Erdafitinib

A *First-In-Class* Agent for Patients with Metastatic or Surgically Unresectable Urothelial Carcinoma and Fibroblast Growth Factor Receptor (*FGFR*) Alterations

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Agenda

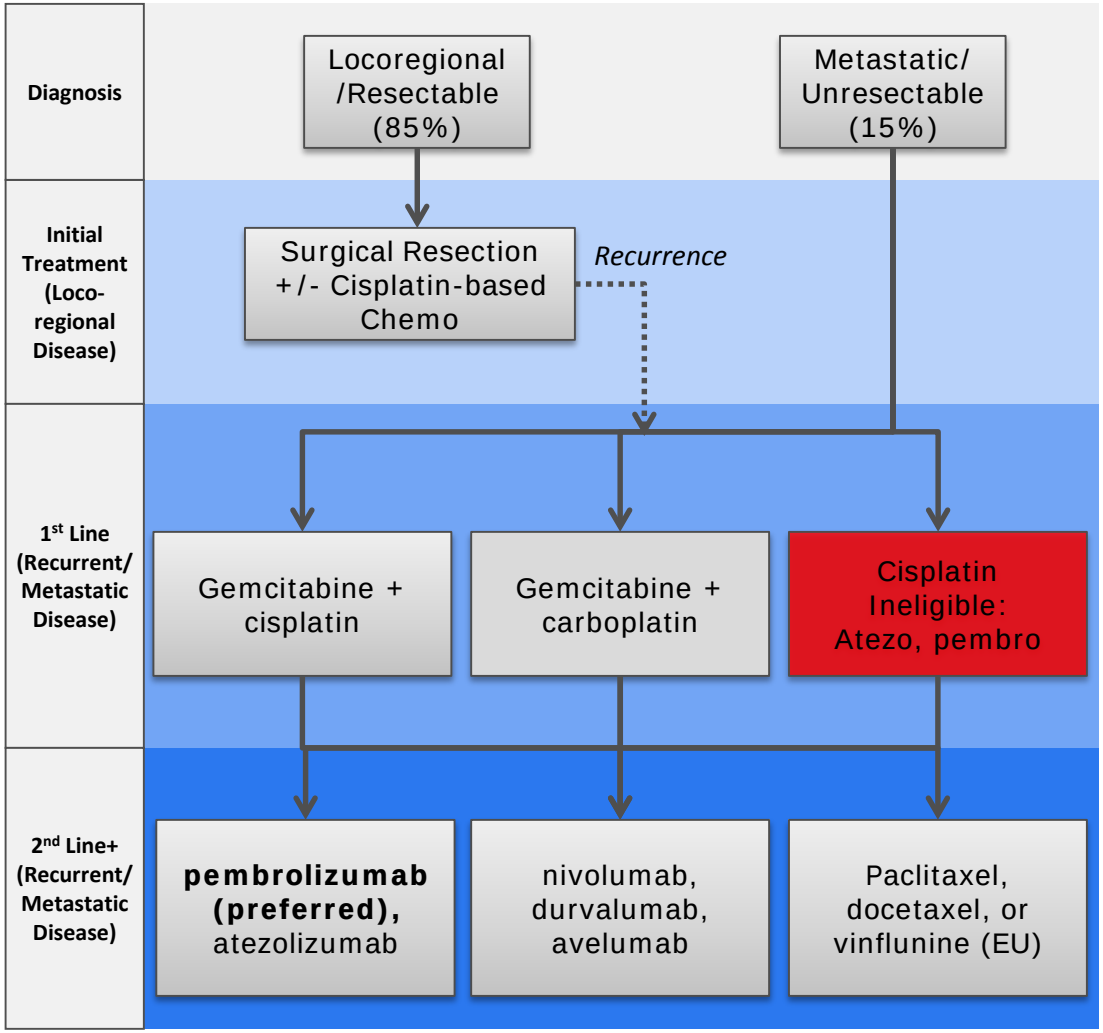
- Bladder Cancer Key Statistics
- Treatment Landscape
- FGFR Alterations in Solid Tumors
- Mechanism of Action of Erdafitinib
- Review of Clinical Data
- Conclusions
- Questions

