

Urothelial Cancer: New Strategies



Chong-xian Pan, MD, PhD, MS

Professor of Medicine and Urology
UC Davis Comprehensive Cancer Center
University of California Davis School of Medicine
Sacramento, CA, USA

Staff Physician
VA Northern California Health Care System
Mather, CA

UC DAVIS
COMPREHENSIVE
CANCER CENTER

NCI
CCC
A Comprehensive Cancer
Center Designated by the
National Cancer Institute

DISCLOSURE

I have filed 6 patents that have been licensed by:

Name	Role	Funding
Accelerated Medical Diagnostics	Co-founder and shareholder	3 SBIR Phase I, 1 SBIR Phase II
LP Therapeutics		1 SBIR Phase I, 1 SBIR Phase II
Pandomedx		1 SBIR Phase I, 1 SBIR Phase II

Management of Bladder Cancer

Urothelial Cancer (UCa)

Non-myoinvasive

TUR +/- intravesical treatment

Cystoscopy followup

- 75-80% cases
- High recurrence (60% at 2 yr)
- 25% disease progression
- Lifetime cystoscopy
- The highest cost per case

Locally invasive

Neoadjuvant chemotherapy

Radical cystectomy

- 15-20% cases
- <40% CR after neoadj chemo, 85% OS at 5 yrs
- If not CR, 35% at 5 yrs.
- The worst HR QOL

Metastatic

Chemotherapy immunotherapy

No standard salvage chemo

- 50% RR with chemo
- ImmunoTx RR: 20%
- FGFR3i in <20% UCa
- No standard salvage chemoTx
- Many trials going on

TUR: transurethral resection; CR: complete remission; RR: response rate; HR QOL: Health-related quality of life.

Management of Locally advanced Bladder Cancer

Urothelial Cancer -Locally advanced

Neoadjuvant chemo

Radical cystectomy

Adjuvant chemotherapy
(if no neoadj Tx before)

How to improve the efficacy of neoadjuvant therapy:

- **Chemotherapy:** Accelerated MVAC and dose-dense MVAC.
- **Anti-PD1/PD-L1 immunotherapy single agents:**
- **Targeted therapy:** FGFR3 mutation <20%, and response rate 40%
- **Combination therapy**
 - Chemotherapy plus immunotherapy: BLASST-1 (Nivolumab + GC), Chemo + nivolumab +/- BMS-986205;
 - Immunotherapy combination: DUTRENEO (Drvalumab plus tremelimumab), BLASST-2 (Durvalumab + oleclumab), nivolumab +/- urelumab
 - Immunotherapy plus targeted therapy: NEODURVARIB (durvalumab + olaparib)
 - Chemotherapy plus targeted therapy: BLAST (celecoxib plus chemo)

Management of Locally advanced Bladder Cancer

Urothelial Cancer -Locally advanced

Neoadjuvant chemo

Radical cystectomy

Adjuvant chemotherapy
(if no neoadj Tx before)

Radical cystectomy is associated with the worst health-related quality of life of ALL CANCER TYPES

Bladder preservation treatment (XRT plus chemotherapy) is performed in selected patients: 5- and 10-yr OS 57% and 39%, respectively ; 5-yr salvage cystectomy 29%.*

Immunotherapy can possibly induce durable response.

Several trials combining immunotherapy plus chemo or radiation is currently going on:

- NCT03702179 IMMUNOPRESERVE: Duvalumab + tremelimumab + XRT
- NCT03558087: GC + nivolumab
- NCT02662062 PCR-MIB: pembro + chemoradiation
- NCT03775265 XWOG/NRG 1806: ChemoXRT +/- atezolizumab

*: Giacalone et al. Eur Urol. 2017; 71:952.

Management of Locally advanced Bladder Cancer

Urothelial Cancer -Locally advanced

Neoadjuvant chemo

Radical cystectomy

Adjuvant chemotherapy
(if no neoadj Tx before)

Less than 20% eligible pts receive neoadjuvant chemotherapy

Cancer recurrence ranges from 30-80% depending on stages at surgery

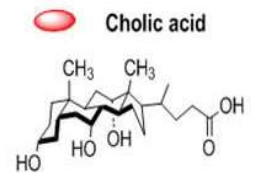
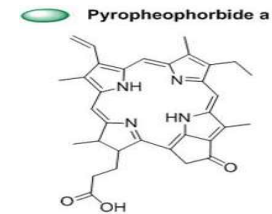
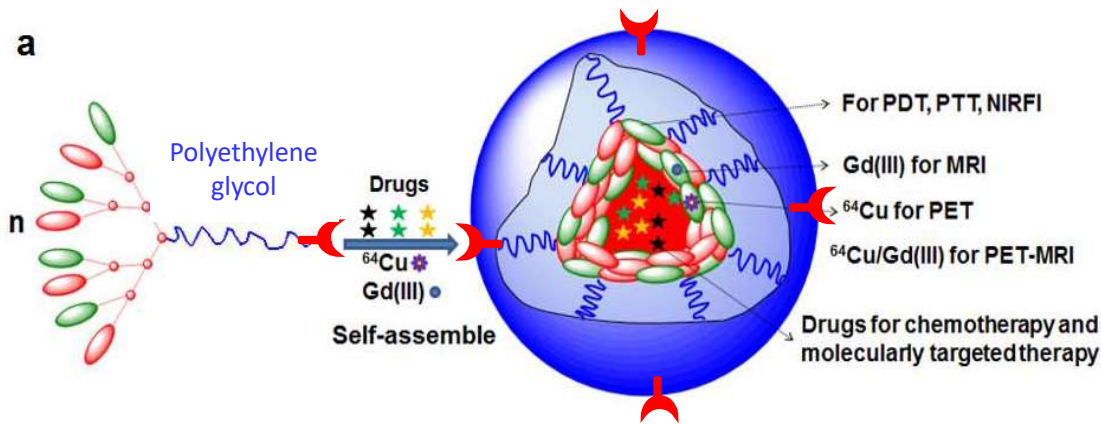
Adjuvant chemotherapy is indicated in some patients.

