.5)	77%	63%	NR
Erlangen (415)	T1-4 Carbo/Cis/FU	50.4-59.4 (1.8)	72%	50%	42%

Adapted from Rodel et al *J Clin Oncol* 24:5536-5544; 2006

Bladder Preservation for Muscle-Invasive TCC

Picking Optimal Patients

No mass on Exam under Anesthesia
No ureteral obstruction
Small solitary tumor
Visibly complete TUR
No disease in the prostate/prostatic urethra

Take-home Points for Patients with MIBC

1. Patients treated with cisplatin-based combination neoadjuvant chemotherapy have the best survival. No benefit for chemoRX without cisplatin!!
2. Cystectomy and PLND after neoadjuvant chemotherapy is an absolute requirement for maximal survival. An intergroup trial exploring DNA Damage Repair gene defects to select for bladder preservation is ongoing
3. No definitive data from individual phase 3 trials that adjuvant chemotherapy improves survival though substantial composite data supports benefit
4. Adjuvant nivolumab for high risk patients after surgery improves survival
5. Adjuvant chemotherapy for resected upper tract disease improves survival
6. Cisplatin-ineligible patients best served by surgery alone at present
7. Tri-modality therapy a SOC, but outcome a function of proper selection
8. Investigational trials evaluating immunotherapy are ongoing in both cisplatin-eligible and ineligible patients

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Memorial Sloan Kettering Cancer Center

Advanced Disease: Role of Chemotherapy

MVAC: methotrexate, vinblastine, doxorubicin, cisplatin

HD MVAC: High dose MVAC (q2 rather than q4 weeks

GC: gemcitabine plus cisplatin

GCP: GC + paclitaxel

GC-bev: GC + bevacizumab

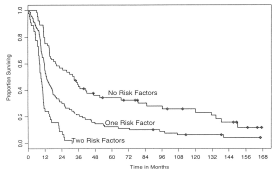
G-C: Gemcitabine +carboplatin

M-CAVI: methotrexate, vinblastine, carboplatin

M-VAC: The First Curable Regimen (Sternberg et al. 1989) Prognostic Factors for Survival (1999)

MSKCC Prognostic Score
***KPS ≤ 80%**
***Visceral Disease**

0 = none
1 = one factor
2 = both factors



Risk #	KPS	Visceral Mets	Median	Alive at 5 years
0	≥ 80	No	33.0	33%
1	≥ 80	Yes	13.4	11%
	< 80	No		
2	< 80	Yes	9.2	0%

Bajorin JCO 1999

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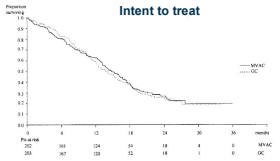
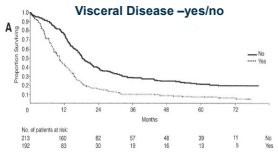
Phase III GC vs MVAC (von der Maase, 2000 and 2005)

End Point	GC (months)	MVAC (months)	Treatment Effect HR†	95% CI	P	Treatment Effect When Adjusted for Prognostic Factors† HR†	95% CI
Median overall survival	13.8	14.8	1.04	0.82-1.32	.75	0.95	0.74-1.22
Median TTPD	7.4	7.4	1.05	0.85-1.30	.66	0.99	0.79-1.24
Median TTTF	5.8	4.6	0.89	0.72-1.10	.27	0.84	0.67-1.04
Response rate,‡ %	49.4	45.7	0.97	0.62-1.52	.51	0.99	0.63-1.56

Intent to treat



Visceral Disease –yes/no



High Dose M-VAC vs standard dose M-VAC

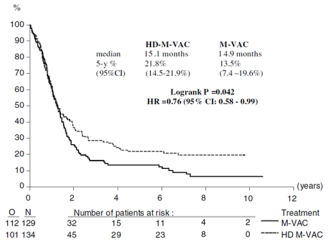
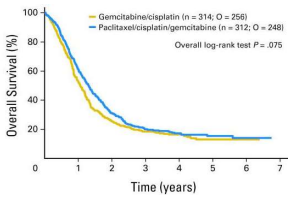


Fig. 3 – Overall survival.

Sternberg CN et al. *Eur J Cancer*, 2006

GC +/- paclitaxel phase 3 trial (n=626)

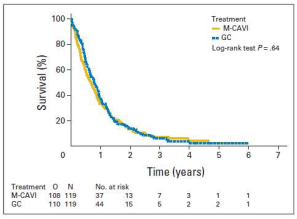
Best Overall Response to Treatment	Paclitaxel/Cisplatin/Gemcitabine (n = 312)		Gemcitabine/Cisplatin (n = 314)	
	No. of Patients	%	No. of Patients	%
Complete response	42	13.5	35	11.1
Partial response	131	42.0	102	32.5
Stable disease	69	22.1	97	30.9
Progression of disease	21	6.7	47	15.0
Early death	8	2.6	7	2.2
Not assessable	31	9.9	17	5.4
Treatment never started	10	3.2	9	2.9



Bellmunt et al, *J Clin Oncol*, 2012

EORTC 30986 Phase II/III Trial Gemcitabine + Carboplatin vs Methotrexate + Carboplatin + Vinblastine (M-CAVI) in Pts Unfit for Cisplatin-Based Chemotherapy DeSantis et al. *J Clin Oncol* 2011

Primary end point: median OS of 9.3 months in the GC arm and 8.1 months in the M-CAVI arm. ORR in patients receiving GC was 41.2% and 30.3 % in those receiving M-CAVI.