Bladder Cancer: Key Statistics

- Estimates for 2018
  - New cases: 81,190
  - Deaths: 17,240
- Demographics
  - Median Age: 72
  - 75% Male (*3rd most common cancer in men*)
  - 25% Female (*11th most common cancer in women*)
- Presentation
  - 10–15% are estimated to present with metastasis
  - 80-90% painless gross hematuria
  - 20-30% irritative bladder
- 5-Year Survival
  - Stage I: 88%
  - Stage II: 63%
  - Stage III: 46%
  - Stage IV:15%
- Risk of Progression
  - Grade I: 2-4%
  - Grade II: 5-7%
  - Grade III: 33-64%

American Cancer Society: Cancer Facts and Figures 2018. Atlanta, Ga: American Cancer Society, 2018. Available online. January 2018.

Treatment Landscape



Systemic Therapy for Recurrent or Metastatic Disease

- Platinum doublets have been the preferred 1L treatment advanced UC
- A substantial portion of patients (~40-50%) cannot receive cisplatin due to renal impairment or other comorbidities; for these patients, gemcitabine + carboplatin is preferred
- Five PD-(L)1 agents are approved for 2L treatment after progression on platinum-based chemo. Pembrolizumab has become preferred 2L SOC.

https://www.cancer.gov/types/bladder/hp/bladder-treatment-pdq

Treatment Options for Metastatic or Recurrent Bladder Cancer

- L1 Platinum-Based Chemotherapy
  - Gemcitabine/Cisplatin or MVAC
    - Median OS: 13.8 months
    - Median Time to Progression: 7.4 months
  - Gemcitabine/Carboplatin *(Cisplatin-Ineligible)*
    - Median OS: 9.3 months
    - Median PFS: 5.8 months
- L2 Single Chemotherapy
  - Taxanes (Paclitaxel, Docetaxel Nab-Paclitaxel), Gemcitabine, Premetrexed, Ifosfamide
    - Median OS: ~9 months
    - ORR: ~10-12%
- L1 Cisplatin-Ineligible Immunotherapy
  - Pembrolizumab (PD-1Ab)
    - Median OS: 11.5 months
    - ORR (all subjects): 28.9%
  - Atezolizumab (PD-L1 Ab)
    - Median OS: 11.4 months
    - Median PFS: 2.1 months
    - ORR (all subjects): 23.5%
- L2 Immunotherapy
  - Pembrolizumab
    - Median OS: 10.3 months
    - Median PFS: 2.1 months
    - ORR: 21.1%
  - Atezolizumab
    - ORR: 14.8%
  - Avelumab (PD-L1 Ab)
    - ORR: 17%