New Strategies

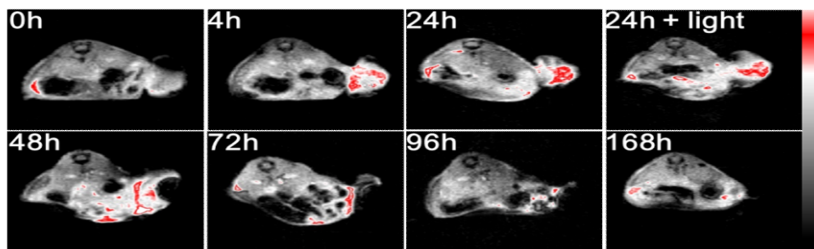
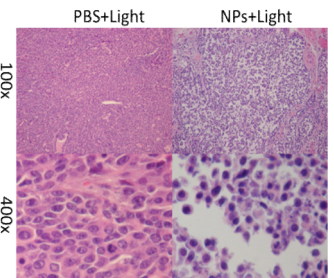
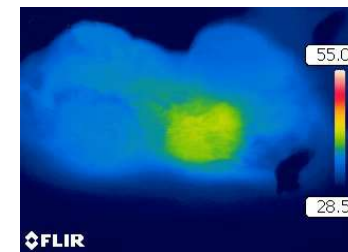
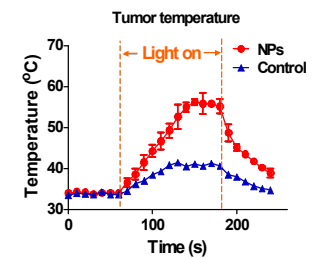
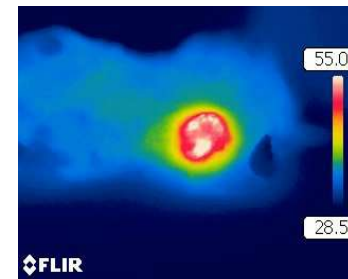
- Adjuvant Immunotherapy: NCT03244384 AMBASSADOR (pembro vs placebo); NCT02632409 CheckMate 274 Inivolumab vs placebo)
- Neoadjuvant plus immunotherapy adjuvant: NCT03732677 NIAGARA (neoadj: durvalumab + GC; adj durva); NCT03661320 (Neoadj chemo + nivo +/- BMS-986205; adj nivo +/- BMS 986205);
- Immunotherapy plus radiation: NCT02891161 (Durva + XRT with adj durva)
- Chemo plus XR plus immunotherapy: NCT02621151 (pembro + gemcitabine + XRT)
- Immunotherapy + targeted therapy.

Management of Locally advanced Bladder Cancer

Bladder cancer-specific PLZ4-nanoporphyrin



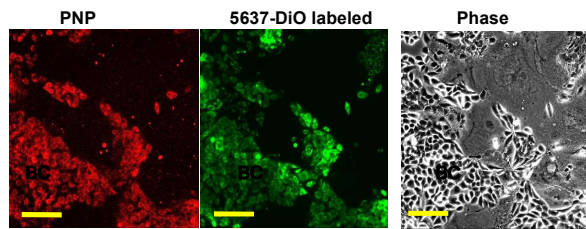
1. Photodynamic diagnosis
2. Photodynamic therapy
3. Photothermal therapy
4. Chelation of Gd(III) for MRI
5. Chelation of ^{64}Cu for PET
6. Chelation of ^{67}Cu for radiation
7. Targeted delivery of chemo
8. combination of the above



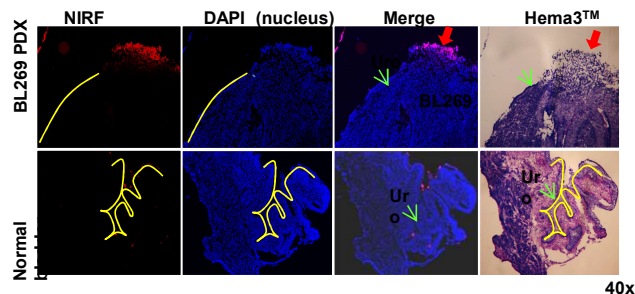
Management of Locally advanced Bladder Cancer