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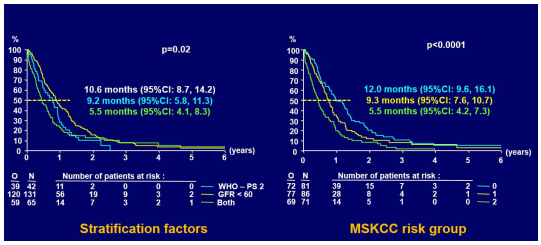
EORTC 30986 Phase II/III Trial Gemcitabine + Carboplatin vs Methotrexate + Carboplatin + Vinblastine (M-CAVI) in Pts Unfit for Cisplatin-Based Chemotherapy

Prognostic Factor Analysis



MSKCC Risk Factors: Visceral disease and Poor performance status

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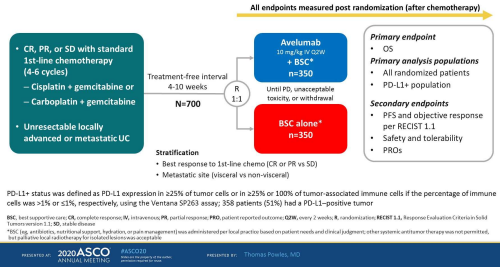
JAVELIN Bladder 100 study design (NCT02603432)



Presented By Thomas Powles

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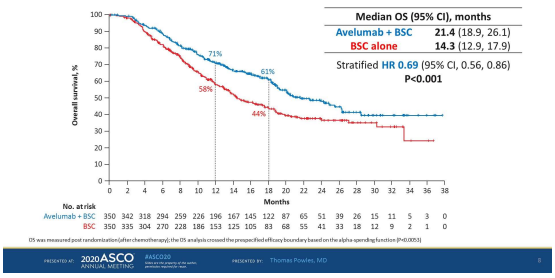
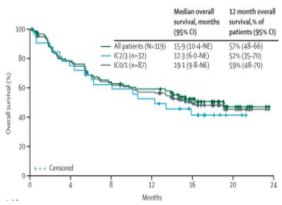
OS in the Overall Population



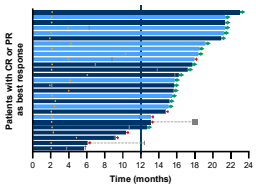
Presented By Thomas Powles

Atezolizumab 1st Line in Urothelial Cancer

Overall Survival

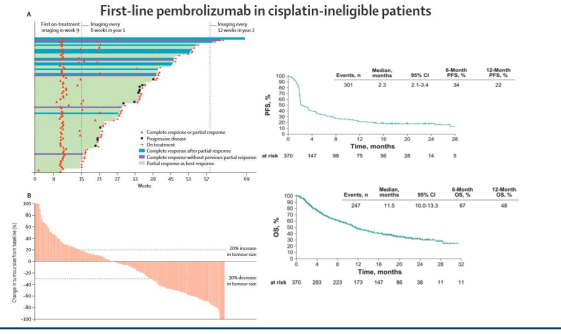


Durability of Response



Balar et al, Lancet Oncology

First-line pembrolizumab in cisplatin-ineligible patients



Take-home Points for Urothelial Cancer Patients Treated with Chemotherapy

1. M-VAC, High dose M-VAC and GC are all standards of care for cisplatin-eligible patients, but with median survivals of ~14-16 months
2. Long-term survival is ~10% better in patients with lymph node only disease in contrast to those with metastatic visceral disease
3. Adding a 3rd chemotherapy drug (paclitaxel) to the GC doublet does not improve survival
4. Gemcitabine plus carboplatin is the standard of care for cisplatin-ineligible patients but median survival is ~9 months with rare cures
5. Immunotherapy, both atezolizumab and pembrolizumab, are FDA-approved as 1st-line therapy for pts ineligible for cisplatin-therapy
6. Maintenance avelumab improves survival when given immediately after initial chemotherapy in stable or responding patients

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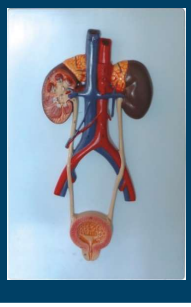
Memorial Sloan Kettering Cancer Center

Advanced Disease: Role of Immunotherapy Single Agent Therapy



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Prior to 2016: Second-line Agents for Bladder Cancer

Reference	Agent	Pt #	CR (%)	PR (%)	ORR (%)	MS (months)	
Witte	Ifosfamide	56	9	11	20	NR	
Witte	Topotecan	44	0	9	9	6.3	
Roth	Piritrexim	35	0	7	7	7	
Moore	Oxaliplatin	18	0	6	6	NR	
Paz-Ares	Pemetrexed	31	0	29	29	9.5	
Sweeney	Pemetrexed	47	6	21	28	9.6	
Galsky	Pemetrexed	13	0	8	8	NR	NCCN
McCaffrey	Docetaxel	30	0	13	13	9	
Vaughn	Paclitaxel	31	0	10	10	7.2	
Culine	Vinflunine	51	0	18	18	6.6	EMA
Petrylak	Vinflunine	114	0	14.9	14.9	8.3	
Wulfing	Lapatinib	59	0	3	3	4.5	
Gomez-Abuin	Bortezomib	20	0	0	0	NR	