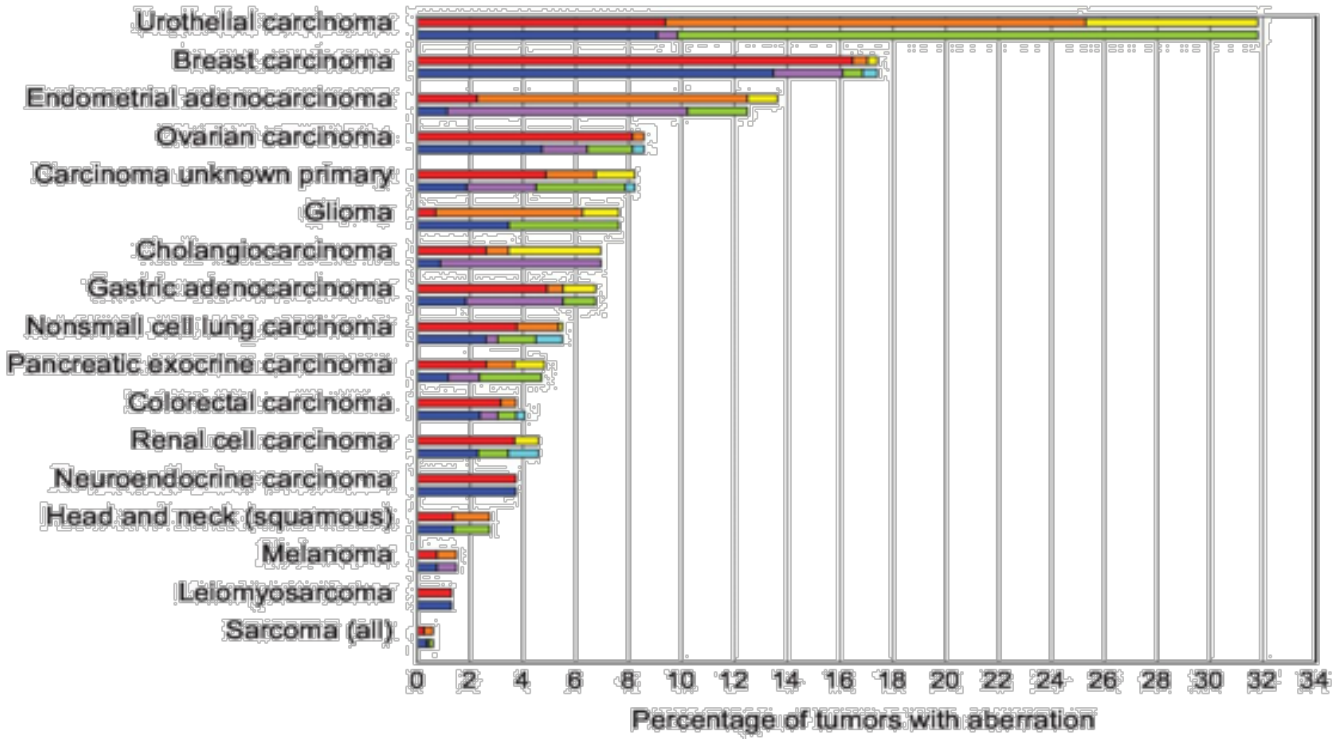
Abbreviations: L1- Line 1 or front line; L-2:Line 2 or second line; OS-overall survival; PFS-progression free interval; ORR-overall response rate; MVAC-Methotrexate, Vinblastine, Doxorubicin, Cisplatin

https://www.cancer.gov/types/bladder/hp/bladder-treatment-pdq

Aberrant FGFR Signaling Plays a Critical Role in Cancer

- Common FGFR alterations leading to pathway activation in cancer subtypes include gene amplifications, chromosomal translocations, and mutations[1]
- *FGFR3* is commonly altered in bladder cancer, and these alterations result in constitutive FGFR3 activation[2]

Frequency and Distribution of FGFR Aberrations Among Cancer Subtypes[3,4]



- FGFR3 mutations occur in **60%–80%** of non–muscle-invasive bladder cancer and **15–20%** of muscle-invasive disease

1. Turner N, Grose R. *Nat Rev Cancer*. 2010;10:116-129.
2. Haugsten EM, et al. *Mol Cancer Res*. 2010;8:1439-1452.
3. Helsten, et al. *Clin Cancer Res*. 2016;22:259-267.
4. Touat, et al. *Clin Cancer Res*. 2015;21:2684-2694

FGFR Alterations Are Common in Cancer

Cancer type	Frequency of *FGFR* alterations[1]
Metastatic UC	15-20%
NMIBC	40-70%
Cholangiocarcinoma	14-22%
NSCLC	4%
Hepatocellular carcinoma (FGF19 amp by FISH)	21%
Glioblastoma	23%
Breast cancer	3-5%
Ovarian cancer	7%
Head and neck cancer	9-17%

FGFR3 mutations are particularly common (37%) in upper tract UC.[2]

Abbreviations: *FGFR*, fibroblast growth factor receptor gene; FISH, fluorescence in situ hybridization; NMIBC, non-muscle-invasive bladder cancer; NSCLC, non-small cell lung cancer; UC, urothelial carcinoma