Bladder cancer-specific PLZ4-nanoporphyrin

Photodynamic diagnosis

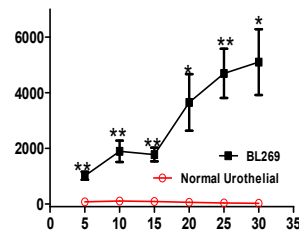


Human bladder cancer cell line 5637



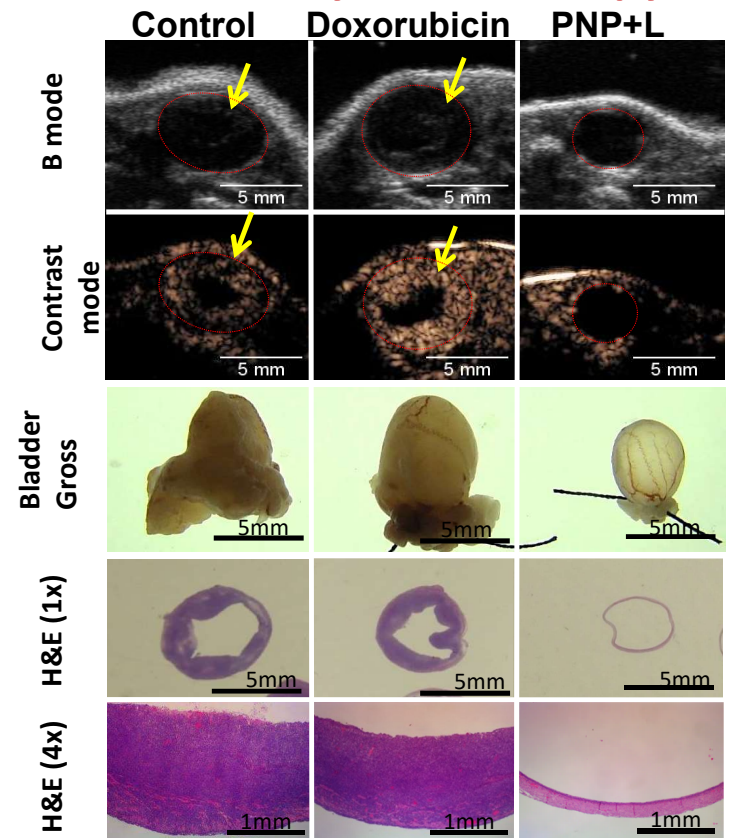
Human patient-derived xenograft

30-40X difference



2-3X for 5-ALA

Photodynamic therapy

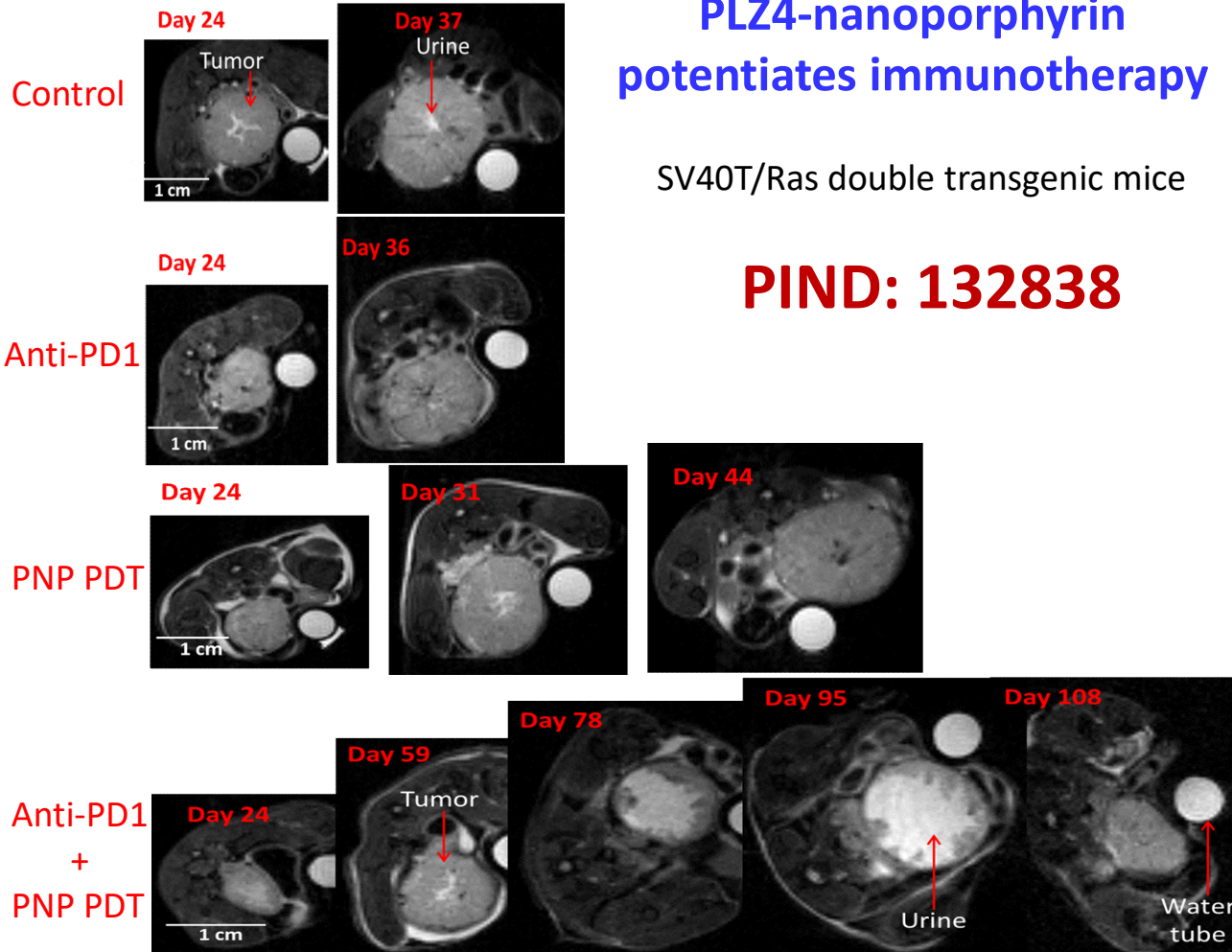


Management of Locally advanced Bladder Cancer

PLZ4-nanoporphyrin potentiates immunotherapy

SV40T/Ras double transgenic mice

PIND: 132838



Group	Ear Tag#	Survival	Median Survival
Control	#539	31 days	33.5 days
	#150	28 days	
	#1191	36 days	
	#2032	23 days	
	#1737	37 days	
PD1 Ab	#900	48 days	42 days
	#649	42 days	
	#536	38 days	
	#542	38 days	
	#825	48 days	
Nano-porphyrin (PNP)	#899	44 days	49.5 days
	#560	45 days	
	#581	31 days	
	#582	34 days	
	#1791	55 days	
	#1783	45 days	
	#1809	67 days	
#1845	68 days		
PD1+Nano porphyrin (PNP)	#651	54 days	83.5 days
	#898	40 days	
	#1843	60 days	
	#1994	77 days	
	#535	96 days	
	#538	158 days	
		90 days	

Management of Bladder Cancer

Urothelial Cancer (UCa)

Non-myoinvasive