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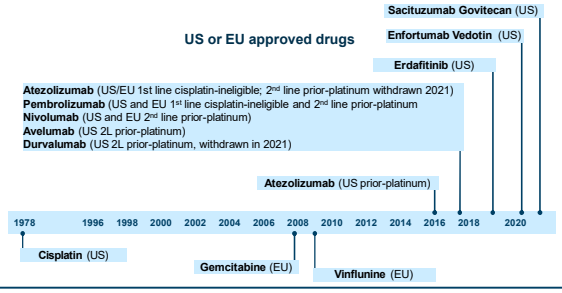
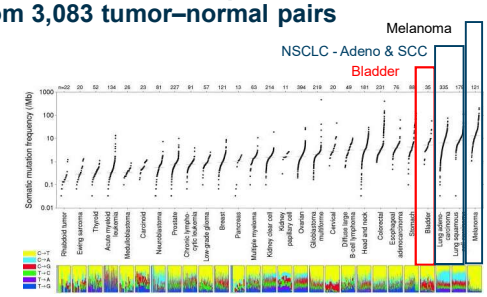
Timeline of Approved Urothelial Cancer Treatments

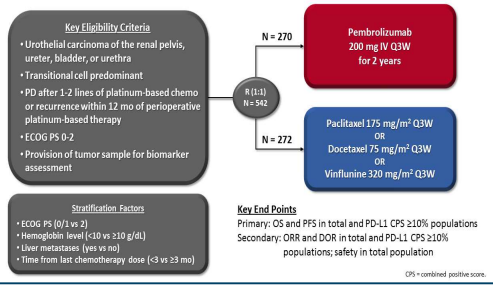


Somatic mutation frequencies observed in exomes from 3,083 tumor–normal pairs



MS Lawrence *et al. Nature* 2013 Jul 11;499(7457):214-8

Keynote-045 Study Design (NCT02256436)



Baseline Characteristics

n (%)	Pembro (N = 270)	Chemo (N = 272)
Age, median (range), y	67.0 (29-88)	65.0 (26-84)
Men	200 (74.1)	202 (74.3)
Race		
White	188 (69.6)	201 (73.9)
Asian	64 (23.7)	58 (21.3)
Other or not specified	18 (6.7)	13 (4.8)
Current or former smoker	165 (61.1)	186 (68.4)
Upper tract disease (renal pelvis/ureter)	38 (14.3)	36 (14.1)
PD-L1 CPS ≥1%	107 (40.2)	108 (42.4)
PD-L1 CPS ≥10%	74 (27.4)	90 (33.1)

n (%)	Pembro (N = 270)	Chemo (N = 272)
Hemoglobin ≥10 g/dL	219 (81.1)	223 (82.0)
ECOG PS[a]		
0	119 (44.1)	106 (39.0)
1	143 (53.0)	158 (58.1)
2	2 (0.7)	4 (1.5)
Visceral disease	240 (88.9)	233 (85.7)
Liver metastases	91 (33.7)	95 (34.9)
Time since completion of most recent prior therapy		
≥3 months	166 (61.5)	167 (61.4)
<3 months	103 (38.1)	104 (38.2)

[a]ECOG PS was missing for 6 patients in the pembro arm and 4 patients in the chemo arm.
Arrows indicate stratification factors.
Data cutoff date: Sep 7, 2016.

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Baseline Characteristics (cont.)

n (%)	Pembro (N = 270)	Chemo (N = 272)
Setting of most recent prior therapy[a]		
Neoadjuvant	19 (7.0)	22 (8.1)
Adjuvant	12 (4.4)	31 (11.4)
First line	183 (67.8)	157 (57.7)
Second line	55 (20.4)	60 (22.1)
Third line	0	1 (0.4)
Type of prior platinum		
Cisplatin	198 (73.3)	213 (78.3)
Carboplatin	70 (25.9)	56 (20.6)
Oxaliplatin or nedaplatin	1 (0.4)	2 (0.7)

n (%)	Pembro (N = 270)	Chemo (N = 272)
Prior cystectomy or nephroureterectomy	209 (77.4)	221 (81.3)
Prior BCG	32 (11.9)	22 (8.1)
No. of risk factors[b]		
0	54 (20.0)	44 (16.2)
1	96 (35.6)	97 (35.7)
2	66 (24.4)	80 (29.4)
3-4	45 (16.7)	45 (16.5)

[a]Setting, time from completion, and prior platinum were all missing for 1 patient in each arm.
[b]Includes Bellmunt risk factors of ECOG PS >0, hemoglobin level <10 g/dL, and liver metastases (*J Clin Oncol* 2010;27:1850-1855) + time from prior chemotherapy <3 mo (*Eur Urol* 2013;63:717-723).
Data cutoff date: Sep 7, 2016.