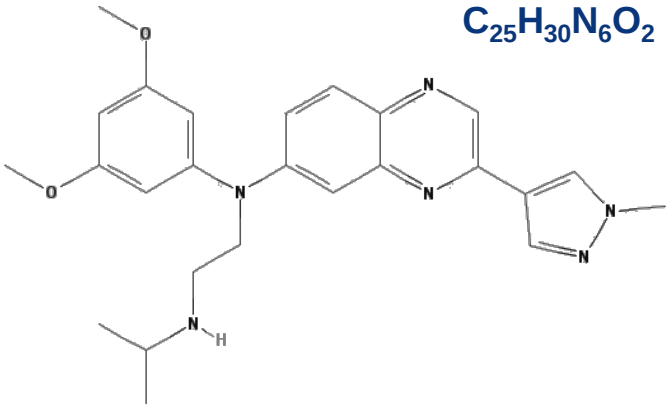
1. TCGA and Genie genomic alteration databases (July 2017).
2. Li Q, et al. *Curr Urol Rep*. 2016;17:12.

Erdafitinib Is a Potent pan-FGFR Inhibitor

- Erdafitinib is an oral pan-FGFR (1-4) inhibitor with IC_{50}* in the single-digit nanomolar range[1]

- Erdafitinib has demonstrated promising activity in patients with metastatic or unresectable UC and other histologies (eg, cholangiocarcinoma) with *FGFR* alterations[2-5]

Erdafitinib Structure



$C_{25}H_{30}N_6O_2$

Molecular Weight : 446.555 g/mol

*IC_{50}, drug concentration at which 50% of target enzyme activity is inhibited

1. Perera TPS, et al. *Mol Cancer Ther*. 2017;16:1010-1020.
2. Tabernero J, et al. *J Clin Oncol*. 2015;33:3401-3408.
3. Soria J-C, et al. ESMO 2016. Abstract 781PD.
4. Loriot Y, et al. ASCO GU 2018. Abstract 411.
5. Siefker-Radtke A, et al. ASCO GU 2018. Abstract 450.

Abstract 4503

First Results From the Primary Analysis Population of the Phase 2 Study of Erdafitinib (JNJ-42756493) in Patients With Metastatic or Surgically Unresectable Urothelial Carcinoma and *FGFR* Alterations

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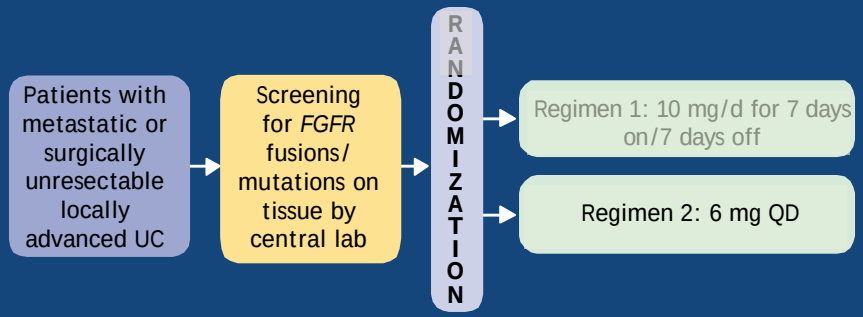
PRESENTED BY: Arlene O. Siefker-Radtke

Phase 2 BLC2001 Study Design



Regimen 3[a]:
8 mg QD with PD Uptitration to 9 mg QD
n = 99

Primary end point
ORR
Secondary end points
PFS, DoR, OS, safety, predictive biomarker evaluation, and PK

Patients

- Progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo
  OR
- Chemo-naïve: cisplatin ineligible per protocol criteria[b]
- Prior immunotherapy was allowed

Primary hypothesis:
- ORR in Regimen 3 is > 25%
- One-sided α = 0.025
- 85% power

[a]Dose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.
[b]Ineligibility for cisplatin: impaired renal function or peripheral neuropathy.

Abbreviations: DoR, duration of response; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; QD, daily; TRAEs, treatment-related adverse events.