TUR +/- intravesical treatment

Cystoscopy followup

- 75-80% cases
- High recurrence (60% at 2 yr)
- 25% disease progression
- Lifetime cystoscopy
- The highest cost per case

Locally invasive

Neoadjuvant chemotherapy

Radical cystectomy

- 15-20% cases
- <40% CR after neoadj chemo, 85% OS at 5 yrs
- If not CR, 35% at 5 yrs.
- The worst HR QOL

Metastatic

Chemotherapy immunotherapy

No standard salvage chemo

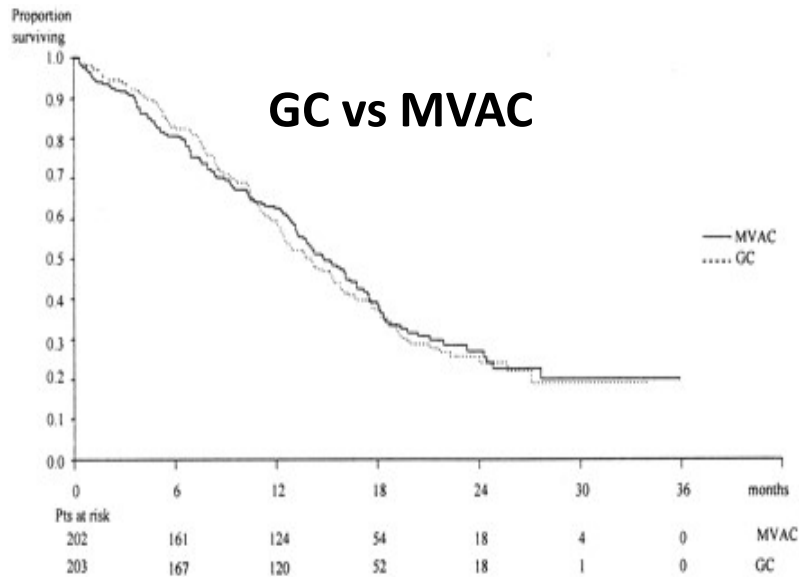
- 50% RR with chemo
- ImmunoTx RR: 20%
- No salvage chemoTx
- FGFR3i just approved
- No change in OS over decades

TUR: transurethral resection; CR: complete remission; RR: response rate; HR QOL: Health-related quality of life.

Management of Metastatic Bladder Cancer

Metastatic bladder cancer

-First-line: Pt-based chemotherapy



von der Maase et al. J Clin Oncol. 2000; 18:3068

Regimen	Trials	Pt No	RR	PFS	OS
Dose-dense MVAC, q14D	Phase III	263	62%	9.1 M	15.5 M
GC regimen, q4w	Phase III	405	49%	7.4 M	13.8 M
M-VAC, q4w	Phase III	269	39-46%	10 M	12.5 M

If no contraindication, prefer dose-dense MVAC.