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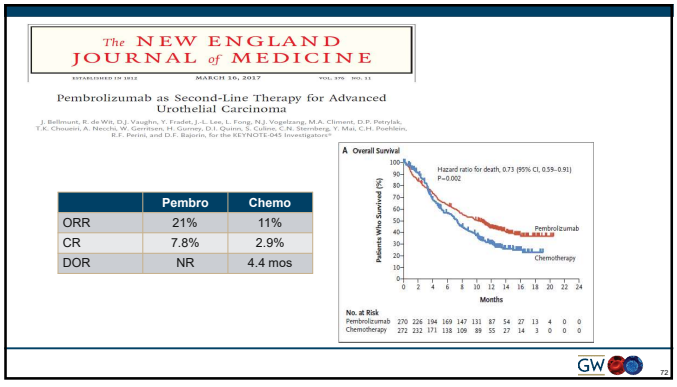

	Pembro	Chemo
ORR	21%	11%
CR	7.8%	2.9%
DOR	NR	4.4 mos

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Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial

Thomas Powles, Ignacio Durán, Michiel S van der Heijden, Yohann Loriot, Nicholas J Vogelzang, Ugo De Giorgi, Stéphane Oudard, Margitta M Retz, Daniel Castellano, Aristotelis Bamias, Aude Fléchon, Gwenaëlle Gravis, Syed Hussain, Toshimi Takano, Ning Leng, Edward E Kadel III, Romain Banchereau, Priti S Hegde, Sanjeev Mariathasan, Na Cui, Xiaodong Shen, Christina L Derleth, Marjorie C Green, Alain Ravaud

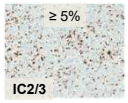
Treatment: atezolizumab 1200 mg or chemotherapy (physician's choice: vinflunine 320 mg/m², paclitaxel 175 mg/m², or 75 mg/m² docetaxel) intravenously every 3 weeks.

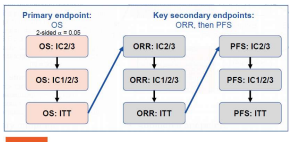
Randomization: stratified by PD-L1 expression (expression on <1% [IC0] or 1% to <5% [IC1] of tumor-infiltrating immune cells vs ≥5% of tumor-infiltrating immune cells [IC2/3]), chemotherapy type (vinflunine vs taxanes), liver metastases (yes vs no), and number of prognostic factors (none vs one, two, or three).

Primary endpoint: overall survival was tested hierarchically in prespecified populations: IC2/3, followed by IC1/2/3, followed by the intention-to-treat population.

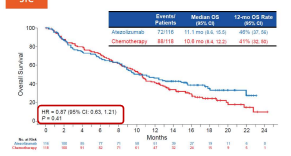
IMvigor 211 Study Design and Clinical outcomes

	IC2/3 n = 100	IC1 n = 107	IC0 n = 103
ORR	28% (19, 38)	11% (6, 19)	9% (4, 16)
CR	**15%** (9, 24)	**4%** (1, 9)	**2%** (0, 7)

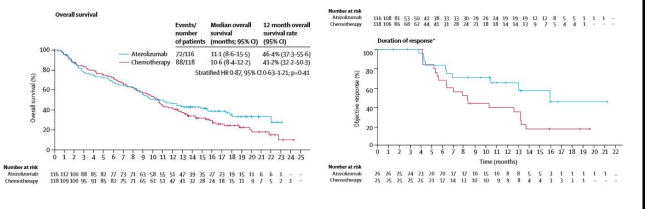




OS Analysis: IC2/3 Population



Powles T et al. 2017, EAS



CheckMate 275: Phase II Study

Patients: • Metastatic or locally advanced mUC • Disease progression on a prior platinum-based therapy • Evaluable PD-L1 tumor tissue sample[a]

Treatment: Nivolumab 3 mg/kg IV Q2W N=270 → Treat until progression[b] or unacceptable toxicity

Blinded independent review committee (BIRC) assessment of response using RECIST v1.1

Outcome, %	All N=265[b]	PD-L1 <1% n=143	PD-L1 ≥1% n=122	PD-L1 ≥5% n=81
Confirmed ORR by BIRC[a]	19.6	16.1	23.8	28.4
95% CI	15.0–24.9	10.5–23.1	16.5–32.3	18.9–39.5
Best overall response				
Complete response	2.3	<1	4.1	4.9
Partial response	17.4	15.4	19.7	23.5
Stable disease	22.6	17.5	28.7	28.4
Progressive disease	39.2	46.9	30.3	25.9
Unable to determine	18.5	19.6	17.2	17.3

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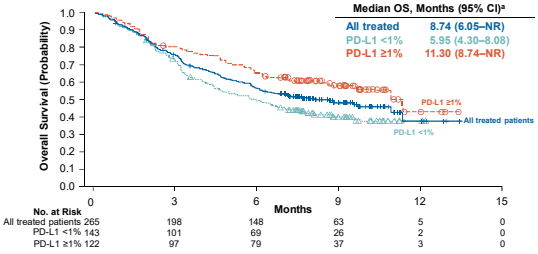
GW 76