BLC-2001 Met Primary Objective

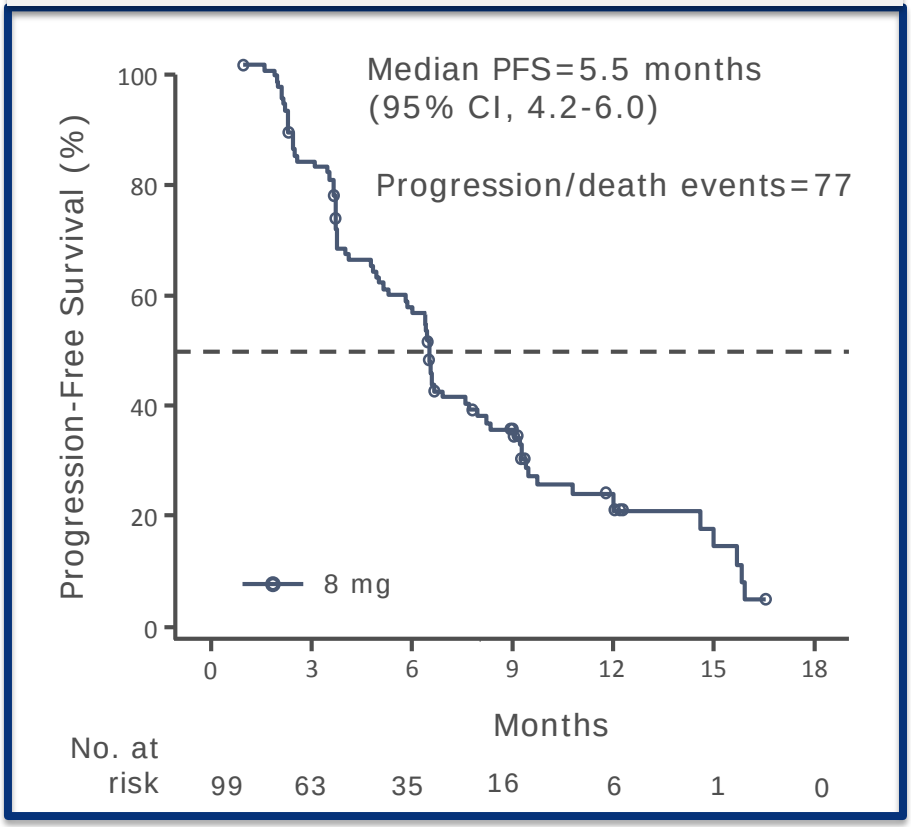
		[95% CI]
Patients, n	99	
Response per investigator assessment[a,b], n (%)		
ORR	**40 (40.4)**	[30.7-50.1]
Complete response	3 (3.0)	
Partial response	37 (37.4)	
Stable disease	39 (39.4)	
Progressive disease	18 (18.2)	
Median time to response	1.4 months	
Median duration of response	5.6 months	[4.2-7.2]
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)	

[a]Confirmed with second scan at least 6 weeks following the initial observation of response.
[b]Response in 2 patients was unknown.

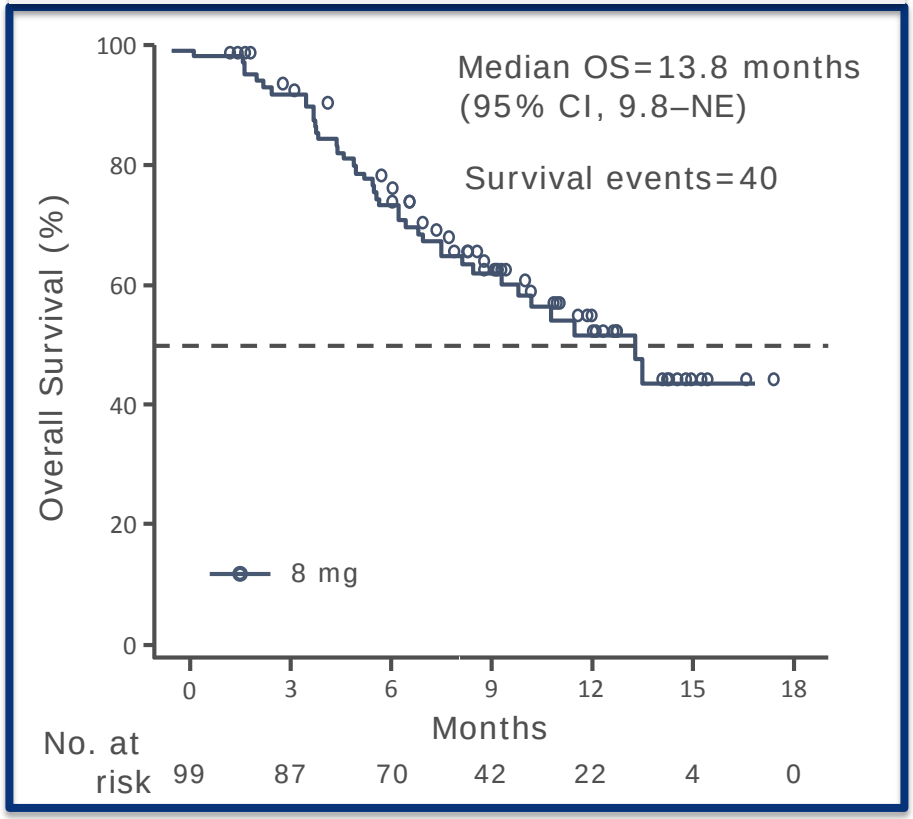
21.2% of patients remained on study treatment after 11 months of follow-up