Management of Metastatic Bladder Cancer

Metastatic bladder cancer

-Second-line: immunotherapy

Drug name	Approved date	Indications	ORR	Median OS	Median PFS	Grade ^{3/4} irAEs
Atezolizumab	May 18, 2016	1, 2	13.4%	8.6 mos	2.1 mos	20%
Nivolumab	Feb 2, 2017	1	19.6%	8.7 mos	2.0 mos	18%
Durvalumab	May 1, 2017	1	17.8%	18.2 mos	1.5 mos	6.8%
Avelumab	May 9, 2017	1	17%	6.2 mos	1.5 mos	8%
Pembrolizumab	May 18, 2017	1, 2	21.1%	10.3 mos	2.1 mos	15%

1. Locally advanced or metastatic urothelial carcinoma that has disease progression during or following platinum-containing chemotherapy or has disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
2. Locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy

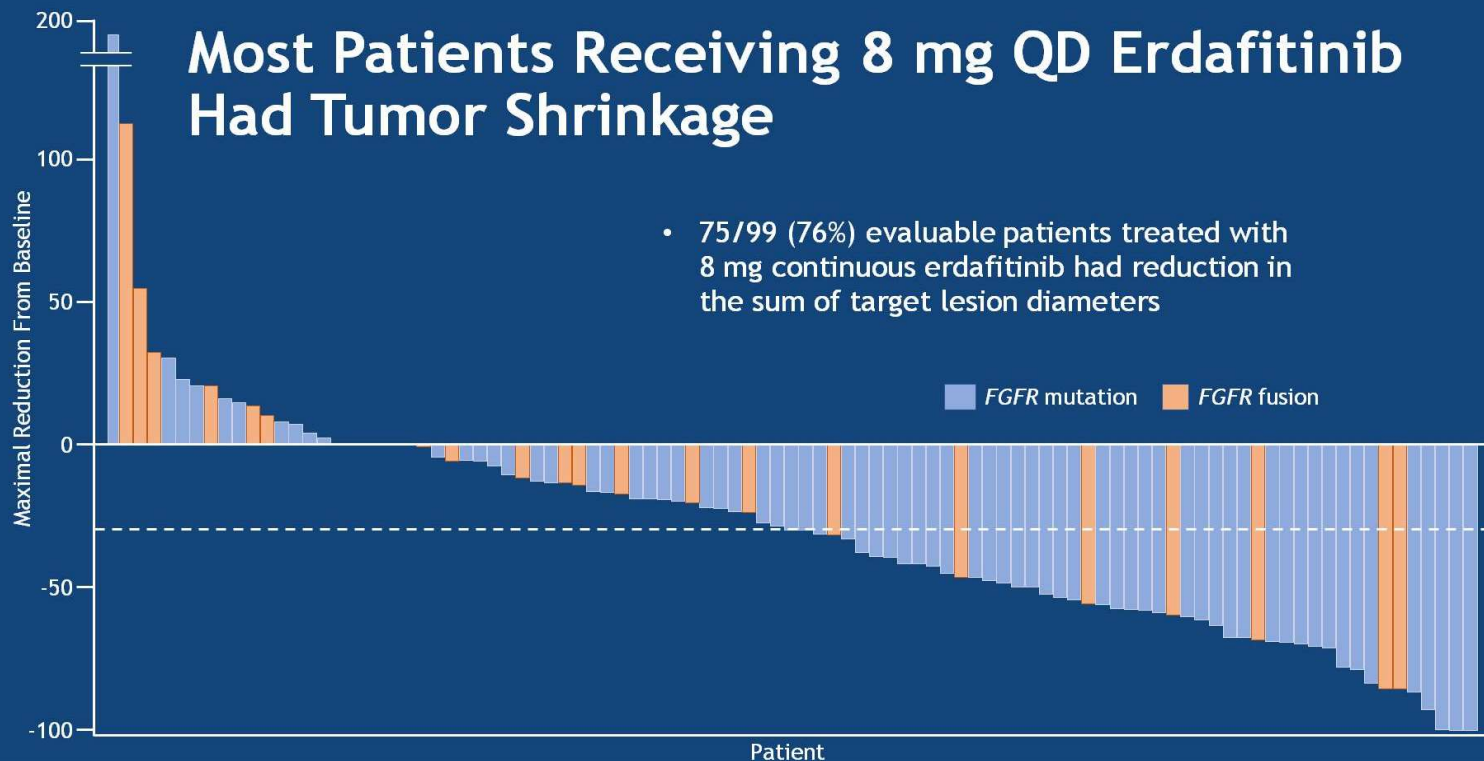
Management of Bladder Cancer

Metastatic bladder cancer

-Second-line: Targeted therapy--FGFR3 inhibitor erdafitinib

Phase 2 BLC2001 Study Design

Most Patients Receiving 8 mg QD Erdafitinib Had Tumor Shrinkage



Management of Metastatic Bladder Cancer

Unmet needs for the management of metastatic bladder cancer

- Moderately effective of the first-line platinum-based chemotherapy: RR: ~50%
- Even though recurrent genetic alterations exist in bladder cancer, only erdafinitb is approved.
- Disappointing immunotherapy: RR: 20%

Management of Metastatic Bladder Cancer

Moderately effective of the first-line platinum-based chemotherapy: RR: ~50%

Lessons learned from other cancer types:

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

L. Horn, A.S. Mansfield, A. Szczesna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D.S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinavar, W. Lin, A. Sandler, and S.V. Liu, for the IMpower133 Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

Is the future for bladder cancer also chemotherapy plus immunotherapy combination?