Overall Survival

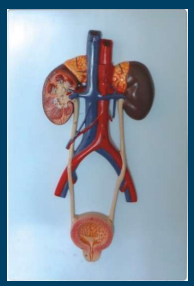


[a]Similar results were seen using the 5% PD-L1 tumor expression cutoff; NR, not reached

GW 77

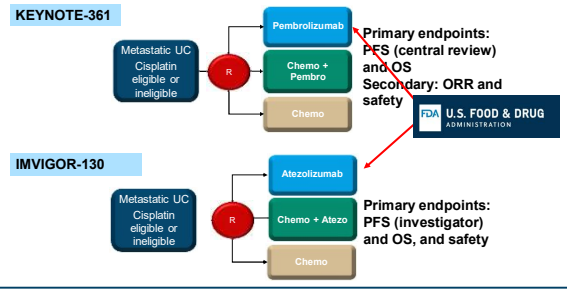
Memorial Sloan Kettering Cancer Center

Advanced Disease: Immunotherapy Combinations and Novel Targeted Therapy



GW 78

Chemotherapy Plus ICB as First-line Treatment for Metastatic UC



Keynote-361:
Pembrolizumab plus Chemotherapy Versus Chemotherapy

Baseline Characteristics

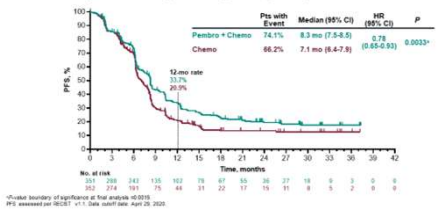
Characteristic, n (%)	Pembro + Chemo (N = 351)	Pembro (N = 307)	Chemo (N = 352)
Age, median (range), yrs	69 (41-91)	68 (29-89)	69 (36-90)
Male	272 (77.5)	228 (74.3)	262 (74.4)
ECOG performance status			
0	150 (42.7)	134 (43.6)	168 (47.7)
1	178 (50.7)	148 (48.2)	162 (46.0)
2	23 (6.6)	25 (8.1)	22 (6.3)
Visceral metastasis	259 (73.8)	239 (77.9)	252 (71.6)
Lymph node only metastasis	81 (23.1)	64 (20.8)	94 (26.7)
Liver metastasis	78 (22.2)	65 (21.2)	74 (21.0)
Hemoglobin <10g/dL	33 (9.4)	34 (11.1)	26 (7.4)
PD-L1 CPS ≥10[a]	159 (45.3)	159 (51.8)	159 (45.2)
Lower tract disease	287 (81.8)	242 (78.8)	270 (76.7)
Choice of chemotherapy[a]			
Cisplatin	160 (45.6)	138 (45.0)	160 (45.5)
Carboplatin	191 (54.4)	169 (55.0)	192 (54.5)

[a]Based on data entered in KEYNOTE-361 IVRS at randomization. Data cutoff date: April 29, 2020.

Alva A, et al. ESMO 2020. Abstract LBA23.

Keynote-361: PFS
Pembrolizumab plus Chemotherapy Versus Chemotherapy

PFS by BICR: Pembro + Chemo vs Chemo, ITT Population (Primary Endpoint)

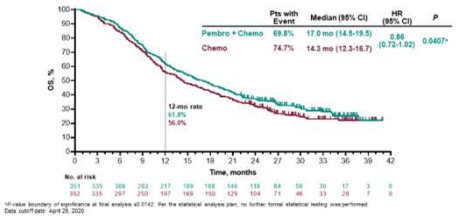


*Two-sided boundary of significance at final analysis =0.0019.
PFS assessed per RECIST v1.1. Data cutoff date: April 29, 2020.

Alva A, et al. ESMO 2020. Abstract LBA23.

Keynote-361:
Pembrolizumab plus Chemotherapy Versus Chemotherapy

OS: Pembro + Chemo vs Chemo, ITT Population

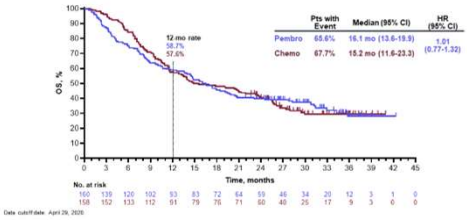


*If p-value boundary of significance at final analysis ≤0.0142. Per the statistical analysis plan, no further formal statistical testing was performed.
Data cutoff date: April 29, 2020

Alva A, et al. ESMO 2020. Abstract LBA23.

Keynote-361:
Pembrolizumab plus Chemotherapy Versus Chemotherapy

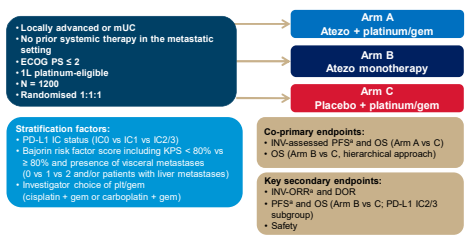
OS: Pembro vs Chemo, Patients With CPS≥10 Tumors



Data cutoff date: April 29, 2020

Alva A, et al. ESMO 2020. Abstract LBA23.

IMvigor130 Study Design



[a] per RECIST 1.1.