Secondary Endpoints: PFS and OS

Median PFS



Median OS



Exploratory Analysis: *FGFR* Alterations May Select for Patients With UC Unlikely to Respond to PD-(L1) Inhibitors	8 mg continuous dose (n=99)
Patients treated with prior immuno-oncology agent (IO), n	22
Patients with response (per investigator) to prior IO, n (%)	1/22 (5)*

*Patient had been previously treated with PDL-1 inhibitor (progressive disease) and PDL-1 inhibitor combination (complete response).

The ORR to erdafitinib was 59% in patients with prior IO treatment

IO, immunotherapy.

Siefker-Radtke AO, et al. ASCO 2018. Oral presentation. Abstract 4503.

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Most Common TRAEs and AEs of Special Interest

	8 mg Continuous Dose (n=99)	
AEs Reported in >20% of Patients, n (%)	**Any Grade**	**Grade ≥ 3**
Hyperphosphatemia	72 (73)	2 (2)
Stomatitis	54 (55)	9 (9)
Dry mouth	43 (43)	0
Diarrhea	37 (37)	4 (4)
Dysgeusia	35 (35)	1 (1)
Dry skin	32 (32)	0
Alopecia	27 (27)	0
Decreased appetite	25 (25)	0
Hand-foot syndrome	22 (22)	5 (5)
Fatigue	21 (21)	2 (2)
AEs of Special Interest, n (%)		
Hyperphosphatemia	76 (77)	2 (2)
Dry skin	32 (32)	0 (0)
Hand-foot syndrome	23 (23)	5 (5)
Onycholysis	18 (18)	2 (2)
Paronychia	17 (17)	3 (3)
Nail dystrophy	16 (16)	6 (6)
Central serous retinopathy (CSR)	23 (23)	3 (3)
Non-CSR ocular events*	54 (55)	6 (6)

*Most common non-CSR ocular events included dry eye (19%), blurry vision (17%), conjunctivitis (13%) and increased lacrimation (11%).

- Majority of AEs were Grade 1/2, no Grade 4 or 5 TRAEs were reported
- Serious TRAEs were reported in 9 patients (9%)
- Seven patients discontinued erdafitinib due to AEs of special interest. CSR led to discontinuation in three of the seven patients, and no patient had retinal vein or artery occlusion

Abbreviations: TRAE- treatment related adverse events; AE- adverse events

Siefker-Radtke AO, et al. ASCO 2018. Oral presentation. Abstract 4503.

Conclusions

- Urothelial cancer is a significant disease among Medicare patients.
- Some Medicare enrollees will likely need Erdafitinib as inpatients
- Erdafitnib may provide significant clinical improvement
- On the basis of these results, the FDA has granted erdafitinib Breakthrough Therapy Designation status (March 2018)
- Anticipated approval date of Q1 2019

Questions