Management of Metastatic Bladder Cancer

Moderately effective of the first-line platinum-based chemotherapy: RR: ~50%

KEYNOTE 361
NCT02853305

Pembrolizumab (pembro) with or without chemotherapy versus chemotherapy alone in advanced urothelial cancer

IMVIGOR 130
NCT02807636

Atezolizumab (atezo) +/- platinum-based combination vs chemo in locally advanced or metastatic urothelial carcinoma

CheckMate 901
NCT03036098

Nivolumab (Nivo) plus ipilimumab vs Nivo plus chemo vs chemotherapy in Untreated Inoperable or Metastatic Urothelial Cancer

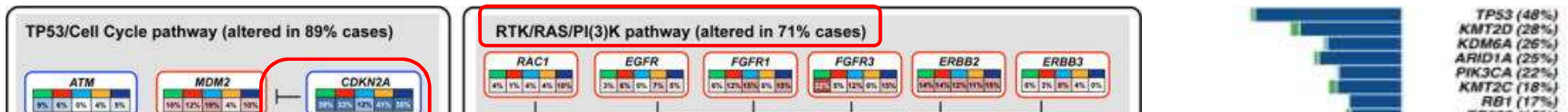
NILE
NCT03682068

Durvalumab (Durva) + chemo vs Durva + tremelimumab + chemo vs chemo in unresectable Urothelial Cancer

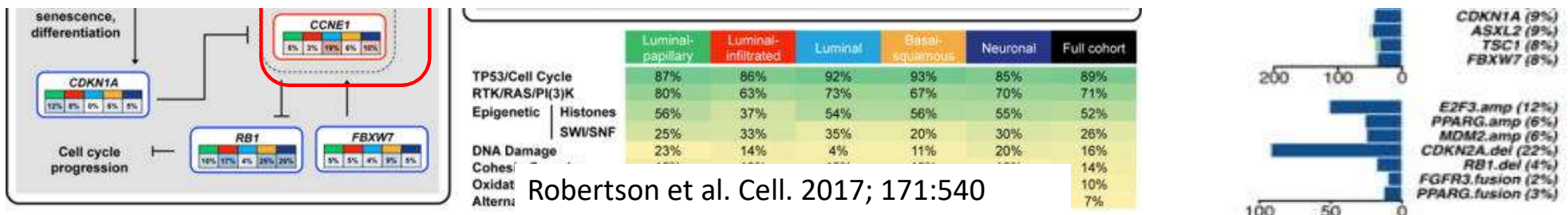
Management of Metastatic Bladder Cancer

Unmet needs for the management of metastatic bladder cancer

- Moderately effective of the first-line platinum-based chemotherapy: RR: ~50%
- Even though recurrent genetic alterations exist in bladder cancer, only erdafinitb is approved.



Can some of these alterations be targeted for the treatment of bladder cancer?



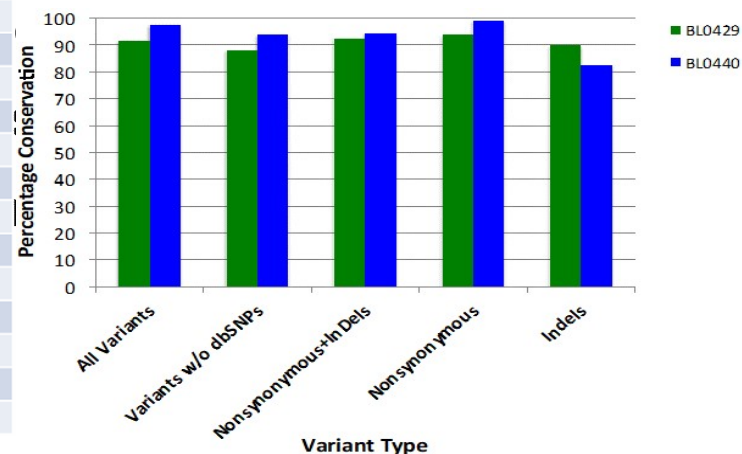
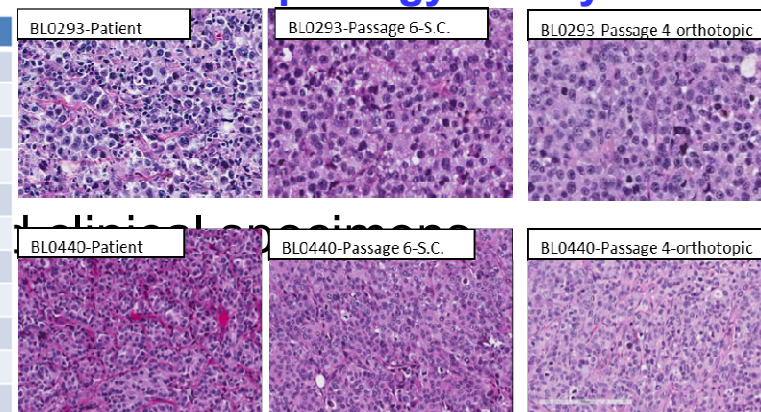
Management of Metastatic Bladder Cancer