Adapted from Grande et al. ESMO 2019

IMvigor130 Baseline Characteristics

Characteristic	Atezo + plt/gem (*n* = 451)	Placebo + plt/gem (n = 400)[a]	Atezo (n = 362)
Median age (range), y	69 (31-87)	67 (33-89)	67 (36-87)
ECOG PS, n (%)			
0	182 (40)	173 (43)	157 (43)
1	209 (46)	187 (47)	174 (48)
2	60 (13)	40 (10)	31 (9)
Bajorin risk factor score, n (%)			
0	176 (39)	162 (41)	151 (42)
1	169 (37)	149 (37)	134 (37)
2 and/or liver mets	106 (24)	89 (22)	77 (21)
PD-L1 status on IC, n (%)			
IC2/3	108 (24)	91 (23)	88 (24)
IC1	195 (43)	179 (45)	160 (44)
IC0	148 (33)	130 (33)	114 (31)
Cisplatin ineligibility[b]	204 (45)	140 (35)	107 (30)
Renal impairment	113 (25)	94 (24)	65 (18)
Investigator choice of chemotherapy[c]			
Carboplatin	314 (70)	264 (66)	227 (63)
Cisplatin	137 (30)	136 (34)	135 (37)

[a] n = 359 for comparisons to atezo monotherapy arm. [b] Per Galsky criteria per protocol, excluding New York Heart Association functional classification.
[c] Of the patients considered cisplatin eligible at study entry, 52% received carboplatin, while 10% of patients who were cisplatin ineligible received cisplatin.

Adapted from Grande et al. ESMO 2019

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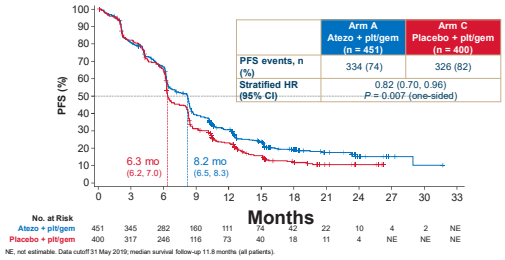
Imvigor 130 Final PFS, ITT
Atezolizumab plus Chemotherapy vs Chemotherapy



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

NE, not estimable. Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

Adapted from Grande et al. ESMO

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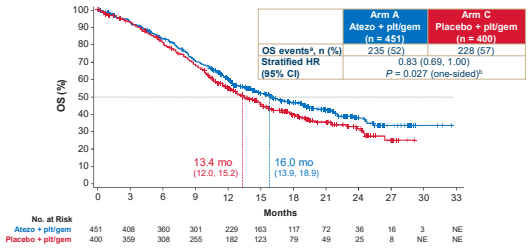
Interim OS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). [a] 5% of patients from Arm A and 20% of patients from Arm C received non-protocol immunotherapy. [b] Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function.

Adapted from Grande et al. ESMO 2019

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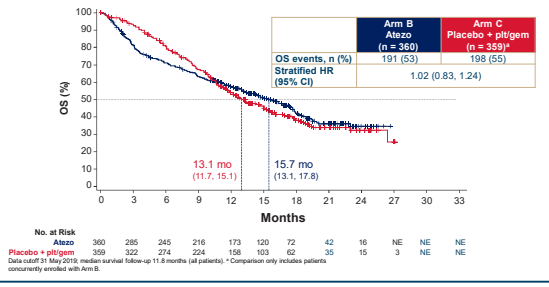
Interim OS for Monotherapy: ITT (Arm B vs Arm C)

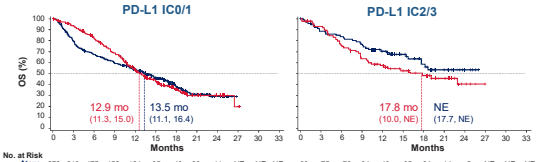


	Arm B Atezo (n = 360)	Arm C Placebo + plt/gem (n = 359)*
OS events, n (%)	191 (53)	198 (55)
Stratified HR (95% CI)	1.02 (0.83, 1.24)	

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). * Comparison only includes patients concurrently enrolled with Arm B.

Adapted from Grande et al. ESMO 2019

Interim OS: PD-L1 status (Arm B vs Arm C)



	Arm B Atezo (n = 272)	Arm C Placebo + plt/gem (n = 274)
OS events, n (%)	158 (58)	156 (57)
Unstratified HR (95% CI)	1.07 (0.86, 1.33)	

	Arm B Atezo (n = 88)	Arm C Placebo + plt/gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR (95% CI)	0.68 (0.43, 1.08)	

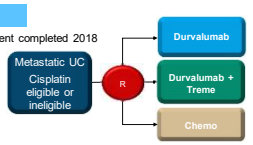
Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