Molecularly targeted therapy in bladder cancer:

Morphology fidelity

Clinical Characteristics of the donor patients

Stages	Tumor ID	Age (yrs)	Stage	Surgery	Prior chemo
Myoinvasive bladder cancer	BL0269F	58	pT4 N0 Mx	Cystectomy	No
	BL0293F	77	pT2a N2 Mx	Cystectomy	No
	BL0307F	78	pT3b N2 Mx	Cystectomy	No
	BL0382F	82	pT2 Nx Mx	TURBT	No
	BL0428F	70	pT2 Nx Mx	TURBT	No
	BL0429F	60	pT4a N3 M1	Cystectomy	No
	BL0479F	78	pT2b Nx Mx	Cystectomy	YES (carbo/gem/PTX)
	BL0440F	71	pT4a N2 Mx	Cystectomy	YES (gem/cis)
	BL0515F	78	pT3bN0Mx	Cystectomy	YES (Gem/Cis)
	BL0545F	70	pT2 N0 Mx	Cystectomy	No
	BL0601F	83	pT3 N0 Mx	Cystectomy	No
	BL0629F	74	pT3 N0 Mx	Cystectomy	No
	BL0645F	75	pT4a N2 Mx	Cystectomy	YES (MVAC)#
	BL0648	71	pT4a N2 Mx	Cystectomy	No. AdenoCa
Non-myoinvasive bladder cancer	BL0262F	64	pTa High	TURBT	No
	BL0364F	76	pTa Low	TURBT	No
	BL0381F *	60	pTa High	TURBT	No
	BL0398F *	60	pT1 No Mx	Cystectomy	No
	BL0470F	55	pTa Nx Mx	TURBT	No
	BL0591F	65	pTis N0 Mx	Cystectomy	No
	BL0606F	77	pT1Nx Mx	TURBT	No
	BL0622F	63	pTis	cystectomy	
	BL0674F	54	pT1N0Mx	cystectomy	NO

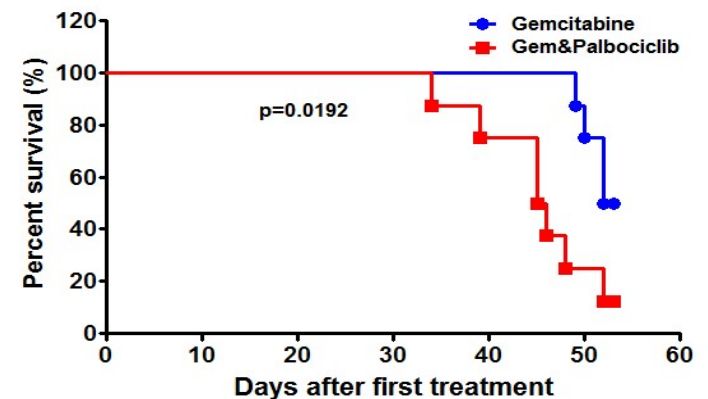
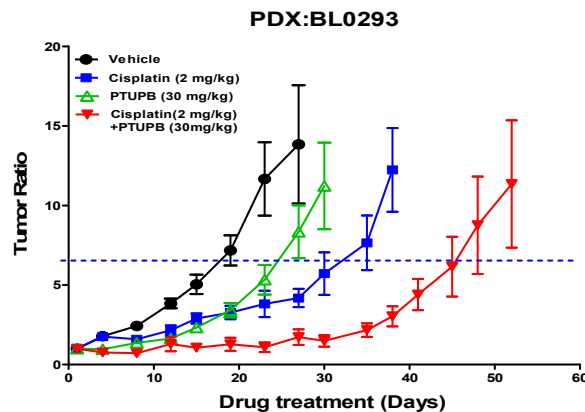
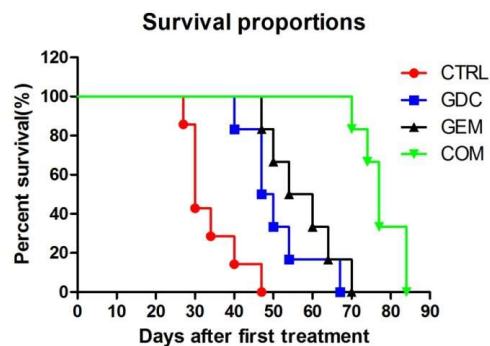
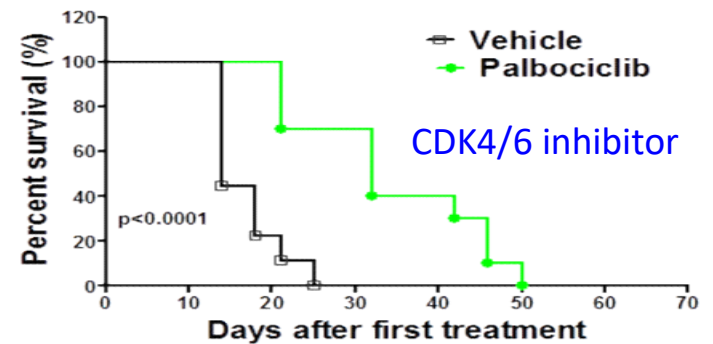
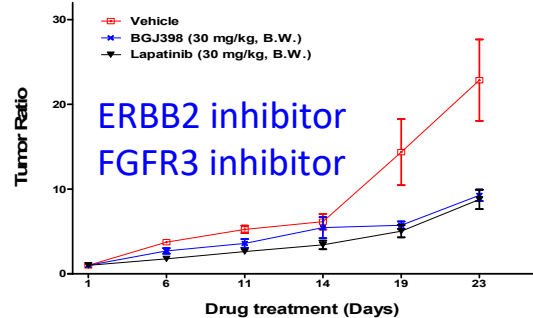
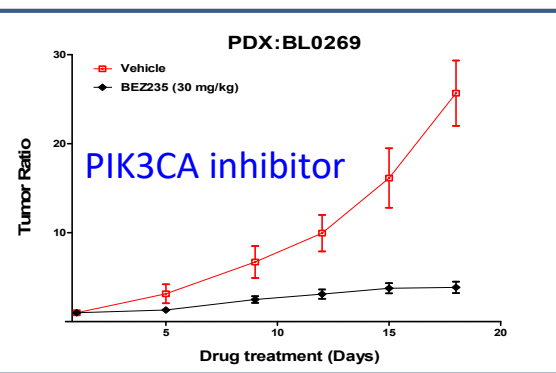