Adapted from Grande et al. ESMO 2019

IO Doublet versus Chemo as 1st Line Treatment for Metastatic UC

DANUBE

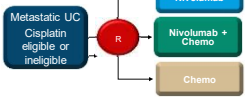
N=1340, Enrollment completed 2018



Primary endpoints:
PFS and OS of durva-treme combo vs standard of care

CheckMate 901

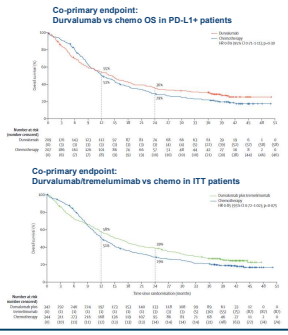
N=690, Est. completion: 2020



Primary endpoints:
PFS and OS in cisplatin-ineligible pts

Secondary:
PFS and OS in all pts;
EORTC QLQ-C30

Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial



Powles et al. Lancet Oncol 2020

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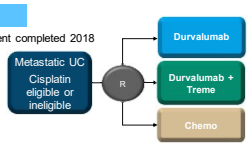
IO Doublet versus Chemo as 1st Line Treatment for Metastatic UC

DANUBE

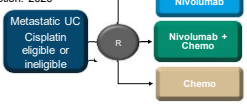
N=1340, Enrollment completed 2018



Primary endpoints:
PFS and OS of durva-treme combo vs standard of care

CheckMate 901

N=690, Est. completion: 2020



Primary endpoints:
PFS and OS in cisplatin-ineligible pts

Secondary:
PFS and OS in all pts;
EORTC QLQ-C30

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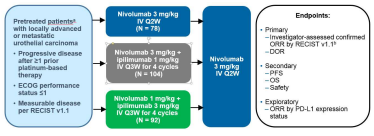
Ipilimumab + Nivolumab in Post Platinum Metastatic UC



Characteristic	NIVO3 (N = 78)	NIVO3+IPI1 (N = 104)	NIVO1+IPI3 (N = 92)
Confirmed ORR, %	25.6	26.9	38.0
95% CI	16.4–36.8	18.7–36.5	28.1–48.8
Best overall response, %			
Complete response	10.3	7.7	6.5
Partial response	15.4	19.2	31.5
Stable disease	26.9	23.1	25.0
Progressive disease	38.5	42.3	21.7
Unable to determine	9.0	7.7	13.0
Not reported	0	0	2.2

• Rosenberg et al. 2018

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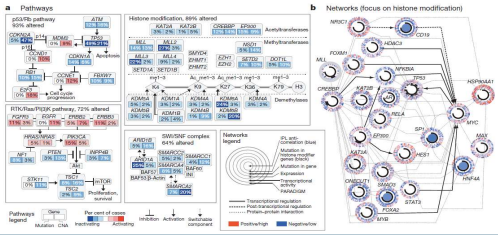
ARTICLE

OPEN

doi:10.1038/nature12965

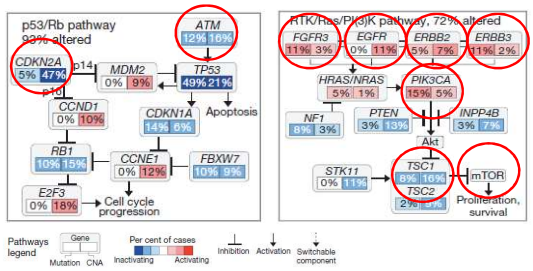
Comprehensive molecular characterization of urothelial bladder carcinoma

The Cancer Genome Atlas Research Network*



GW 94

Potentially Actionable Mutations in Urothelial Cancer



TCGA-Bladder Cancer; *Nature*, 2014

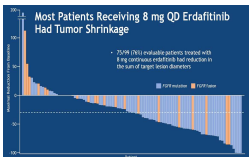
GW 95

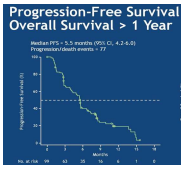
FGFR Inhibitors in previously treated patients

Erdafitinib- Pan-FGFR(1-4)
- 40% response in 99 pts
- 3 of 99 achieved clinical CR

		[95% CI]
Patients, n	99	
Response per investigator assessment[1,2], n (%)		
ORR	40 (40.4)	[30.7-50.1]
Complete response	3 (3.0)	
Partial response	37 (37.4)	
Stable disease	39 (39.4)	
Progressive disease	18 (18.2)	
Median time to response	1.4 months	
Median duration of response	5.6 months	[4.2-7.2]
ORR among patient subgroups, n (%)		
Chemo-naïve vs progressed/relapsed after chemo	5/12 (41.7) vs 35/87 (40.2)	
With vs without visceral metastases	30/78 (38.5) vs 10/21 (47.6)	

[1]Confirmed with second scan at least 4 weeks following the initial observation of response.
[2]Response in 2 patients was unknown.



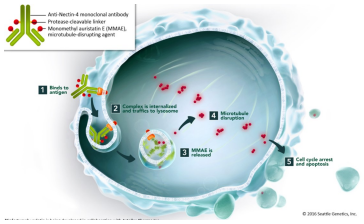


Siefker-Radtke et al. ASCO 2018

GW 96

Enfortumab Vedotin is an Antibody-Drug Conjugate Targeting Nectin-4

- Enfortumab vedotin (EV) is a fully humanized monoclonal antibody against Nectin-4 conjugated with the microtubule-disrupting agent monomethyl auristatin E by a protease-cleavable linker
- Nectin-4, a transmembrane cell adhesion molecule[1], was found to be highly expressed in 97% of mUC patient samples[3]



Rosenberg ASCO 2018

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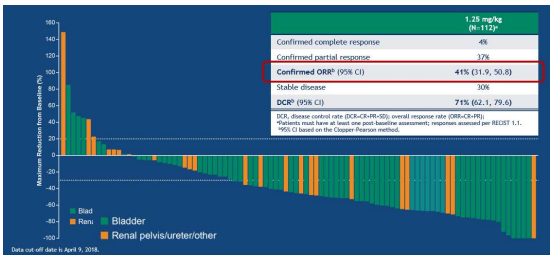
Phase II Enfortumab Vedotin: Response Rate



	1.25 mg/kg (N=112)[a]
Confirmed complete response	4%
Confirmed partial response	37%
Confirmed ORR[b] (95% CI)	41% (31.9, 50.8)
Stable disease	30%
DCR[b] (95% CI)	71% (62.1, 79.6)

DCR, disease control rate (DCR=CR+PR+SD); overall response rate (ORR=CR+PR).
[a]Patients must have at least one post-baseline assessment; responses assessed per RECIST 1.1.
[b]95% CI based on the Clopper-Pearson method.

Rosenberg ASCO 2018

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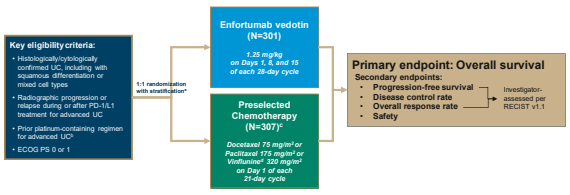
EV-301 Open-Label Phase 3 Trial Design



*Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.

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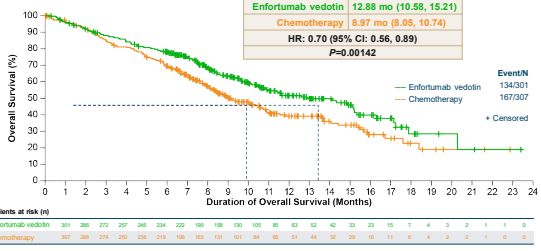
Overall Survival

Median OS	
Enfortumab vedotin	12.88 mo (10.58, 15.21)
Chemotherapy	8.97 mo (8.05, 10.74)
HR: 0.70 (95% CI: 0.56, 0.89)	
P=0.00142	



Patients at risk (n)

Enfortumab vedotin	301	286	272	257	246	234	222	190	158	130	105	85	63	52	42	33	23	15	7	4	3	2	1	1	0
Chemotherapy	307	288	274	250	238	215	186	163	131	101	84	66	51	44	32	28	16	11	6	4	2	2	1	0	0

Data cut-off: July 15, 2020

Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

PRESENTED BY: Thomas Powles

GW 100

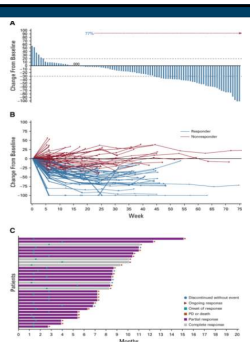
Sacituzumab Govitecan Trophy-U-01 Trial

Cohort 1 (100 patients): patients with mUC who progressed after prior platinum-based and CPI-based therapies

Cohort 2 (40 patients): patients with mUC ineligible for platinum-based therapy and who progressed after prior CPI-based therapies‡

Sacituzumab govitecan 10 mg/kg

Days 1 and 8, every 21 days



Cohort 1 included 113 patients. At a median follow-up of 9.1 months, the ORR was 27% (31 of 113; 95% CI, 19.5 to 36.6); median progression-free survival and OS of 5.4 months (95% CI, 3.5 to 7.2 months) and 10.9 months (95% CI, 9.0 to 13.8 months), respectively.

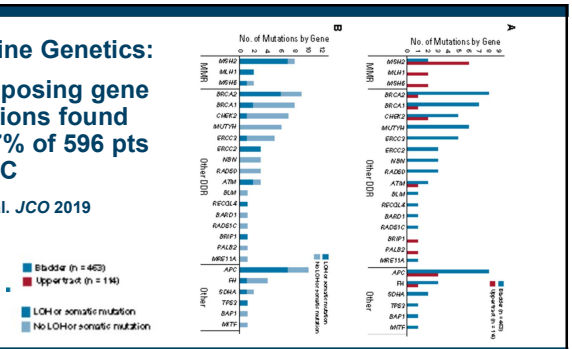
Tagawa et al. JCO 2021

GW 101

Germline Genetics:

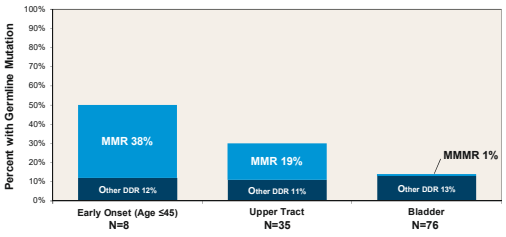
Predisposing gene alterations found in 13.7% of 596 pts with UC

Carlo et al. *JCO* 2019



GW 102

Urothelial Cancer Patient Germline Mutation Prevalence by Age and Site of Primary



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Thank You

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