UC Davis and The Jackson Laboratory

Genetic aberrations: 92-97% identity

Management of Metastatic Bladder Cancer

Molecularly targeted therapy in bladder cancer:



PIK3CA inhibitor + Chemo

PTUPB: COX2 and sEH dual inhibitor

Antagonism between palbociclib and gemcitabine

Management of Metastatic Bladder Cancer

Unmet needs for the management of metastatic bladder cancer

- Moderately effective of the first-line platinum-based chemotherapy: RR: ~50%
- Even though recurrent genetic alterations exist in bladder cancer, only erdafinitb is approved.
- Disappointing immunotherapy: RR: 20%

Strategies:

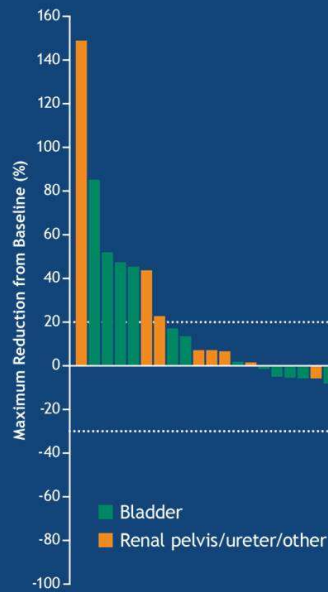
- Immunotherapy Plus chemotherapy
- Immunotherapy plus targeted therapy
- Immunotherapy plus radiation
- Immunotherapy plus vaccine
- Immunotherapy plus immunotherapy

Numerous clinical trials going on.

Management of Bladder Cancer

Enfortumab vedotin: Ab-MMAE targeting nectin-4

Change in Tumor Burden From Baseline



Data cut-off date is April 9, 2018.

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)

Abbreviations: DCR, disease control rate (DCR=CR+PR+SD); ORR, overall response rate (ORR=CR+PR).
^aPatients must have at least one post-baseline assessment; responses assessed per RECIST 1.1.
^b95% CI based on the Clopper-Pearson method.

Management of Bladder Cancer

Urothelial Cancer (UCa)

Non-myo-invasive

TUR +/- intravesical treatment

Cystoscopy followup

- 75-80% cases
- High recurrence (60% at 2 yr)
- 25% disease progression
- Lifetime cystoscopy
- The highest cost per case

Locally invasive

Neoadjuvant chemotherapy

Radical cystectomy

- 15-20% cases
- <40% CR after neoadj chemo, 85% OS at 5 yrs
- If not CR, 35% at 5 yrs.
- The worst HR QOL

Metastatic

Chemotherapy immunotherapy

No standard salvage chemo

- 50% RR with chemo
- ImmunoTx RR: 20%
- No salvage chemoTx
- FGFR3i just approved
- No change in OS over decades

TUR: transurethral resection; CR: complete remission; RR: response rate; HR QOL: Health-related quality of life.

UCaMP U54 PDX program

1U54CA233306

University of California Minority Patient-Derived Xenograft (PDX) Development and Trial Center (UCaMP) to Reduce Cancer Health Disparities

Contact PI: Chong-xian Pan; Multi-PI: Moon Chen and Luis Carvajal-Carmona

- 1. Establish 200 patient-derived xenografts (PDXs) of bladder, lung, gastric and liver cancers; >60% from minority patients.**
- 2. Annotate these PDXs with clinical information**
- 3. Annotate with exome and transcriptome sequencing**
- 4. Use for translational and cancer health disparity.**
- 5. Look for collaboration (\$100,000 per year for pilot studies)**
- 6. Contact email: cspan@ucdavis.edu**

Management of Bladder Cancer

Thank you very much.

Questions?